Multiple sclerosis impairs ability to detect abrupt appearance of a subliminal stimulus

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Objectives: The study was designed to find evidence that brain electrical activity associated with processing the abrupt appearance or disappearance of a sensory stimulus differed in the presence and absence of the neuropathological changes that are characteristic of multiple sclerosis (MS).
Methods: A subliminal stimulus (electrical field) was applied, and the onset and offset responses from patients with MS were compared with the responses of study participants in two age- and gender-matched control groups, using a novel type of non-linear dynamical analysis that had been developed in earlier studies.
Results: An onset response occurred in 27% of the patients with MS, compared with 85% in the control groups. Among the three patients who exhibited onset-induced changes in brain electrical activity, the average latency of the effect was less and the magnitude of the change was greater than the corresponding values in the control group.
Discussion: Non-linear analysis of electroencephalograms recorded during the sudden presentation of a subliminal stimulus potentially could serve as the basis of a functional test to help diagnose MS. A larger cohort of patients with MS needs to be assessed to validate the results of this study.

Keywords: Complexity conjecture, functional test, onset response, whole-brain states

Introduction

Multiple sclerosis (MS) has typically been regarded as an immune-mediated disease of the human central nervous system that affects genetically predisposed young adults following exposure to yet unidentified environmental agents[1]. Recent neuropathological and imaging studies revealed significant gray-matter involvement in MS[2], even during early-stage disease[3]. Although knowledge is scarce regarding the basic pathological processes in gray matter and their relation to those in white matter, the documented involvement of gray matter indicates that MS should be conceptualized as a disease that affects the whole brain[4].

Improved methods for assessing disease-related functional changes would also be helpful in diagnosing and treating MS. Cognitive activity is mediated by temporal–spatial electrical interactions between localized brain networks[5]. The instantaneous dynamical synchronization is reflected in and constitutes part of the electroencephalogram (EEG). In principle, therefore, analysis of scalp electrical measurements could provide the basis of a method for monitoring general brain function.

Traditional electrophysiological measurements of stimulus-induced responses, visual evoked potentials (EPs) for example, are designed to evaluate specific neural pathways by means of linear techniques (time averaging or spectral analysis). Although they can demonstrate an EP in the fewest trials[6,7], use of these techniques entails an assumption that the latency, duration and waveform of all EPs in a series of trials are identical, which is not true for successive whole-brain electrical states that occur during cognitive processing; instead, these states change profoundly from moment to moment because they are governed by non-linear dynamical laws[8].

The human brain contains specialized cortical and subcortical networks for detecting the abrupt appearance or disappearance of sensory stimuli[9]. Many studies indicated that the responses to the onset and offset of stimuli were mediated by independent pathways[10–12]. We generalized the notion of evoked potentials by developing a method to characterize electrical states of the whole brain in relationship to an abrupt change in a stimulus, without the necessity of assuming a linear response[13,14]. That method was used here to ascertain whether whole-brain electrical states in individual subjects were sensitive to the presence of MS. Specifically, we determined whether the onset and offset responses to a subliminal sensory stimulus differed between the presence and absence of MS.

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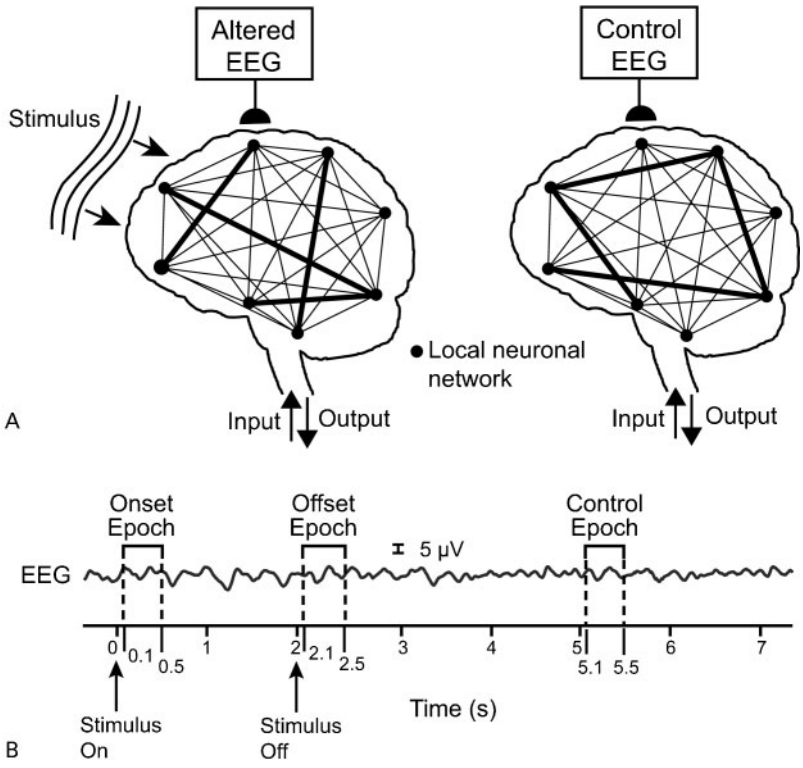

