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# Event-related Desynchronization during Action Observation is an early predictor of recovery in subcortical stroke: An EEG Study.

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Ferrara, June 28th 2023

Dear Editor,

On behalf of all authors, I am excited to submit our manuscript "*Event-related Desynchronization during Action Observation is an early predictor of recovery in subcortical stroke: An EEG Study*.", for review and ultimately publication in Annals of Physical and Rehabilitation Medicine.

Cerebral stroke is a leading cause of death and long-term disability worldwide. Tailoring of therapy approaches has great potential to improve outcomes, but requires a better understanding of specific path of recovery. The most appropriate therapy can be established leveraging meaningful biomarkers, which are essential to predict the recovery as early as possible. EEG biomarkers related to action observation (AO) may be useful, as they could document the residual functional contributions of mirror neurons to motor recovery after stroke. While the role of cortical areas in the Mirror Neuron System has been well characterised, the contribution of subcortical regions, a very frequent stroke lesion site, is less clear. Thus, we analysed the relationship between EEG measures (i.e., Event-Related Desynchronization) recorded in the motor area during AO 4 weeks after a subcortical stroke, and arm motor recovery at 12 weeks. Sixteen patients with first subcortical brain stroke underwent 14 minutes of EEG recording during AO (i.e. reaching and grasping). We observed that a poor recovery at 12 weeks, measured by the Fugl-Meyer Motor Assessment Scale, was linked to presence of vicariate functions of the affected hemisphere in the unaffected one, especially in the frontal area. Conversely, better recovery at 12 weeks was linked to the affected hemisphere showing reorganization of its activities early after the stroke (4 weeks). We confirm the role of ERD during AO as an early predictor of motor recovery in stroke patients.

The preliminary results of our study were presented at the 8th Congress of the European Academy of Neurology (EAN) in Vienna in 2022. Please see the abstract book at the following link (abstract number EPO-469):
https://www.ean.org/fileadmin/user_upload/ean/congress-2022/EAN2022AbstractBook.pdf

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We initially presented our work as an Original Article and now, on the advice of the Editor in Chief, Professor Dominic Pérennou, we converted it into a Letter to the Editor form, enhancing our most important findings and removing the less salient parts of our study.
No part of this work has been published. The authors state that no conflict of interest exists. All authors have approved this submission.
We look forward to hearing from you at your earliest convenience.
Sincerely,

Dr. Sofia Straudi, MD, PhD

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- EEG biomarkers of action observation could provide data on stroke motor recovery
- Event-Related Desynchronization is an early predictor of stroke motor recovery
- When the healthy hemisphere vicariates the affected one, the prognosis is poor

# Event-related Desynchronization during Action Observation is an early predictor of recovery in subcortical stroke: An EEG Study.

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**Abbreviations:** EEG: Electroencephalography; ERD: Event-related Desynchronization; ERS: Event-related Synchronization; MNS: mirror neuron system; AOT: Action-Observation Therapy; AO: Action Observation; FMA: Fugl-Meyer Motor Assessment Scale; FMA-UE: Fugl-Meyer Motor Assessment Scale-Upper Extremity; AH: affected hemispheres; UH: unaffected hemispheres; F: Frontal; C: Central; P: Parietal.

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## *1. Introduction*

Cerebral stroke is the second leading cause of death and long-term disability worldwide[1]. After a stroke, the central nervous system generally tries to restore impaired functions by reorganizing cortical networks in both the damaged and the healthy hemispheres, to recover and vicariate the activities originally performed by the harmed areas[2]. This process is favoured by increased cortical plasticity following a stroke, which is found in a narrow time interval of only a few weeks[3]. In this critical timeframe, biomarkers that can predict prognosis and assist the choice of rehabilitation treatments are crucial[4]. Considering the complexity of the reorganization of motor networks after a stroke, it is important to integrate clinical information with other data to characterize prognosis and tailor treatment options[2]. Electroencephalography (EEG) has proven to be a non-invasive, low-cost and reliable tool for obtaining useful information from a rehabilitation perspective[2,5]. Great attention is currently focused on Event-Related Potentials, i.e. the time-locked electrophysiological response related to an internal or external event. An ERP can be linked to a change in the EEG (not time-locked) that shows increased or reduced coordination of activity, labeled Event-related Desynchronization (ERD) or Event-related Synchronization (ERS), respectively[6]. Of note, research on the mirror neuron system (MNS) has shown that the neurons that are activated during voluntary movements are also recruited during the

