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## Absent movement-related cortical potentials in children with primary motor stereotypies

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## Abstract

**Background**—The underlying pathophysiologic mechanism for complex motor stereotypies in children is unknown with hypotheses ranging from an arousal to a motor control disorder. Movement-related cortical potentials (MRCPs), representing the activation of cerebral areas involved in the generation of movements, precede and accompany self-initiated voluntary movements. The goal of this study was to compare cerebral activity associated with stereotypies to that seen with voluntary movements in children with primary complex motor stereotypies.

**Methods**—Electroencephalographic (EEG) activity synchronized with video recording was recorded in 10 children diagnosed with primary motor stereotypies and 7 controls. EEG activity related to stereotypies and self-paced arm movements were analyzed for presence or absence of early or late MRCP, a steep negativity beginning about one second before the onset of a voluntary movement.

**Results**—Early MRCPs preceded self-paced arm movements in 8 out of 10 children with motor stereotypies and in 6 out of 7 controls. Observed MRCPs did not differ between groups. No MRCP was identified before the appearance of a complex motor stereotypy.

**Conclusions**—Unlike voluntary movements, stereotypies are not preceded by MRCPs. This indicates that premotor areas are likely not involved in the preparation of these complex movements and suggests that stereotypies are initiated by mechanisms different from voluntary movements. Further studies are required to determine the site of the motor control abnormality within cortico-striatal-thalamo-cortical pathways and to identify whether similar findings would be found in children with secondary stereotypies.

## Keywords

Motor stereotypies; Movement-related cortical potentials; EEG; Motor control

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## Introduction

Motor stereotypies are “repetitive, rhythmic movements that have a predictable pattern and location, seem purposeful but serve no obvious function, tend to be prolonged, and stop with distraction” (1). Common examples of complex motor stereotypies include bilateral arm flapping, hand waving, and finger fluttering often accompanied by mouth opening and neck extension. Movements typically begin before the age of three years, have a duration of seconds to minutes, appear multiple times per day, and are triggered by periods of engrossment, excitement, stress, fatigue, or boredom. Complex stereotypies are subdivided into a “primary” category indicating its presence in an otherwise developmentally normal child, and “secondary” for those children with autistic spectrum disorders, developmental delays, sensory impairment, a variety of syndromes, etc.

The prevalence and pathophysiology of primary motor stereotypies are unknown. Psychological hypotheses have included a disorder of arousal, modulation of sensory stimuli, part of imaginative activities, a coping mechanism, learned behavior, and a component of a psychiatric disorder (2). In contrast, support for an underlying neurobiological abnormality includes the presence of complex motor stereotypies in otherwise normally developing children with no evidence for underlying psychological or psychiatric issues (3,4). In addition, stereotypies have appeared in individuals with cortical and sub-cortical dysfunctions (5–9), can be induced by drugs in both humans and rodents (10–14), and may be inherited (3). The framework for understanding habitual behaviors as a motor control abnormality would involve cortico-striato-thalamo-cortical circuits (2). In order to test the hypothesis that stereotypies result from an abnormal cortico-striato-thalamo-cortical motor command, we proposed that cerebral activity associated with stereotypies would differ from that accompanying voluntary movements. Our goal was to define whether primary complex motor stereotypies are preceded by a movement-related cortical potential (MRCP), as is observed before voluntary movements. We hypothesized that cerebral activity preceding voluntary movements in these children would be similar to that observed in healthy children, but no pre-movement potentials would precede the stereotypic movement.

## Methods

### Population

10 patients (mean age  $\pm$  SD of  $9.8 \pm 2.1$  years, 5 males, 5 females) presenting with primary motor stereotypies (Table 1) and 7 controls ( $11.1 \pm 2.7$  years, 2 males, 5 females) were included in the study. Patients were screened by a neurologist (HSS) to assure they met the following inclusion criteria: normally developing child, presence of complex-motor stereotypies with predominant movements consisting of repetitive arm flapping, hand waving, or finger wiggling movements; the predominant stereotypic movements must have started before four years of age, have been present for at least four months and occur at least 10 times a day. Exclusion criteria included (for patients and controls): diagnosis of autism, autistic spectrum disorder, Pervasive Developmental Disorder NOS, or mental retardation (IQ < 70); any concurrent significant medical, neurological, or psychiatric condition and use in the past 3 months of tranquilizers, psychotropic drugs or medications which could modulate the cortical activity. All children were attending regular classes and getting good grades (at least A's and B's) and school performance was rated as good by parents for all subjects.

