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ASSESSMENT OF SEVERAL EEG ACTIVE PARADIGMS IN LOCKED-IN SYNDROME

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ABSTRACT: At first glance, Brain-computer interfaces (BCIs) appear to offer promising solutions for people who have global paralysis and are unable to operate conventional communication devices. However BCI efficacy remains low. To better assess the possible clinical reasons for this lack of efficacy, we conducted a study comparing the performance of patients in three paradigms: motor attempt, sustained auditory attention and spatial selective auditory attention. We included 14 persons with locked-in syndrome (LIS), one person in complete LIS and 27 healthy subjects. Preliminary results show that for the patient in complete LIS and a significant proportion of LIS patients, we could not detect their voluntary modulation of brain signals. Surprisingly, this absence of attentional biomarkers seem more prevalent in brainstem injury than in ALS. We discuss the possible impact of global paralysis on brain signals that are used to control BCIs.

INTRODUCTION

Brain-computer interfaces (BCIs) could help restoring environmental control and communication for people with severe motor disability. Although their aetiologies differ, these typical BCI end-users share a clinical state of total paralysis resulting from some acquired damage to the cortico-spinal pathway or the peripheral nervous system. The 'classical' locked-in syndrome (LIS) is caused by an injury to the ventral pons, most often due to a stroke [1], [2]. The patient is totally paralysed except for vertical eye movements and blinks, which enable them to maintain communication. Others are behaviourally non-responsive because of damage to the third and seventh cranial nerves needed for these movements [2], [3]. This condition can also be encountered in the later stages of amyotrophic lateral sclerosis (ALS), a neurodegenerative disease of the motor neurons in which oculomotor muscles are usually preserved [4], except at a very advanced late stage. Then these patients are often considered to be in the complete locked-in state (CLIS), i.e. conscious, but non-responsive.
Another possible cause of a non-responsive state is severe diffuse brain injury due to stroke or anoxia following a cardiac arrest. After being in a comatose state for up to four weeks these patients sometimes remain in a state with preserved vegetative functions (e.g. autonomous respiration and eye opening) but no sign of awareness. They are said to suffer from disorders of consciousness (DOC). Some of these patients could be conscious, but a combination of impairments (motor, sensory, cognitive) prevents them from understanding and/or following instructions. Active EEG paradigms that were developped to detect consciousness in these patients are close to the one used in BCI (e.g., motor attempt [5], or attentional focus on sounds [6]).

As a matter of fact, BCIs work poorly with both CLIS [7], [8], [9] and DOC patients [10]. Moreover, there is also a subpopulation of patients with severe motor disabilities who cannot control a BCI [11], [12], [13], [14]. This proportion is higher than for healthy subjects. As visual modality is often used in BCI, it was argued that it is problematic for patient with severe motor disability, as they can present oculomotor impairment [15], [16]. Also, when the motor system is altered, it could impact the robustness of sensorimotor rhythms used in motor imagery BCI. But, more surprisingly, even auditory BCIs turn out to be hard to control for these patients [14]. This may be due to the cognitive impairments and altered electrophysiological signals that some of these patients sometimes present [17], [18], but it is still unclear what factors impact the most BCI performance in this clinical context. Thus, the possible clinical reasons for this lack of efficacy need to be better understood.

We propose here to test three different paradigms: motor imagery, auditory selective attention and auditory sustained attention. None of these paradigms require visual input. We will then confront them to clinical data, hoping to find some predictors of the results.

Our project aims to test the robustness of these three BCI protocols with people in locked-in syndrome, as well as with one patient in CLIS.

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MATERIALS AND METHODS

We are evaluating three active EEG paradigms, oculomotor control and limb motor control. We also assessed the functional impact of paralysis with the ALS-FRS revised scale. Ethical authorizations have been obtained (Clinical trial registration N° NCT02567201).