observation of the same motor acts, with important implications from a neurophysiological and rehabilitation perspective[7]. Specifically, the so-called Action-Observation Therapy (AOT) leverages the MNS to promote motor recovery in patients who are unable to perform movements adequately[8]. However, while the role of cortical areas in MNS has been well characterised, the function of subcortical regions is less well understood, especially in the context of stroke[7,9]. Therefore, it seems very useful to evaluate the characteristics of these neurophysiological biomarkers during Action Observation (AO) in subcortical stroke patients. Here, we studied electrophysiological activity recorded in the motor area during AO at 4 weeks after stroke as a predictor of arm recovery at 12 weeks.

## *2. Methods*

This is a longitudinal observational clinical study conducted at Ferrara University Hospital (NCT04637984). Procedures conformed to the Declaration of Helsinki and were approved by the local ethics committee. Inclusion criteria: right-handedness, aged 18 years or older; diagnosis of first cerebral stroke (ischemic or haemorrhagic) in a subcortical site verified by brain imaging with onset within four weeks; motor deficit of the upper limb. Exclusion criteria: cerebellar or bilateral cerebral stroke; medical or neurological condition interfering with protocol safe completion or with ability to give informed consent; severe cardiopulmonary, renal, or hepatic disease; upper limb somato-sensory disorders; spatial neglect; pregnancy. The 20-min AO session, conducted four weeks after stroke (T1), included observing a transitive gesture on video (a hand – contralateral to the affected hemisphere – shown reaching for and grasping a can) with simultaneous EEG recording, while seated in a dimly lit room at 90 cm distance from a 20" CRT monitor. Videos were presented 20 times, interspersed with a fixation interval. EEGs were acquired with the BrainAmp System (Brain Vision Recorder and Brain Products, Munich, Germany), with 32-channels, sampled at 1000 Hz, referenced at electrode FCz, with a 50-Hz notch filter, and impedances <20 KΩ. Stimulus and EEGs were synchronized via E-Prime 2.0. Clinical evaluations at 12 weeks (T2) from stroke included the Fugl-Meyer Motor Assessment Scale Upper Extremity FMA (FMA-UE).

We labelled participants with FMA≤ 25 as severe and FMA> 25 patients as moderate[10]. Offline EEG analysis was conducted in Matlab (R2019a, The Mathworks) with FieldTrip. Data were segmented into 20 epochs, each 4s long, including 1s before and 3s after stimulus onset. Trials with motion-driven artefacts or amplitude >100 μV were excluded, only subjects with at least 80% of clean trials were included. Independent Component Analysis further removed components endowing artefacts. Time-frequency analysis of each epoch was performed with Morlet wavelets (5-32 Hz). ERS/D was computed as *100·(E-R)/R*, with *E* the power in the 0-2.5s time after video onset, and *R* the power in the (-0.5,-0.1)s range before onset (baseline). ERS/D in alpha band (8-13 Hz) were computed at electrodes (F3, F4) for premotor areas, (C3, C4) for primary motor cortex, and (P3, P4) for sensorimotor integration. Statistical analyses used Jamovi, to compare alpha ERD/S in the severe and moderate groups. Within-group and between-group differences were tested using paired and unpaired t-tests, respectively, while Spearman's correlation was used to identify any significant correlation. Statistical significance was set at $p<0.05$.

### *3. Results*

We screened and enrolled sixteen patients. Participants' characteristics at baseline are reported in the table below for all subjects and, separately, for patients with severe motor impairment (FMA ≤ 25), and mild/moderate motor impairment (FMA > 25) (Tab. 1).

