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TOWARDS ANSWERING QUESTIONS IN DISORDERS OF CONSCIOUSNESS AND LOCKED-IN SYDROME WITH A SMR-BCI

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ABSTRACT: Sensorimotor rhythm-based brain-computer interfaces (SMR-BCI) may enable patients with prolonged disorders of consciousness (PDoC) or severe physical impairment to learn to intentionally modulate motor cortical neural oscillations. SMR-BCI could mitigate the need for movement-dependent behavioural responses, hence providing diagnostic information and/or communication strategies. Here, an SMR-BCI was evaluated in a three-staged protocol for PDoC. Stage I assessed awareness and capacity to modulate brain activity intentionally. Stage II facilitated SMR-BCI learning via stereo-auditory feedback training. Stage III tested use of SMR-BCI to answer closed categorized yes/no questions. Out of 14 patients with PDoC and locked in syndrome (LIS), eight patients showed capacity to modulate brain activity during stage I and thus participated in stage II. For practical reasons only five of these patients completed stage III. Two able-bodied participants were enrolled for benchmarking. Five of the eight participants performed significantly greater than chance level in 50-100% of runs ($p<0.05$). Average top run performance accuracy correlated with diagnoses category. Participants across the PDoC spectrum showed capacity to engage with SMR-BCI to answer closed questions.

INTRODUCTION

A gold standard assessment tool for Prolonged Disorders of Consciousness (PDoC) is yet to be realized, and communication strategies are difficult to establish. Consciousness requires arousability and awareness. Patients with PDoC have altered states of consciousness whereby, unresponsive wakefulness syndrome (UWS) is defined by clear signs of arousal but absence of awareness; minimally conscious state (MCS) is defined by preserved arousal level and distinguishable yet shifting signs of awareness. An individual with locked-in syndrome (LIS) is both conscious and aware, yet unable to communicate verbally or move. In LIS, usually blinking and vertical eye movements are retained and occasionally used to communicate [1], [2].

Standardization of PDoC clinical evaluation has been established through response scales such as the Coma Recovery Scale-revised (CRS-R) or Wessex Head Injury Matrix (WHIM). The CRS-R Scale is composed of six sub scales testing: audition, vision, motor, oromotor/ verbal, yes-no communication and arousal [3]. The WHIM is a 62-item hierarchical scale of defined behaviours that are considered to be sequentially more advanced [4]. These assessments are intended to decipher discrimination and localization from reflexive behaviours, and degree of patient interaction with environment, to establish the state of consciousness. However, since the introduction of several behavioural scales (including the aforementioned) as recommended by the Royal College of Physicians National Clinical Guidelines (RCP NCG) [5], misdiagnosis rates are still reportedly ~15-40% indicating an enduring unmet need for better assessment protocols [6], [7].

Applying sensorimotor rhythm (SMR)-brain-computer interfaces (BCI) to PDoC may augment clinical evidence supporting diagnoses and/or increase response reliability as a movement-independent communication channel. The primary sensorimotor cortex consists of topographic mapping dedicated to sensory and motor processing of anatomical divisions of the body. The SMR denotes localized frequencies in the μ (8–13 Hz) or β (15–30 Hz) range of electroencephalography (EEG) recorded across the sensorimotor cortices [8]. μ-rhythm decreases/ desynchronization is observed contralateral to left/right hand motor imagery (MI), similar to preparation or execution of movement. Classification of different motor imageries through SMR-BCI could facilitate discriminatory choice-making, independently of motor pathways, yet dependent on purposeful modulation of the motor cortex. Based on the premise that a PDoC patient is able to achieve above chance performance accuracy (AC) in SMR-BCI, it may be inferred that the individual has intact short-term memory in order to recall instructions, an ability to remain attentive for periods, and some degree of awareness. Cruse et al. [9], [10] showed 19% (three out of 16) UWS and 22% (five out of 23) MCS patients were able to perform command following via imagining squeezing their right hand or moving their toes in a single session. Coyle et al. showed that patients with PDoC can modulate visual and auditory feedback when learning to control an SMR-BCI and pilot data showing response to questions [11]–[13].