During the screening visit, 2 scales were used in order to further characterize and quantify the severity and frequency of the symptoms: the Repetitive Behavior Scale-Revised (RBS-R) (15) and the Stereotypy Severity Scale (SSS) (16). Lastly, the children's handedness was assessed by the Edinburgh Handedness Inventory (17).

### Patient consents

The study was approved by the Institutional Review Board (IRB) of the National Institute of Neurological Disorders and Stroke (NINDS). All participants as well as one of their parents or legal guardians gave their informed oral and written consents before the experiments in

accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and NINDS guidelines.

### Study procedures

Each patient spent a single day in the pediatrics inpatient unit of the NIH Clinical Center, in a private room, accompanied by at least one of their parents or legal guardians. During the first 15–20 minutes, the children were asked to perform voluntary, self-paced arm movements, mimicking their major stereotypies while sitting in a comfortable armchair, with at least 10 seconds between each movement. At least 50 movements were recorded. This control condition was performed to define whether premovement potentials could be recorded in this patient population, similar to most controls. No particular task was required of the children for the remainder of the day. They were free to spend their time as they desired and were encouraged to perform the activities that would usually trigger their stereotypic movements. Throughout the day, their cerebral activity was monitored and synchronized with video. The entire recording process lasted for 5 to 6 hours. The EEG activity of healthy volunteers was recorded in the regular NIH EEG lab. Controls were asked to mimic the stereotypic movements of one, matching patient. At least 50 movements were recorded, separated by at least 10 seconds.

### Recordings

EEG was recorded using 19 Ag/AgCl scalp electrodes positioned according to the international 10/20 system: FP1, FP2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, Pz, P3, P4, T5, T6, Oz, A2. Recordings were made in reference to the right ear lobe and the ground was placed in front of Fz. Electromyographic (EMG) activity of muscles involved in the stereotypic and voluntary movements was recorded using 7 pairs of tin surface electrodes. Bilateral activity of the following muscles was registered: abductor pollicis brevis (APB), abductor digiti minimi (ADM), extensor carpi radialis (ECR), flexor carpi ulnaris (FCU), biceps, triceps and deltoid. APB and ADM were recorded in a belly-tendon montage. The other EMGs were recorded in a bipolar montage, with at least 3 cm separating the 2 electrodes. EEG and EMG impedances were kept below 5 kOhm. EEG and EMGs were recorded at a 1 kHz sampling rate. EEG was acquired with a DC-100 Hz bandpass filter. EMGs were recorded using a 5–200 Hz bandpass filter.

For patients' recordings, the EEG/EMG signals were synchronized with a video monitoring using a portable EEG/video system (Neurofax  $\mu$  EEG-9100, © Nihon Kohden). With controls, EEG and EMGs were recorded with the SynAmps / Scan 4.3 system (Compumedics NeuroScan, Charlotte, USA).

### Signal analysis

MRCPs were evaluated, in relation to voluntary (for patients and controls) and involuntary movements (patients only). Prior to the analyses, EEG data were re-referenced using a linked-earlobe montage. Off-line EEG/EMG data visual inspection was performed to obtain artifact-free EEG epochs surrounding each movement. For patients, stereotypic movements were identified in accordance with the movements observed on the video during the stereotypies recording. EEG data were analyzed with respect to EMG onset (time 0), defined

as the first EMG peak observed on the EMG signals. Thus for each participant, it was determined which muscle was more appropriate for the analyses according to the movement pattern. The chosen muscle was then used to trigger the EEG signal. EEG was segmented in epochs starting 3 s before movement onset and ending 200 ms after. Averaging in reference to movement onset was performed to obtain MRCPs. Latency of early MRCP onset (measured as the time when the linear regression line of the early negative potential crossed the zero line (18)), maximal amplitude and location of late MRCP were analyzed and compared between groups and conditions. In order to rule out whether our results might be artefactual, data were systematically re-analyzed by averaging all the epochs and by comparing the results with two separate averages involving the odd and even numbers of epochs.