INSERT TABLE 1 HERE

We compared EEG data recorded at T1 with clinical scales collected at T2, in particular ERD and FMA, respectively. A greater alpha desynchronization in the affected parietal ($R^2$= 0.47; P= 0.03) and central electrodes ($R^2$= 0.53; p= 0.017) at four weeks correlated negatively with FMA at 12 weeks in the moderate patient group. This implies that the more the desynchronization was evident at four weeks, the more marked the motor recovery was at 12 weeks. In contrast, there was a positive correlation between alpha desynchronization in the unaffected frontal electrodes and FMA in patients with severe arm paresis ($R^2$= 0.93; p=0.03), revealing that greater alpha desynchronization was a predictor of poor motor

outcome at 12 weeks. The ERD/ERS expressed as a percentage have been graphically rendered in the following images, grouped based on severity (mild-moderate vs severe). All patients with a left lesion were mirrored, "shifting" the lesion to construct a meaningful representation. Hence, although the following images show a lesion on the right side, they are illustrative of the entire sample. Alpha ERD/ERS was calculated for both moderate and severe patients, and negative values (range 0-30%) show a desynchronization, while positive values (range 0-10%) indicate a synchronization (Fig. 1).

Figure 1: Topoplot of ERD in alpha dynamics according to the degree of impairment (this image must be printed in colour).

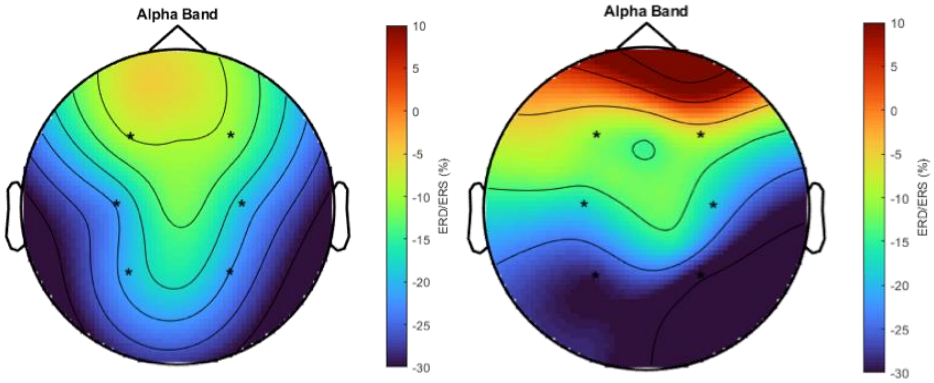


Figure 1: Topoplot of Event-Related Desynchronization (ERD) in alpha dynamics for mild-moderate patients (on the left) and severe patients (on the right). Right side = affected hemisphere.

Power spectrograms during AO show a significant alpha desynchronization in the affected central electrodes in the moderate patients' group, which starts approximately 0.3 seconds after the onset of the AO and lasts for the entire time window (Fig. 2, left side). A similar pattern was highlighted in the affected parietal electrodes but with less power (Fig. 2, right side). In the severe patients' group, there is a focal frontal desynchronization in unaffected hemispheres (UH) in the time range between +1 - +1.5 seconds, which starts in the theta band, peaks in the alpha band (skimming the low beta band), and then decreases until +2 seconds from the AO onset (Fig. 2, on the bottom).

Figure 2: Power spectrogram during AO (this image must be printed in colour).