Participants: The subjects in LIS were in need for an augmentative and alternative communication device (i.e. eye-tracking or letter board) due to paralysis. They were expected to have both a score at 0 for the first speech item of the ALS-FRS (on speech), and a score smaller or equal to 1 at the 14th item of the ALS-FRS-EXT scale (Wicks, 2009) (i.e. the patient cannot use fingers to control a communication device). Etiologies encompass Guillain Barré syndrome, ALS or brainstem injury. Their age ranges from 20 years-old to 80 years-old.

The CTRL group was composed of 30 healthy subjects, aged 20 to 80 years-old. We excluded subjects that presented a psychiatric or neurological disease.

Clinical evaluation: For patients, we performed a motor assessment thanks to the ALS-FRS scale revised, some items from the ALS-FRS-EXT study (Wicks, 2009), and the BELIS scale (ref). We also realized a clinical oculomotor assessment. The patients with a preserved communication code underwent neuropsychological assessments adapted to severe motor disability (BELIS scale [17]). We collected the medication at the time of the EEG experiments.

Active EEG paradigms: We used three previously published EEG paradigms that have been independently validated with other participants. All participants realized the paradigms in the same order: first the auditory BCI, then, after a break, the motor attempt one and finally the Active-Passive auditory protocol.

– The **auditory BCI paradigm** is described in [14]. This paradigm includes one stream of “Yes” sounds delivered to the right ear, and one stream of “No” sounds delivered to the left ear. We used a SOA of 400 ms and a variable number of deviants, that were balanced between conditions. The proportion of deviants was one out of 6, and was fixed for each trial. We then varied the length of the trials. Patients were asked to alternatively count left or right ear deviants. In some trials, randomly, patients were asked to report the result of this count in order to check that they understood the instructions and that they are able to perceive and detect the deviant sounds. There were 36 trials in total.

– The **Active-Passive paradigm** was described in [6]. We performed only the most discriminant conditions: one where the subjects are mentally navigating in their houses when hearing sounds (diverted attention), versus the other condition where they focus on the sounds (focused attention). We could thereby increase the number of stimulations per condition in order to improve the signal-to-noise ratio.

– The **motor attempt** paradigm is the one that is used in [5]. There are 48 trials, 24 for the left hand and 24 for the right hand. Each attempt lasts five seconds, and is followed by 5 seconds of rest. Patients have to try to move their hand, whereas healthy subjects have to imagine moving their hand.

Material: We used a Vamp amplifier (16 channels, BrainProducts), with a sampling rate of 1000 Hz. We recorded EEG (13 channels) with reference on the nose, EOG right and left (2 channels), as well as ECG and breathing with a thoracic belt. For EEG, we included Fp1, Fp2, F3, Fz, F4, C3, Cz, C4, TP9, CP5, Pz, CP6, TP10. This aimed to cover both motor and parietal regions. Temporal electrodes were used to visualize the Mismatch negativity in the Active-Passive paradigm.

Extracted variables:
The signal processing and statistical analysis were similar to the ones described in the original publications. All raw EEG signals underwent a bandpass filter between 1 to 30 Hz. We also used the same measures and decision criteria, namely:

- **Active-Passive**: presence of a “Count” effect, and of a “FOC versus DIV” effect. The “Count” effect reflects the presence of electrophysiological responses to oddball sound when the subject is actively counting deviants. The “FOC versus DIV” effect reflects the attentional modulation of evoked potentials when subjects count the deviant versus when they tend ignore them, by performing spatial navigation imagery (see Morlet et al 2022 for more details).
- **Motor attempt**: accuracy of the classification between “movement” and “rest” trials. Each of the 48 trial was divided in 3 epochs of 2 seconds for the “moving” condition, and 3 epochs of 2 seconds for the rest condition. Then a cross validation with a SVM was performed, and compared to a permutation test. If less than 5 % of the random permutations gave better results than the real dataset, then the participant was considered as a “responder”.
- **Auditory BCI**: accuracy of the classification between “attended” and “unattended” sounds.

Statistical analysis: We employed Generalized Linear Models (GLMs). For all analysis, we used R packages including FactoMineR, lme4, afex, emmeans, and sjPlot.

We first compared demographical characteristics of the CTRL and LIS groups. Our variables to be explained were the group and our predictors were the age and educational level.