### Statistical analyses

Since data were not Gaussian, non-parametric analyses were performed. MRCPs amplitude and latencies were compared between groups using Mann-Whitney tests. Correlations between symptoms severity (SSS Scores) and MRCPs amplitude or latency were evaluated using Spearman tests. Data were considered significant if  $p < 0.05$ . Statistical analyses were performed using SPSS 13.0 (SPSS inc., Chicago, USA).

## Results

All participants tolerated the entire protocol without difficulty, and 36 to 68 stereotypic events were observed and analyzed for each patient.

### Patients

The stereotypic events consisted, for each patient, in the main stereotypic behavior reported in Table 1. MRCPs were observed before self-paced, voluntary movements in 8 out of 10 patients (Table 2, Figure 1A). No significant correlations were observed between the “instructed” condition MRCPs and stereotypy symptom severity ( $p > 0.05$ ). No MRCP was identified prior to the onset of the motor stereotypy (Figure 2). In four patients, a small positivity was observed over parietal electrodes just before movement onset. In the voluntary movement condition, the median early MRCP onset was observed 1588 ms before movement (95% confidence interval of mean  $[-1985 \pm -971 \text{ ms}]$ ), and the late MRCP amplitude reached  $-8 \mu\text{V}$  (95% confidence interval of mean  $[-12 \pm -5 \mu\text{V}]$ ).

### Controls

An MRCP was observed prior to movement onset in 6 out of the 7 subjects (Table 2, Figure 1B). The median early MRCP onset was identified 1905 ms before movement (95% confidence interval of mean  $[-2466 \pm -1105 \text{ ms}]$ ), and the median late MRCP reached  $-8 \mu\text{V}$  of amplitude (95% confidence interval of mean  $[-11 \pm -6 \mu\text{V}]$ ).

Statistical analyses showed no significant differences between groups in terms of latency or amplitude of the pre movement potentials ( $p=0.852$  and  $p=0.282$ , respectively). In terms of localization, in patients and controls, early and late MRCP were observed over fronto-centro-parietal regions. In 2 patients and 2 controls, maximal amplitude was found over the

lateral central electrodes C3 or C4. In the other participants, maximal pre movement potentials were observed medially, over Cz, Pz, and Fz in 2 patients (although the scalp map would suggest a maximal amplitude over FCz, which was not recorded).

## Discussion

Similar to controls, an MRCP was found over the premotor and sensorimotor areas when children with primary motor stereotypies performed voluntary, self-paced upper limb movements. In most, the MRCP was maximal over medial fronto-central areas or central areas contralateral to the movement's side, whereas some were maximal over frontal areas. The latter is in accordance with prior data demonstrating a more frontal cortical activation during voluntary movements in children, as compared to adults (19).

The cortical sources of early MRCP have been localized to the bilateral supplementary motor area (SMA), lateral premotor cortices, and primary motor cortices (M1) (20,21). It is generally accepted that both early and late MRCP reflect the activation of the premotor/motor areas responsible for movement planning and execution. In accordance with a previous study, MRCP's maximal amplitude seemed to be lower than the one usually reported in adults (22), suggesting that children present a lower degree of activation of cortical areas involved in voluntary motor planning. Although motor and premotor areas were less activated than that usually seen in adults, results demonstrated that the cortical activity corresponding to voluntary motor control is normal in children presenting with primary motor stereotypies.