Here, an SMR-BCI protocol is evaluated in PDoC to further evidence its potential to assess awareness, and to develop an understanding of the influence multisession, SMR stereo-auditory feedback training in preparation

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for patients to engage with a Q&A system, whereby imagined movements are used to answer closed questions with known answers. The Q&A paradigm is derived from three main influences: a BCI-functional near-infrared spectroscopy study in amyotrophic lateral sclerosis [14]; the Montreal Cognitive Assessment (MOCA) [15]; and annex 1a of the NCG - Operational evaluation of parameters for demonstrating consistent functional communication using autobiographical and situational questions [5].

MATERIALS AND METHODS

The study involved two able-bodied (AB) participants (as a benchmark) and 14 patients: eight with unresponsive wakefulness syndrome (UWS), three with minimally conscious state (MCS), and three with locked-in syndrome (LIS). Two participants with UWS were included in previous studies: [13], [16], [17]. The study was approved by National Rehabilitation Hospital of Ireland and carried out in accordance with the Declaration of Helsinki. Proxy-consent was given by participants' families. Trials were conducted in patient homes, care homes and hospitals in the Rep. of Ireland. EEG was recorded from 14 channels, Fp1, Fp2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, PO7, Oz, PO8 (g.Nautilaus amplifier with active electrodes (g.tec Medical Engineering, Austria)) at a sampling rate of 250Hz. The reference electrode was fixed on the right earlobe and the ground electrode was mounted on the forehead. The data were resampled at 125Hz. Bad channels were identified and removed via spectrum and kurtosis thresholding functions from an EEGLAB toolbox [18]. The number of channels removed varied from 0-4 channels. Data recorded were visually inspected for significant artefacts (e.g., eye-blinks). Trials with strong artefacts in most of the electrodes were removed.
Stage I (Session 1) entailed a block design assessment. Participants were asked to imagine one movement per block, cued with an auditory tone circa every 8s (6 blocks, 15 trials/block). In Stage II, following assessment, real-time stereo-auditory feedback was given as broadband (pink) noise or music samples (see [17] for details), over 5-10 sessions of 1-4 runs (60 trials/run, randomized equal number per class) cued with voice command e.g., "left", "feet" or "right" to matching ear via earphones: cue at 3s, feedback at 4-7s, followed by a “relax” cue. Feedback was modulated by continually varying the sound's azimuthal position between ±90° via imagined movement. Stage III, following training with auditory feedback, involved 4-6 question-answer runs (over 2-5 sessions) of 48 closed yes-no questions. Instructions were repeated at the start of each run and participants were asked to respond yes or no with respective hand/feet imagery. 96 unique closed questions were asked in total and were repeated across runs. Four question categories were evaluated: biographical, situational, basic logic, and numbers and letters. The questions and statements posed were adapted from the MOCA and NCG for PDOC [5], [15]. "Yes" questions had semantically similar "no" questions e.g., "You are 33 years old" vs "You are 47 years old". Recordings of family members reading questions were played back to participants in a timed paradigm. Familiar voices were recorded in order to encourage participants engagement through self-relevant stimuli [19], [20]. A CRS-R and WHIM assessment was conducted each day BCI sessions took place with UWS and MCS participants.

BCI setup: Throughout each stage of the experimental paradigm (i.e. assessment, stereo-auditory feedback and Q&A) the cue occurred at 3s and the window of interest was 3s prior and 5s post cue. During Q&A the cue was the end of each question, which lasted no longer than 7s. Event related offline peak accuracy (AC) was compared to random accuracy (RA) (class labels for the trials in the test sets were permuted randomly) and offline pre-cue (baseline) accuracy, respectively. The AC during the task execution period should be significantly higher than RA and the pre-cue accuracy (baseline period). Online single-trial accuracies were computed too.
Offline analysis was conducted through a filter bank common spatial patterns (FBCSP) framework, detailed in [21], to train a classifier to be applied in the auditory feedback runs. In this FBCSP framework, the EEG data are filtered into 9 frequency bands as shown in Fig. 1, and common spatial pattern (CSP) features are extracted from each band on a 2s sliding window. The features from all the frequency bands are concatenated together, and then between 4 and 12 features are selected using mutual information. The best individual feature mutual information was used as detailed in [21].

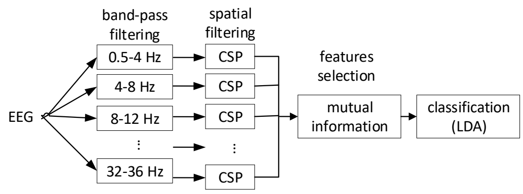

Fig. 1: The FBCSP-based framework.