Figure 1 **Detection of changes in the EEG induced by the presence of a subliminal stimulus (electrical field).** (A) **Complexity conjecture for effect of the stimulus on whole-brain electrical activity. The instantaneous strength of the connectivity between local neuronal networks is represented by the thickness of the line that joins them.** (B) **EEG trial showing the locations of the epochs used to detect the effect of the stimulus**

Materials and methods

Patients

Patients with MS were recruited from the outpatient neurology clinic from August 2007 to March 2008. Inclusion criteria were: definite MS[15] with a relapsing–remitting course[16], but in remission; expanded disability status scale (EDSS) score $\leqslant 3{\cdot}0$[17], assessed by the treating neurologist; absence of acute relapses and intravenous corticosteroid treatment for at least 60 days before inclusion in the study; no changes of EDSS score for at least 3 months before inclusion in the study. The criteria resulted in the identification of ten patients who volunteered to participate in the study, all of whom were females; an additional MS patient was recruited in April 2009 because the magnetic resonance imaging (MRI) scan of one of the enrolled patients was unavailable for quantitative analysis (see below). The average age of the patients was 33 years (range: 18–52 years); all patients were being treated with β-interferons or glatiramer acetate. Two gender- and age-matched control groups were used: (1) females assessed and examined in the neurology clinic who complained of headaches but who were otherwise healthy (average age: 33 years, range: 19–52 years); (2) females recruited from the general population who had no medical complaints (average age: 34 years, range: 24–53 years).

All participants were informed of the goals, methods and general design of the investigation, but were not told exactly when during the experimental session, the stimulus would be applied or for how long. Written informed consent was obtained from each participant. The institutional review board at the Louisiana State University Health Sciences Center approved all experimental procedures.

Approach

Our approach was based on the complexity conjecture[13,14] (*Figure 1A*). Stimuli are transduced by specialized cells resulting in afferent and efferent signals; cognition is mediated by electrical activity in localized neuronal networks and by internetwork electrical synchronization[18–20]. The overall process generates a time-dependent, spatially-extended three-dimensional distribution of electrical potential that can be sampled on the scalp. Our hypothesis was that cognitive processing would be altered in the presence of MS.

Stimulus

We chose an electrical field (350 V/m, 60 Hz) as the stimulus because the response it produces is subliminal[21], thereby avoiding the possibility that the putative signature of the disease would be masked by the typical robust linear response from cortical generators that occurs during auditory or visual EP determinations. The electrical field was generated by applying a voltage to two parallel metal plates located on each side of the head. The stimulus was applied for 2 seconds, with a 5 second interstimulus period (7 second trials) to facilitate assessment of the onset and offset responses, which occur with latencies of 100–500 ms (*Figure 1B*)[21].

The study participants were exposed (eyes closed) in an isolation chamber to reduce the effect of

random ambient stimuli. All electrical equipment was located outside the chamber; the absence of both uncontrolled sensory cues and direct perception of the field was verified by interviewing each subject at the end of the experimental session.

Electroencephalograms

Electroencephalograms were recorded from O_1, O_2, C_3, C_4, P_3 and P_4 (International 10-20 System) referenced to linked ears, using gold-plated electrodes attached to the scalp with conductive paste; the signals were filtered (0·3–35 Hz), digitized and analysed offline. Application of the stimulus produced a spike artifact (30 ms) that was deleted before analysis. Trials containing artifacts (as assessed by visual inspection) were discarded (<5% of the trials). All results were based on data from at least 50 artifact-free trials. Each participant underwent 80 stimulus trials and 80 sham-stimulus trials; the former were used to determine the effect of the stimulus and the latter served as a negative control.

Imaging

Brain MRI was performed using a 1·5 T scanner with a standard quadrature head coil; contiguous T2-weighted axial images (5 mm thick sections) were analysed using a conventional spin echo sequence with a 250 mm field of view and a 256 × 256 image matrix. A neuroradiologist (E. Gonzalez-Toledo) identified the lesions based on predetermined guidelines[22] and measured lesion volume using morphometric analysis (MIPAV, National Institutes of Health, Bethesda, MD, USA) while blinded to the electrophysiological data. Separate measurements were made for periventricular[23] and non-periventricular lesions.