No MRCP was observed before motor stereotypies. These results imply that motor preparation of primary motor stereotypy does not require the preliminary involvement of premotor areas usually observed in voluntary motor control. Similar results have been reported in patients with motor tics. Obeso et al. (23) reported no MRCP before motor tics in 5 out of 6 patients, whereas Karp et al. (24) reported only the presence of a late MRCP in 2 out of 5 patients. These results suggested that the initiation of motor tics, similarly to motor stereotypies, is physiologically distinct from that of voluntary movements. In both, the release of movements might be more dependent on cortical areas other than area 6 or on subcortical regions. The absence of MRCP, however, cannot be clearly interpreted as a sign of involuntariness. The presence of MRCP with involuntary movements in conversion disorders is a strong argument that the MRCP does not indicate voluntariness (25). Moreover, neither the early or late MRCPs correlate with the onset of movement intention (18). Reduction in MRCP amplitude might be correlated, however, with an automatic movement done without paying much attention to it. The positivity observed over parietal electrodes in four patients, just before stereotypies onset, was not related to the frontal negativity. Although there is no clear interpretation of this positive shift, it is not felt to be related to motor planning recognizing that when parietal areas are involved in movement preparation, a negative shift is usually observed (26).

Basal ganglia, in particular the striatal dopaminergic system, may have a prominent role in causing motor stereotypies (27–32). Injections of dopamine D1 receptor agonists in the striatum of rodents induced motor stereotypies (28,30,33–35), and blockade of dopaminergic

transmission stopped the movements (33,36–38). Other dopamine agonists, such as amphetamine (39), ketamine (40,41), or L-DOPA (42) have been shown to induce motor stereotypies. D1 agonists have also induced motor stereotypies when injected in the bilateral lateral ventricles (27), the nucleus accumbens (27) and the ventromedial nucleus of the thalamus (29) in rodents. Further, spontaneous stereotypies have been associated with elevated glutamate and aspartate striatal levels in deer mice, a mouse model of spontaneous and persistent motor stereotypies (38). In other models, motor stereotypies have been associated with striatal and thalamic transmission of acetylcholine and serotonin (43–45). Thus, it seems likely that alterations in some of the excitatory and inhibitory pathways of basal ganglia might be responsible for motor stereotypies. This hypothesis has been reinforced by volumetric reductions in bilateral caudate nuclei and frontal white matter in children with primary motor stereotypies (32). Lesions of the right caudate nucleus were also reported in a patient presenting with an adult onset of motor tics with the presence of stereotypies (46). Kates and colleagues (32) concluded that children with primary motor stereotypies might suffer from a dysfunction of the cortico-striato-thalamo-cortical pathways. In line with this hypothesis, the absence of MRCP before stereotypies suggests subcortical control of such involuntary movements. It is also noteworthy that, since abnormal MRCPs have been reported in patients suffering from cerebellar lesions (especially involving the dentate nucleus) (47–49), and since secondary motor stereotypies have been observed in children with brainstem-cerebellar abnormalities (2), it could also be hypothesized that the lack of MRCP in stereotypies could reflect abnormal activity in the cortico-cerebello-thalamo-cortical motor loop, as the cerebellum plays a role in the BP (50).

In summary, data suggest that primary motor stereotypies could be due to a motor command release that is independent from the cortico-striato-thalamo-cortical motor loops usually involved in voluntary motor control. This motor command would most probably originate from the basal ganglia and activate a different pattern of sensorimotor loops. A limitation of our study resides in the small number of controls. Further studies, involving larger populations are required to determine the site of the motor control abnormality within cortico-striatal-thalamo-cortical pathways or within cortico-cerebello-thalamo-cortical loops and to identify whether similar findings would be found in children with secondary stereotypies.