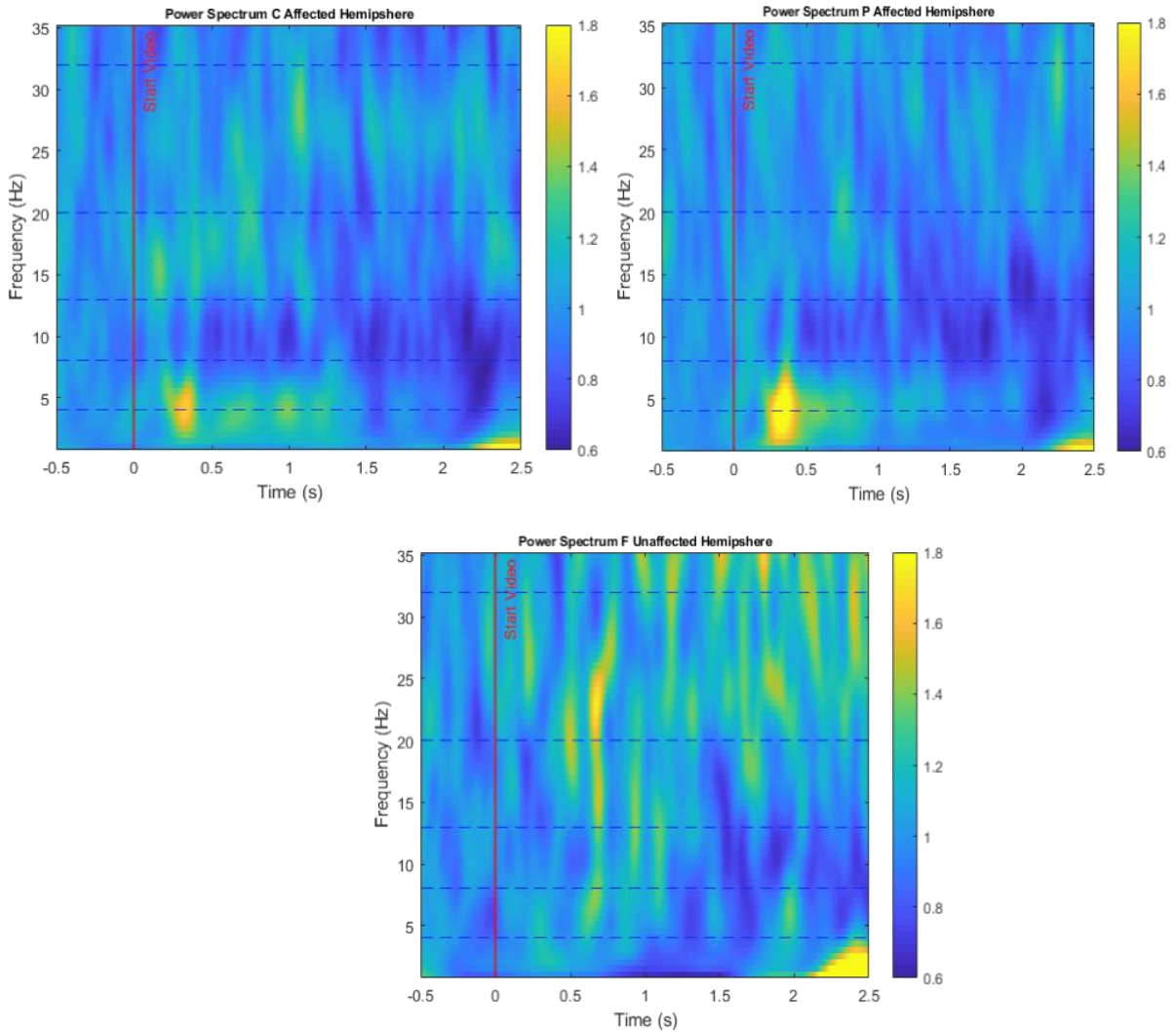


Figure 2: power spectrogram during Action Observation (AO) in the affected Central (on the top, left side) and Parietal (on the top, right side) electrodes in mild/moderate patients and the unaffected Frontal electrodes in severe patients (on the bottom).

### *4. Discussion*

As recently highlighted, EEG can provide information on cortical reorganization processes related to post-stroke plasticity, useful to guide clinicians in choosing the best rehabilitation strategies[11]. A recent study has shown, using a method similar to the one described in this study, that AO has greater effects than simple Motor Imagery in stroke patients, with the former increasing ERD power twice as much as the latter[12]. Our results confirm those of Tani's group, showing that ERD is particularly informative even in patients with severe