Analysis and statistics

The EEG from each derivation was analysed to detect the effects of stimulus onset and offset; a portion of the interstimulus period (t=5·1–5·5 seconds) served as the control (*Figure 1B*). Our method[13] involved embedding the EEG in a mathematical phase space, calculating recurrence plots, and quantifying them using two distinct but related quantifiers called percent determinism and percent recurrence[24]. The measured characteristics of the response were the magnitude of quantifiers (expressed as a percent of the corresponding value of the control) and the latency of the response (in millisecond), assessed at the mid-point of the response[13]. A statistically reliable change in the quantifiers that occurred in association with application of the stimulus was a direct indication of a change in brain electrical activity.

For each statistical test involving an onset or offset response, a comparable test was carried out on the sham data and the results were used to calculate the pairwise error rate (number of false-positive effects in the sham data divided by the total number of tests performed). The error rate thus determined was used to estimate the family-wise error rate (P_{FW}) for the decision that a subject had exhibited a stimulus-induced change in brain electrical activity[14].

To examine for the occurrence of linear changes, the EEG was also evaluated directly (no unfolding in phase space) by time averaging[7]; family-wise error was determined as described above. We regarded a change as non-linear if it was detected by recurrence analysis but not by time averaging.

Results

Onset responses occurred in only 27% of the patients with MS (*Table 1*), compared with 90% of those in the migraine group (*Table 2*) and 80% of the normal subjects (*Table 3*); the onset detection rate in the patients with MS was significantly less than either control group (p<0·05, chi-square test).The rate of detection of stimulus offset in the patients with MS (70%) was comparable to that in the control groups (50 and 70%, respectively, in the migraine and normal groups) (*Tables 2* and *3*).

Among the three patients who exhibited onset-induced changes in brain electrical activity (MS-4, MS-6 and MS-9, in *Table 1*), the average latency of the effect was less and the magnitude of the change was greater than the corresponding values in the control group (p<0·05, t-test) (*Table 4*).

Stimulus-related changes were not seen in any participant when the EEGs were evaluated by time-averaging (data not shown).

Lesion load was quantified in eight of the patients with MS (*Table 1*); in two other cases (MS-10 and

Table 1 Stimulus-induced changes in brain electrical activity in study participants with multiple sclerosis

	Lesion load (cm^3)					
MS participant	Total	Peri.	Onset stimulus	P_{FW}	Offset stimulus	P_{FW}
MS-1 (40)	1·77	0·64	NE*	…	NE	…
MS-2 (34)	1·59	0·39	NE	…	**O_1** O_2 **O_2** P_4	0·000
MS-3 (52)	7·67	5·63	NE	…	O_1 C_3 **C_3***	0·084
MS-4 (32)	0·47	0·47	**O_1 O_2** C_3 **C_3 C_4**	0·003	**C_3 C_4 C_4**	0·014
MS-5 (19)	0·14	0	NE	…	O_2 C_3 P_3	0·001
MS-6 (30)	NA	NA	O_2 **O_2 C_3**	0·029	O_2 C_3 P_3	0·001
MS-7 (18)	2·44	0·92	NE	…	**C_3** C_4 **C_4 P_3 P_4**	0·000
MS-8 (27)	1·82	0·96	C_3 **C_4 P_4**	0·029	**O_2** C_4 P_4	0·024
MS-9 (50)	3·40	2·56	NE	…	NE	…
MS-10 (31)	Diffuse	Diffuse	NE	…	O_1 **O_1 P_3**	0·005
MS-11 (38)	Diffuse	Diffuse	NE	…	O_2 **O_2** C_4	0·005

Results found using the EEG quantifier percent recurrence and percent determinism are shown in non-bold and bold, respectively. Age (years) in parentheses. NE: no effect; NA: not available; Peri.: periventricular; P_{FW}: family-wise error. *False-positive detection.

MS-11), the brain structural changes were too diffuse for measurement. In the onset detectors for which an MRI was available (MS-4 and MS-8), the average total load was 1·14 ml, compared with 2·84 ml in the onset non-detectors; the respective average periventricular loads were 0·72 and 1·63 ml, respectively.