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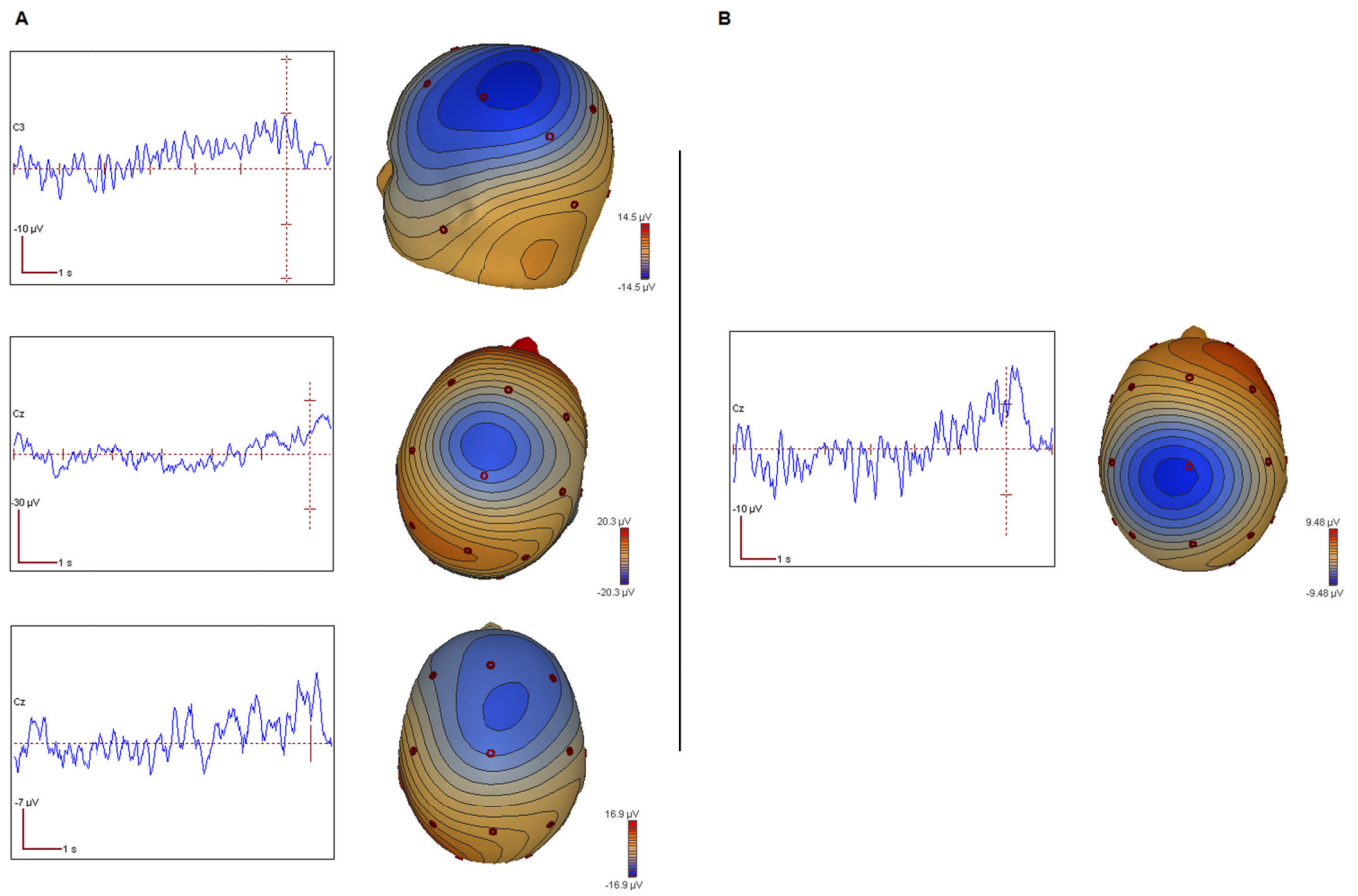
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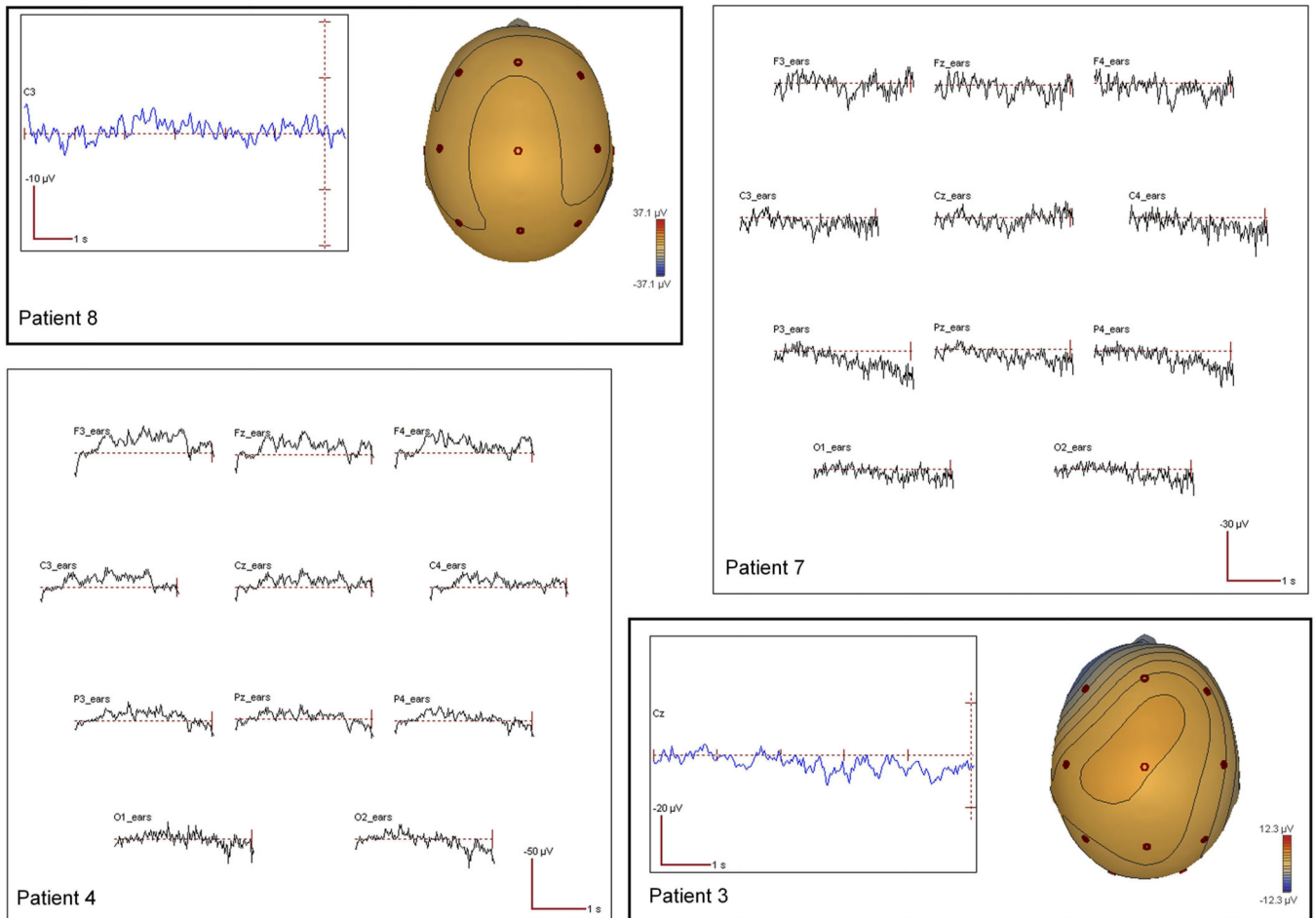