The parameters to be optimized in the FBCSP setup used are the number of features selected and CSP filters pairs (between 1 to 4 pairs). These parameters are optimized in a nested cross-validation (CV): 6-fold-CV with an inner 5-folds-CV. A 2s sliding window was used (with an 80% overlap) in the task related period of the trial. At each window's position the parameters are optimized in the inner 5 folds cross-validation. An LDA, trained on the inner folds' data (i.e., training set of the outer fold) with the optimized parameters, is used to classify the outer fold test set. For each outer fold, the classifier with highest accuracy from different window positions is then used to classify the fold's test set at each time point of the trial segment. The resulting 6 time-courses of accuracy are averaged to get the time-course of cross-validation accuracy (CVAC). The parameters for the FBCSP differ across the 6 folds so the fold with highest accuracy is used to determine the parameters to be applied online. Using these parameters,

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the final classifier to be deployed in the online feedback setup is trained at a 2s window positioned at the time of CVAC peak.

A permutation test was used to evaluate if the AC during the task execution is significantly higher than RA with a 95% confidence interval. The RA is computed by repeating the 6-fold cross-validation 100 times, and each time the trials' labels are randomized. This leads to 100 time-courses of random CVAC corresponding to 100 permutations. At each time-point of non-random CVAC, the probability that the classification accuracy is achieved by chance is computed using expression (1) as in [22]:

$$p = \frac{|\{D' \in \hat{D} : ac(D') \geq ac(D)\}| + 1}{n+1} \qquad (1)$$

where, $\hat{D}$ is a set of n-randomized versions *D'* of the original data *D*, and *ac(D)* is the accuracy achieved with the non-randomized data *D*. The computed *p* is the probability that given the permuted data, we can achieve accuracy level that is higher or equal to the accuracy achieved with non-permuted data. The Null hypothesis that classification accuracy was achieved by chance is rejected for $p < 0.05$. The *p*-value at each time point is computed enabling assessment of the time-course of CVAC significance.

Online feedback setup: For online processing during feedback runs, at each sample point, a distance is computed from the classifier's learned weights vector, distance referred to as time-varying signed distance (TSD) [23] [24]. The TSD value at a given time point *t* during nth trial is given by expression in (2). The distance's sign indicates the classifier's output label and its magnitude measures the classification confidence. The magnitude of the TSD indicates how the direction and amplitude of the audio feedback (panning to the right or left ear). The performance in online auditory feedback runs is given by the percentage of the trials with TSD's sign correctly matching the trial's task (class).

$$tsd_t^{(n)} = w^T \bar{\omega}_t^{(n)} + a_0 \qquad (2)$$

where w^T and a_0 are the slope and bias of the discriminant hyperplane, respectively, of our trained LDA, $\bar{\omega}_t^{(n)}$ is the features vector at the time point *t* of the n^{th} trial. The tsd_t is debiased by subtracting the mean of *tsd* for the past 30-35s.

RESULTS

Six patients were withdrawn from the study after stage I (assessment stage) as AC was not significantly different to baseline (inclusion criteria for stage II). This withdrawal was not necessarily based on an inability to respond to command: it was difficult to acquire clean data from two participants with large frontal and bifrontal craniectomies and data contained noise as a result of persistent movement artefacts. The remaining patients completed study stage II: three UWS, two MCS, three LIS (3 Female). Time since condition onset varied between 11 months and 16 years (median= 3 years). For practical reasons, Stage III was only completed by one UWS, one MCS and three LIS. Clinical data are provided in Tab. 1. The three-staged paradigm was validated on two AB participants, whom achieved average AC of 77% and 84% across all session types. Every run's peak AC was significantly greater than baseline accuracy and RA (p<0.05), aside from three runs whereby peak AC was not significantly different from baseline accuracy. AB participants showed across session improvement, especially 1AB with AC increasing to 98%, but then decreasing to ~78% for Q&A runs (refer to Fig. 4). 3UWS and 5MCS both achieved top ACs of 69% and 77% during Q&A runs. Every participant was able to achieve above 70% accuracy during at least 1 run (refer to Tab. 1), with the top average run AC correlated with severity of diagnosis i.e., ascending from VS, MCS, LIS through to AB participants (Refer to Fig. 3). Across patients, AC did not progressively increase as a function of number of training sessions, and the top AC run did not necessarily appear in the latter half of total runs completed (Refer to Fig. 4). In five participants 50-100% of run ACs were significantly greater than RA (p<0.05). 53%, 57%, 56% and 100% of runs were significantly different from RA in 3UWS, 5MCS, 6LIS,