Discussion

Cortical and subcortical networks sensitive to the abrupt appearance or disappearance of sensory stimuli facilitate unconscious shifting of attention to environmental events, for example, an immediate awareness of the sudden cessation of a sound, like birds singing[9]. Different networks are involved in attention to stimuli onset and offset[11,25–29]. Because structural abnormalities in white matter and gray matter are pathognomic for MS, we hypothesized that a general functional test for the disease might be based on measurements of the electrophysiological correlates associated with detection of the sudden appearance and/or disappearance of stimuli. Analysing responses by directly averaging the EEG, studies of visual evoked potentials for example, offered little hope of success because the characteristics of the putative stimulus-induced change in brain activity could be anticipated to vary from trial to trial; if so, real effects would be averaged away and hence would appear non-existent. We therefore generalized the notion of the evoked potential by quantifying the stimulus-induced change before the averaging step in the analysis, using a non-linear mathematical algorithm. We report here the results obtained using a subliminal stimulus that was not consciously perceived.

The rates at which clinically normal subjects exhibited changes in brain electrical activity in response to the onset and offset of the stimulus (*Table 3*) were as expected based on previous studies[13,14,21]; the detection rates in the migraine group (*Table 2*) were similar to those in the normal group. In the MS group, in contrast, the rate of occurrence of onset responses was significantly lower (*Table 1*). If the absence of a change due to stimulus onset was taken as indicating the presence of MS, then the sensitivity of the test was 73% (eight of 11). A rough measure of test reliability can be obtained from a consideration of the sham data. A total of 62 tests were performed (onset and offset in 31 patients),

Table 2 Stimulus-induced changes in brain electrical activity in study participants who complained of headache

Headache participant	Onset stimulus	P_{FW}	Offset stimulus	P_{FW}
H-1 (53)	O_1 C_3 C_4 P_4	0·000	O_1 **O_1** C_3	0·013
H-2 (29)	O_1 C_3 C_3	0·013	NE	…
H-3 (35)	C_3 **C_3** **P_3**	0·005	C_3 **C_3** C_4	0·035
H-4 (35)	O_2 C_3 C_4 P_3 P_4	0·000	O_2 C_3 C_4 P_3 P_4	0·001
H-5 (28)	O_1 **O_1** P_4*	0·040	O_1 **O_1** O_2 **O_2**	0·001
H-6 (40)	C_4 **C_4** **P_3** P_4 **P_4**	0·029	NE	…
H-7 (34)	**O_1** C_4 **C_4**	0·025	NE	…
H-8 (32)	NE	…	O_1 C_3 C_4	0·052
H-9 (28)	O_2 C_3 P_3	0·001	O_1 O_2 C_3 P_3	0·000
H-10 (24)	O_2 **O_2** P_4	0·040	NE	…

Results found using the EEG quantifier percent recurrence and percent determinism are shown in non-bold and bold, respectively. Age (years) in parentheses. NE, no effect; P_{FW}, family-wise error. *False-positive detection.

Table 3 Stimulus-induced changes in brain electrical activity in study participants who had no medical complaints

Normal participant	Onset stimulus	P_{FW}	Offset stimulus	P_{FW}
N-1 (51)	O_2 **O_2** C_3	0·031	**C_3** **C_4** **P_3**	0·077
N-2 (66)	O_2 C_3 **C_3** P_4	0·001	C_4 **C_4** P_4	0·040
N-3 (22)	NE	…	O_2 **O_2** **P_3**	0·059
N-4 (26)	C_3 C_4 **C_4** P_3	0·001	NE	…
N-5 (23)	C_3 C_4 P_4	0·001	**O_2** C_4 P_3	0·011
N-6 (23)	C_3 **C_3** C_4 **C_4**	0·001	C_4 P_4 **P_4**	0·005
N-7 (23)	**O_1** C_3 **C_3** **P_3**	0·004	O_1 O_2 C_3 P_3 P_4	0·000
N-8 (46)	O_1 **O_1** C_3	0·005	O_1 C_3 P_3	0·001
N-9 (23)	O_1 O_2 C_4 **C_4** P_3 P_4	0·000	C_3 **C_3** P_3 **P_3**	0·000
N-10 (25)	P_3 **P_3** **P_4***	0·084	C_3 P_3 P_4	0·001

Results found using the EEG quantifiers percent recurrence and percent determinism are shown in non-bold and bold, respectively. NE: no effect; P_{FW}: family-wise error. Age (years) in parentheses. *False-positive detection.