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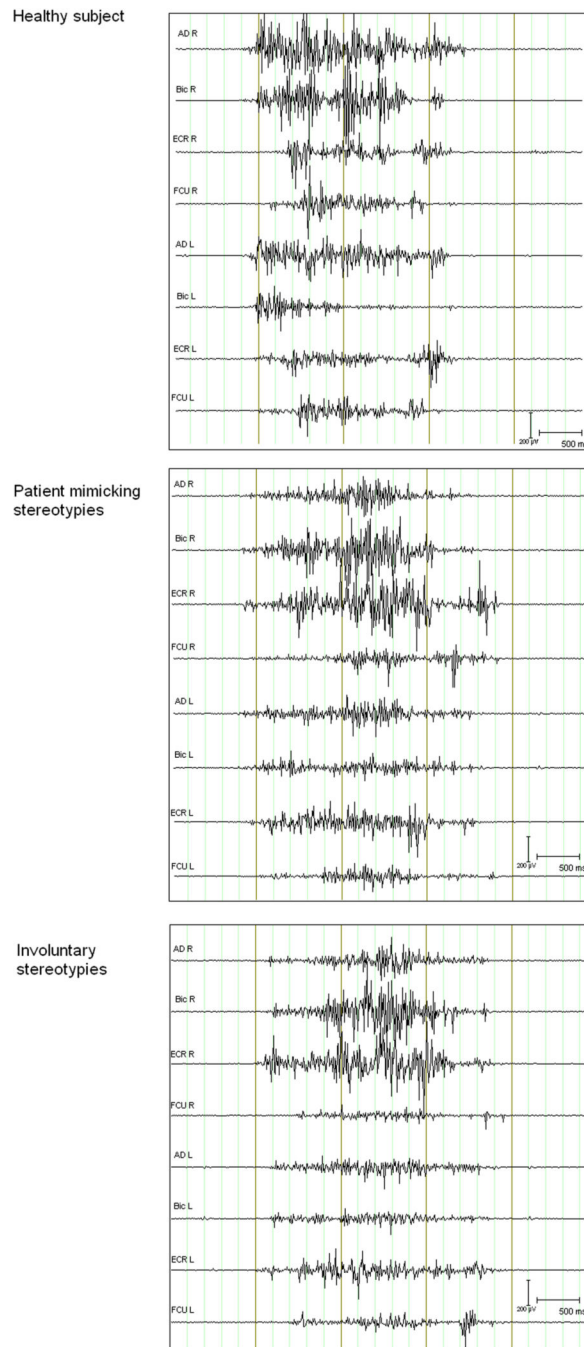
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**Figure 1.** Examples of MRCPs preceding voluntary arms movements in 3 patients (A) and one control (B). Temporal evolution of early and late MRCP over the electrode showing maximal MRCP is plotted. Scalp localization of the maximal MRCP is represented in blue.