Tab. 1: Patient demographics, overall CRS-R and WHIM average scores, and top run performance accuracy with corresponding performance accuracy at 2 seconds during baseline period. UWS-unresponsive wakefulness syndrome, MCS-minimally conscious state, LIS-locked-in syndrome, AB-able-bodied, baseline 2s (A), (F), (Q) represent baseline for Assessment, feedback and Q&A runs respectively. WHIM score reported is the total number of behaviors observed.

ID	Sex	Age	Type of injury	Time since onset (months)	Av CRS-R	Av WHIM	BCI Top run Performance Accuracy (%)					
							Baseline 2s (A)	Assess	Baseline 2s (F)	Feedback	Baseline 2s (Q)	Q&A
1 UWS	M	34	Non-traumatic	192	5	4	55	63	62	72	-	-
2 UWS	M	34	Non-traumatic	103	3	3	61	61	57	76	-	-
3 UWS	M	29	Traumatic	74	5	4	58	69	47	73	54	69
4 MCS	M	49	Non-traumatic	23	11	16	53	66	52	73	-	-
5 MCS	F	56	Traumatic	35	18	17	67	80	57	80	52	77
6 LIS	F	34	Non-traumatic	11	-	-	52	60	50	88	52	81
7 LIS	M	28	Traumatic	25	-	-	71	73	58	75	58	67
8 LIS	F	27	Non-traumatic	36	-	-	70	78	40	68	56	88
1AB	M	20	-	-	-	-	61	69	45	98	42	79
2AB	M	23	-	-	-	-	65	78	52	88	50	79
Average of BCI Top run Performance Accuracy (%):							**61**	**68**	**52**	**79**	**52**	**77**

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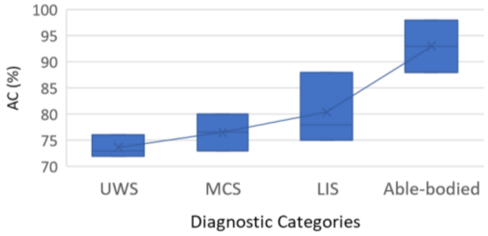

Fig. 3: Whisker-box plot of average top run performance accuracy per participant diagnostic category. X's demarcate the mean, central line is the median, and inclusive median quartile calculation is displayed. Performance is shown to increase across levels of awareness.

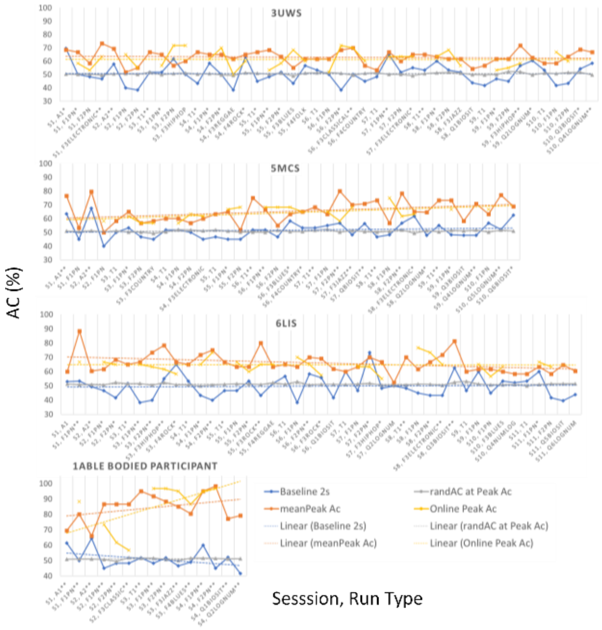

Fig. 4: Run accuracies of best patients and best able-bodied participant across sessions. ss=session, a=assessment run, t = training run, f= feedback run, pn = pink noise, q= q&a run biosit = biographical and situational, lognum = logic and numbers/letters. $p<0.05$ signified by*, $p<0.01$ signified by **(Wilcoxon signed ranks test).