Table 4 Stimulus-induced changes in brain electrical activity (mean ± SD)

Group	Onset latency (ms)	Magnitude (%)	Offset latency (ms)	Magnitude (%)
MS	288·0 ± 56·3 (3, 11)*	53·2 ± 20·9 (3, 11)*	295·9 ± 57·5 (9, 30)	35·6 ± 14·5 (9, 30)
Migraine	291·3 ± 50·4 (9, 32)*	32·7 ± 11·6 (9, 32)	263·1 ± 40·5(6, 23)*	30·3 ± 11·2 (6, 23)
Normal	333·3 ± 44·3 (9, 34)	30·8 ± 12·2 (9, 34)	307·6 ± 55·3 (9, 31)	31·0 ± 12·6 (9, 31)

Numbers in parentheses indicate the number of subjects who exhibited a response and the number of electrode derivations at which a change in brain activity was found, respectively (*Tables 1* and *3*). The magnitude of stimulus-induced changes is expressed as a percent difference from the control value of the recurrence quantifier. *$p<0·05$ (*t*-test) with respect to the normal group.

and only four cases of a false-positive result EP were found (*Tables 1–3*). Thus, the method was unlikely to report a stimulus-induced change where none existed. In the three cases where an onset response was found, its characteristics (latency and magnitude) differed significantly from the controls, on average. Although the number of patients was small, the results raised the possibility that the functional test was sensitive to the presence of MS even in patients who detected the stimulus. The lesion load appeared to be smaller in the detectors (*Table 1*), but too few patients were studied to permit a realistic assessment of the correlation between load and ability to detect the stimulus. Overall, the results suggested that non-linear dynamical analysis of changes in brain electrical activity induced by the abrupt onset of the stimulus might be useful for characterizing brain function in patients with MS.

We previously showed that electrical fields were perceived subliminally[21]. We used a field as the stimulus in this study to lay emphasis on the role of subcortical networks. Moreover, the stimulus receptor cell, believed to be a force-transducing ion channel similar to that present in lower life forms[21], has been located in the head[30], possibly the cerebellum[31]. Thus, we had good reason to suspect that the subcortical networks mediated even the early post-transduction steps in the cognitive processing triggered by the stimulus. The relative advantages and disadvantages of using ordinary stimuli remain to be explored.

Presently, there are no adequate functional tests to assist in diagnosing MS or to characterize end points in longitudinal studies and clinical trials. Evoked potentials have frequently been assessed in patients with MS, but several factors limit their clinical usefulness. Most studies reported increased average latency, but decreased latencies also occurred in particular patients in the MS group[32,33]. Thus, the complex time- and spatially-dependent interplay of degenerative and regenerative processes that occur in the central nervous system of patients with MS prevents both interpretation of latency changes in terms of specific neurological function and determination of the extent of latency changes that can reliably be regarded as clinically meaningful[34–36]. Another restriction on the use of EPs for assessing patients with MS stems from the common use of time-averaging to evaluate the data. Although time-averaging facilitates detection of lesions in specific sensory pathways, it cannot characterize whole-brain electrical activity because only the aspects of the responses that are identical in the trials are captured; the variable parts are averaged away.

Functional magnetic resonance imaging (fMRI) can help reveal the neural basis of motor and cognitive impairment in patients with MS, usually by indicating relative increases in the degree of activation within given brain regions[37,38]. However, changes in activation may be due to differences in task performance between the groups tested, rather than direct effects of the underlying disease process[39]. Additionally, fMRI is susceptible to artifacts related to head motion.

The method described in our study permits an assessment of the extent of synchronization between brain networks, which is precisely the kind of high-level brain function that we would expect would be impaired, given our present perspective that MS is a whole-brain disease. Complicated, expensive equipment is not needed to implement the method, and the algorithms necessary to evaluate the data are available as freeware[40].

The potential advantages of non-linear analysis of whole-brain electrical states are opposed by some notable limitations and uncertainties: (1) the fundamental results of the analysis are not expressed as a brain image, or a familiar scalar quantity such as time or voltage, but rather in terms of unfamiliar quantifiers that have no direct physiological interpretation or meaning; (2) scalp electrical signals can be affected by vascular pathology, brain tumor or stroke; the extent to which altered tissue perfusion affects the interpretation of the dynamical electrical changes has not been evaluated; (3) the disease specificity of the response is an unresolved issue. We found that patients in the headache and MS groups could easily be distinguished, but the specificity issue must be evaluated by considering other diseases like Alzheimer's and Parkinson's diseases; (4) the potential influence of the treatment (β-interferons and glatiramer acetate) on the observed response should be assessed; (5) it remains unclear whether or to what extent the difference in onset response between those who do and do not have MS can be explained by a difference in baseline brain electrical activity.

In summary, non-linear analysis of EEGs recorded during the sudden presentation of a subliminal stimulus could potentially serve as the basis of a functional test to help diagnose MS. A larger cohort of patients with MS needs to be assessed to validate the results of this study.

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