**Figure 2.** Temporal evolution and scalp representations of averaged EEG preceding stereotypic events in four patients. There were no MRCPs preceding motor stereotypies in any of the subjects.



**Figure 3.** Examples of EMG patterns during mimicking of stereotypies by a healthy control, mimicking of stereotypies by a patients and actual involuntary stereotypies from the same patient. Four bilateral couples of muscles (R: right; L: left) are displayed for each example: anterior deltoid (AD), Biceps brachialis (Bic), extensor carpi radialis (ECR), and flexor carpi ulnaris (FCU).

Table 1

## Patients' characteristics

Patient	Age	Gender	Age of onset	SSS score	Predominant stereotypy	Family history of stereotypies
1	14	M	2 years	20	bilateral finger wiggling in front of face	Neg
2	12	F	3 – 4 years	9	flapping movements of hands and arms, opening and closing hands	Neg
3	10	M	2 years	23	clenched hands to face with grimacing	Neg
4	8	F	few months of age	30	bilateral flapping and twisting of hands	Neg
5	11	M	1 year	40	finger wiggling with head extension and mouth opening	Neg
6	10	F	6 – 9 months	19	bilateral arm extension with finger movements	Neg
7	10	F	6 months	7	finger flapping and clenching of hands	Neg
8	7	F	6 months	11	bilateral hand and arm flapping	Pos (cousin)
9	8	M	18 months	31	body tensing with bilateral arm extension and finger wiggling	Pos (cousin)
10	8	M	2 years	5	bilateral hand and arm twisting with finger wiggling	Neg

Age (in years), gender (M = male, F = female), age of stereotypic behavior onset, Stereotypy Severity Scale score (SSS score), predominant stereotypic movement at the time of the study, and family history of stereotypies (Pos=positive, Neg=negative).

**Table 2**

BPs details in patients and controls evoked by the "instructed" condition.

Patient	Electrode	Late BP Amplitude	Early BP onset	Control	Electrode	Late BP Amplitude	Early BP onset
1	C3	-3	-664	1	Cz	-13	-2118
2	/	/	/	2	Pz	-8	-2554
3	Cz	-7	-1094	3	Pz	-8	-1500
4	C3	-6	-2100	4	C4	-7	-2150
5	C3	-9	-2000	5	Cz	-8	-1693
6	Fz	-7	-792	6	C3	-8	-700
7	/	/	/	7	/	/	/
8	Cz	-11	-1176				
9	Fz	-9	-2000				
10	Cz	-16	-2000				

The electrode displaying the maximal late BP's component is shown, as well as the late BP's maximal amplitude (in  $\mu$ V) and latency of early BP onset (in ms).