1AB respectively. For Q&A, five participants presented significant peak ACs relative to RA ($p<0.05$) in 50-100% of runs apart from 6,7LIS (refer to Fig. 4). However, Peak AC was significantly different from baseline AC in ≥50% of Q&A runs for four participants 6,8LIS and AB1,2 ($p<0.05$). Across participants, on average, baseline AC was significantly different from RA in 7% of runs.

Fig. 5 illustrates the time courses of the top AC runs across participants from each group/condition: 3UWS, 5MCS, 6LIS and 1AB, with select corresponding event-related desynchronization (ERDS) plots. Across these runs, AC is at chance level at the start of the trial (cue at 3s) and increases (deviating from chance level) as the participant executes the task. Peak AC during feedback runs are maximal and have a similar time course for 1AB and 6LIS. The maps show the power change with respect to the baseline (pre-cue period of 0.2-3s). For the MI tasks, activation is expected in electrodes placed

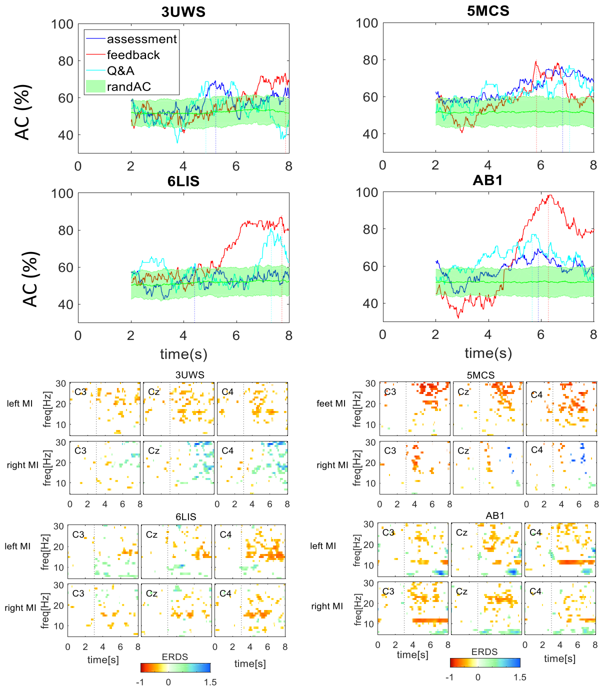

Fig. 5: Example time courses of top performance accuracies (AC) of assessment, feedback and Q&A on best participants per diagnostic group (top 4 panels), green and shaded area indicates mean and variation in accuracy from randomly permutated trials. One example corresponding ERDS map per participant (bottom 4 panels). MI = Motor imagery, left, right refers to hand.

around the motor cortex (C3, Cz, and C4). The ERDS map for 1AB shows clear contralateral activation indicated by mu (8-12Hz) rhythm ERD in the electrodes mounted around the motor cortex (C3 for right MI and C4 for left MI). Patients present task differences for ERD/S plots, however these do not conform entirely to typical observations expected for MI.

Average CRS-R and WHIM for UWS and MCS patients are shown in Tab. 1. As expected, there is strong positive correlation between CRS-R and WHIM scores ($r=0.88$, $p<0.0001$). Average BCI AC during assessment sessions for UWS + MCS was shown to have a positive, yet insignificant, correlation to the average sessional CRS-R ($r=0.4$, $p>0.05$) and WHIM scores ($r=0.4$, $p>0.05$) (2 tailed Spearman's rank correlation). A weak relationship was observed in comparing all average session ACs for UWS+MCS to CRS-R ($r=0.18$, $p>0.05$) and WHIM scores ($r=0.09$, $p>0.05$) (2 tailed Spearman's rank correlation). A Spearman's rank correlation (2-tailed) with average AC for MCS patient, showed a positive correlation to CRS-R scores, $r=0.42$, with a tendency towards significance, $p=0.057$; and an insignificant correlation to WHIM total behavior scores at the participant level $r=0.07$, $p>0.05$.