We then tested the hypotheses of a difference in EEG based classification accuracy between the two groups.

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Therefore, we performed three GLM, one for each of the three active EEG paradigms.

Our main explicative/fixed variables are:
– GROUPS (LIS vs CTRL)
– Age
We used a GLM (Generalized Linear Model).

Whenever one of the above explanatory variables did show a significant effect onto the dependent measure, we conducted post-hoc analyses using t or z tests on the linear predictor scale, with confidence intervals also computed on the linear-predictor scale. P values were corrected for multiple testing using the FDR method.

RESULTS

The 15 patients and 27 control subjects could realize all the three active EEG protocols.
The results are summarized in Table 1. There weren't any significant differences between the ages of the healthy subjects and the patients (Wilcoxon Rank sum test, p = 0.54).
For the auditory BCI, there is a significant different between performances of patients and healthy subjects (p < 0.001). The brainstem injury has a particularly strong negative impact on the BCI control: only 2 out 7 patients (29%) present an attentional modulation, versus 6 out of 8 patients with ALS (75%) and 27 out of 27 healthy subjects (100%). Moreover, none of the patients with brainstem injury has a P300 detected by the automatic pipeline, despite being able to hear the deviant sounds and to count them. Of notes, only two patients could not detect the auditory deviant sounds, and both had ALS at a very advanced stage, with a respirator. None of these two patients could control the BCI. The patient in CLIS did not show any detectable voluntary modulation of brain signal.
Concerning the Active-Passive paradigm, there is also a significantly less detectable attentional modulation for the clinical population (p=0.01).
On the contrary, the motor attempt paradigm do not reveal any difference of performances between patients and healthy subjects. Only an impact of age is observed (p=0.01).

The clinical data on motor level, neuropsychological abilities and medication are currently being acquired and will be analyzed in the coming months, and confronted to these BCI performances.

Table 1: Populations characteristics and main results at active EEG paradigms

	***ALS,* *N = 8*[1]**	***Brainstem,* *N = 7*[1]**	***CTRL,* *N = 27*[1]**
Condition			
CLIS	1 (13%)	0 (0%)	0 (0%)
CTRL	0 (0%)	0 (0%)	27 (100%)
LIS	7 (88%)	7 (100%)	0 (0%)
Age	58 (54, 61)	49 (28, 59)	52 (40, 68)
EEG protocols results			
Auditory BCI			
Mean accuracy	0.93 (0.69, 0.98)	0.61 (0.58, 0.75)	0.97 (0.96, 1.00)
P300*	5 (63%)	0 (0%)	25 (93%)
Sensibility	6 (75%)	2 (29%)	27 (100%)
Motor attempt			
Mean AUC at group level	0.70 (0.57, 0.81)	0.67 (0.60, 0.77)	0.70 (0.62, 0.79)
Sensibility	6 (75%)	5 (71%)	25 (93%)
Active-Passive			
Count effect	3 (38%)	3 (43%)	19 (70%)
Focus versus Diversion effect	1 (13%)	1 (14%)	18 (67%)
Sensibility	3 (38%)	3 (43%)	22 (81%)

*[1] n (%); Median (IQR); *:*
ALS: Amyotrophic Lateral Sclerosis; CLIS: Complete Locked-in Syndrome; CTRL: Healthy subjects

CONCLUSION

Our preliminary results confirm that a significant proportion of patients cannot control BCI. The impact of clinical condition is more visible for BCI based on evoked protocols, and strikingly strong in case of brainstem injury in the case of selective auditory attention. These results are surprising in several ways. First, all paradigms are supposed to be gaze independent, but the prevalence of non-responders is striking. Second, ALS, as a neurodegenerative disease in continuum with fronto-temporal dementia, is supposed to induce more cognitive impairments than an injury in brainstem cortico-spinal pathways. The absence of detection of selective attentional modulation in case of brainstem injury is thus surprising, and it is the first time to our knowledge that this specificity is uncovered, especially in comparison with another etiology. The principal limitation of these results is that we rely at this stage on automatic analysis pipelines, whereas patients' brain signals can be very different from the one observed in healthy subjects **[19], [20]**, and hence some of them would probably require a personalized signal processing. However, in a previous pilot study, we observed a strong correlation between BCI results and the presence or absence of classical electrophysiological biomarkers as P300 **[14]**. An important perspective to better explain these results is the analysis of the possibility of other clinical predictors of BCI performance, as neuropsychological tests results, medication. The functional level of autonomy could also have an impact. Indeed, the possibility to interact physically with the environment is associated to a range of action