deficits. Interestingly, a recent work showed that AO involves the efferent motor system even when the hand used to respond is unable to perform the observed action due to a cortical lesion, further supporting the AOT in stroke motor rehabilitation[13]. Stroke lesion site can also influence motor recovery by different mechanisms[14]. Indeed, a cortical stroke can directly damage the neurons responsible for EEG signals, while a subcortical lesion alters the cortico-subcortical loops, with an expected different effect on neurophysiological measures[15]. Notably, as assessed by FMA, a poor prognosis was documented when the UH had to vicariate the functions of the affected hemispheres (AH) early after the stroke, especially in the frontal area. In contrast, the prognosis was better when the AH could reorganize its activities from the acute stages. These results are consistent with other evidence, which highlight that the lateralization of activity towards the AH and the decrease in activity in the UH are associated with good functional recovery[16]. Indeed, activation of the hemisphere ipsilateral to the movement could indicate the need for more neural resources to perform the action, similar to what happens in healthy subjects during more complex movements[17]. The frontal lobe is the one most involved in tasks requiring high attentional load and cognitive resources[18], and this could be consistent with its involvement in more severe patients. Studies conducted over extended periods have consistently shown that, as effort in performing paretic hand movements decreases, there is a drop in the UH activity[6]. In agreement with our results, Boni et al. showed the absence of activation of the central AH electrodes in patients with more pronounced motor deficits, suggesting a more significant impairment of the MNS in severe patients and, consequently, a lower ability to recruit cortical resources related to a specific action during AO, with important therapeutic implications[19]. Finally, our interpretation is coherent with the model investigated by the seminal study by Di Pino et al., in which it is hypothesized, due to the asymmetry of function between the hemispheres after stroke, that UH exerts an inhibitory effect on AH, thus hindering the actual recovery of impaired function[20]. Our data could therefore facilitate the development of rehabilitation protocols, including non-invasive brain stimulation techniques, that consider this hemispheric asymmetry and its functional implications.

This study has some limitations: the topoplots, which are very intuitive graphical representations of desynchronization on a scalp model using a colour scale, were probably partially affected by the activation of cortical areas linked to vision, which possibly underlies the significant activation observed in the occipito-parietal areas. Furthermore, a t-test comparison of the averages and ERD peaks graphs by individual recording electrodes led to statistical significance only for specific electrodes and in certain frequency bands. In addition, the sample size is limited, which makes it difficult to draw generalizable conclusions. Finally, it would also have been interesting to investigate a more extended time interval after stroke to assess the chronic evolution of EEG measures and their correlation with clinical data.

## *5. Conclusions*

We confirm the role of ERD during AO as an early predictor of motor recovery in stroke patients. The potential role of EEG for assessing changes in the motor network after stroke, even in patients who cannot perform movements through the activation of the MNS during both execution and observation of actions, is very promising in the rehabilitation field. By integrating these neurophysiological measures with clinical data and those provided by other sources (e.g. kinematics), it will be possible to characterize the individual patient at an early stage, thus achieving the prognostic implications and the best treatment choices.

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***Author contributions:*** Sofia Straudi: Conceptualization; Andrea Baroni, Giulia Fregna: Data curation; Martina Galluccio, Paola Malerba: Formal analysis; Sofia Straudi, Fabio Manfredini: Funding acquisition; Annibale Antonioni, Andrea Baroni, Giulia Fregna: Investigation; Sofia Straudi, Thierry Pozzo, Luciano Fadiga: Methodology; Sofia Straudi: Project administration; Sofia Straudi, Paola Malerba, Thierry Pozzo, Luciano Fadiga, Giacomo Koch: Supervision; Annibale Antonioni: Roles/Writing - original draft; Annibale Antonioni, Sofia Straudi: Writing - review & editing.

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***Declarations of interest:*** none.

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Table 1: Baseline characteristics according to the degree of arm paresis severity, as assessed by FMA.

| | Severe (n=6) | Mild/Moderate (n=10) | Total (n = 16) |
|---|---|---|---|
| **Age, years** | 62 (49- 78) | 63.5 (57.75-74) | 63.5 (56.25 – 74) |
| **Gender, no, male (%)** | 3 (50) | 4 (40) | 4(14.3) |
| **Time since stroke, days** | 6.5 (3-12.75) | 7 (3.75-10) | 5 (4-10) |
| **Affected hemisphere, no. left (%)** | 1(16.66) | 5 (50) | 6 (21.4) |
| **MEPs, n(%)** | 3 (50)* | 2(20)* | 4 (12.28)* |
| **Ischemic stroke (%)** | 4 (66.6) | 8 (80) | 10 (35.7) |
| **NIHSS** | 12.5 (6.25-17.75) | 7 (5.75-12) | 8.5 (6-12.5) |
| **FMA 4th week** | 10.2± 4.5 | 61.6±3.8 | 42.3± 26.01 |

Table 1: Baseline characteristics as median and interquartile range, mean and standard deviation or frequency and percentage. *There are some missing data. FMA = Fugl-Meyer Motor Assessment Scale; NIHSS = National Institutes of health Stroke Scale; MEPs = Motor Evoked Potentials.