DISCUSSION

We sought to determine if AC could be used to provide indication of awareness in a 1-2 sessions of assessment (stage I) and whether this corresponded with

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conventional scales (e.g. CRS-R and WHIM). We observed that 3/8 UWS, 2/3 MCS and 3/3 LIS participants were capable of modulating brain activity through SMR strategies during stage I. Both assessment and feedback average ACs in MCS participants, were found to weakly positively correlate with CRS-R scores, and there was no correlation with WHIM scores. UWS participants demonstrated significant above chance AC during multiple runs, which conflicts with their UWS diagnoses. An insignificant correlation between UWS+MCS participants and behavioral scores was found, indicating SMR-BCI may provide supplementary or corroborative diagnostic information in PDoC. These results further demonstrate that EEG-based SMR-BCI provides evidence of awareness not detected by standard behavioral tests in UWS. Some analytical hurdles have been reported concerning block-design [25], [26], however this was necessary for the assessment stage in order for the cue to be demarcated by a tone rather than a word describing the type of MI. This eliminates the likelihood of the response being automatic/unconscious [27] and requires short term memory of the instruction given at the start of the block. In Stage II, during multisession stereo-auditory feedback training runs, most participant ACs were significantly greater than RA, indicating cohort-wide engagement. However, across patients, progressive AC increase as a function of number of completed runs was not observed. ⩾70% accuracies were not consistently reported (AC of 70% being viewed as the lower limit for ability to communicate effectively with a BCI [28]). AC variation across runs and sessions may be influenced by many factors such as patient motivation Proper patient positioning may encourage arousal/ minimize involuntary movements or persistent involuntary hypertonicity that may be induced by frustration due to miscommunication, particularly in LIS. Other studies reported that after post learning during early training, patients AC stabilizes within the first 10–20 training sessions [29]. This is in line with across session performance observations observed here. Individuals were trained over the period of a few weeks, in some cases months due to various interruptions, which may have impacted performance. Our dataset is consistent with other studies in terms of patients obtaining higher inter-run/session and inter-individual variability relative to AB participants [30], [31]. In stage III, ability to encode yes/no responses through motor imageries to closed questions was assessed. The feedback sessions were implemented to encourage SMR learning prior to the more complex Q&A. All diagnostic groups were able to respond at above chance levels in at least one Q&A run demonstrating feasibility of adoption by this patient cohort. High intersession variability is also demonstrated in Q&A runs indicating the importance of multiple sessions, as recommended with behavioural scale assessments by the RCP NCG for PDoC [5]. It is yet to be established whether consistent, sufficient accuracy can be achieved across the patient cohort to enable communication and further sessions with these patients will be conducted. Given availability of more data, AC as a factor of question category could isolate different cognitive deficits in relation to knowledge of self and environment, logic and numbers/letters. It would be interesting to test further iterations of the paradigm e.g. tailoring the response time window. Here, this was set to 5s and might not have been sufficient for some participants. Response time was constrained as AC is hinged on a trade-off between duration/complexity of task/keeping patient fatigue to a minimum and maximizing the amount of trials/answers collected.

PDoC is a challenging patient group to evaluate due to tendencies for; heterogeneity in aetiology and potential neural atrophy and cortical remapping; muscle spasms, seizures, fluctuating arousal, ease of exhaustion; limited memory capacity; medication affecting vigilance e.g. muscle relaxants, anti-epileptics and anxiolytics; and suboptimal EEG recording due to ocular, respiratory and muscular artefacts. EEG quality may have been affected by presence of nutritional life supporting systems or other equipment where private rooms away from other hospital equipment e.g., airbeds was not possible.

In future, it would be ideal to analyse the relationship between AC and type of injury, time since altered consciousness onset, time of day of session. A further investigation might be to add a third “I don’t know” class reflected by another MI to maximize separability for yes/no classes. The existing paradigm assumes the user will polarize their response when the answer is unclear. Having three classes would increase the cognitive load, nonetheless other groups have also experimented with providing options beyond yes/no in PDoC, e.g. a 4-choice auditory oddball EEG-BCI paradigm based on a P300 response [32].

CONCLUSION

This study showed demonstrable feasibility of an initial assessment of SMR engagement; multisession auditory feedback to train SMR-BCI control; and an SMR-BCI Q&A system in PDoC and LIS. Adaptation of the paradigm in order to maximize the number of runs where 70% AC is reached prior to commencing Q&A is crucial to effective adoption by patients with a PDoC. This is the first targeted group of this patient cohort and further training is necessary to progress to open Q&A sessions.

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