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preparations that arise automatically with some percepts **[21]**, and the question of the preservation of this action preparation in paralysis **[22]** and their impact on BCI biomarkers remains open **[7], [9]**.

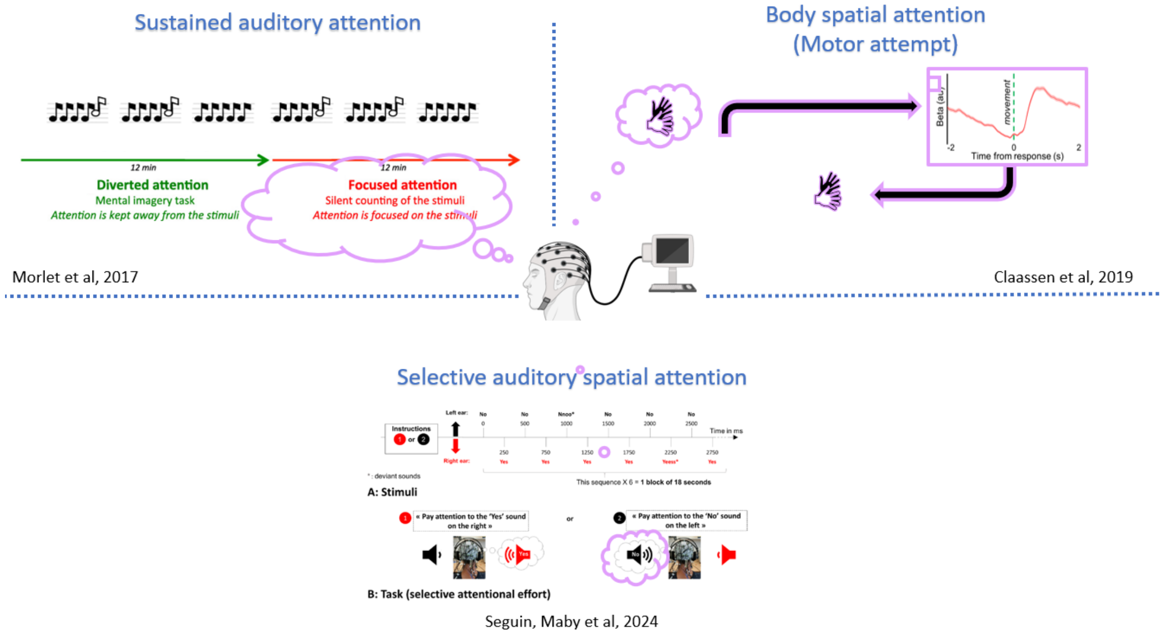

Figure 1: Synopsis of the 3 active EEG paradigms

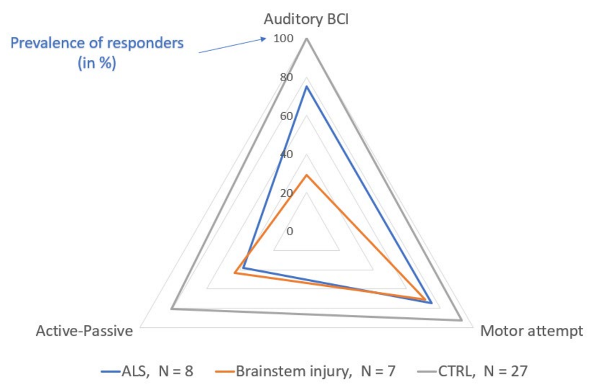

Figure 2: Prevalence of responders for each EEG active paradigm

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