Sense of agency for intracortical brain–machine interfaces

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Sense of Agency for intracortical brain machine interfaces

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Abstract

Intracortical brain machine interfaces decode motor commands from neural signals and translate them into actions, enabling movement for paralyzed individuals. The subjective sense of agency associated to actions generated via intracortical brain machine interfaces, the involved neural mechanisms and its clinical relevance are currently unknown. By experimentally manipulating the coherence between decoded motor commands and sensory feedback in a tetraplegic individual using a brain machine interface, we provide evidence that primary motor cortex processes sensory feedback, sensorimotor conflicts and subjective states of actions generated via the brain machine interface. Neural signals processing the sense of agency affected the proficiency of the brain machine interface, underlining the clinical potential of the present approach. These findings show that primary motor cortex encodes information related to action and sensing, but also sensorimotor and subjective agency signals, which in turn are relevant for clinical applications of brain machine interfaces.

Main text

Introduction

When performing a voluntary movement, motor commands from the brain activate body effectors, which produce a cascade of reafferent sensory (proprioceptive, tactile, visual) cues. Motor commands are also associated with prediction signals about the sensory consequences of the movement. The congruency between motor commands, reafferent sensory feedback, and sensory predictions is at the basis of the sense of agency, our feeling of being in control of our actions[1–3]. In case of damage to the motor system, motor commands that would trigger actions do not reach body effectors, leading to different types of paralysis, depending on the location and severity of damage. Intracortical brain machine interfaces (BMI) bypass such brain-body disconnection by decoding brain signals from different regions (i.e., primary motor cortex (M1), parietal or premotor cortex) and translating them into motor commands for the control of robots, exoskeletons[4,5], neuromuscular functional electrical stimulation[6,7] or other devices[8], enabling different actions (BMI actions) for patients with severe neuromotor impairments[9].

Here we study how it feels to generate movements with an intracortical-BMI, that is what is the sense of agency for BMI actions ((see [10,11] for recent studies with non-invasive brain computer interfaces (BCI)) and search for a potential neural mechanism. In particular, we asked whether motor neurons in human M1 encode not only motor commands, but also sensory feedback and whether these signals covary with agency for BMI actions Finally we tested whether agency also affects the efficiency of the BMI system - i.e. whether agency has a potential therapeutic benefit.

We applied classic approaches from psychophysics, neurophysiology, neuroengineering and virtual reality (VR) to ask these questions in a patient suffering from tetraplegia (caused by severe cervical spinal cord injury; C5/C6), who had been a BMI expert for two years before the start of the present study[6]. The patient had no preserved motor function below the C5 level. His sensory functions were extremely

limited and only showed partially preserved function at the C6 level on the left side and at C5 on the right side (there was also residual sensation for pressure on his right thumb). Concerning proprioception, he had preserved perception for shoulder, elbow and wrist joint position, but no proprioception for digits joint position (see Material and methods for more details).

The BMI consisted of a 96-channel array implanted in the hand area of left M1 and actuated a transcutaneous forearm neuromuscular electrical stimulation (NMES) system (see [6] for a full description of the system) to translate decoded cortical signals into right forearm and hand movements. In order to study the sense of agency for BMI actions and to evaluate its clinical impact, we experimentally manipulated the congruency between the decoded actions and the actions actuated by the BMI-NMES system. As illustrated in Figure 1, the participant was instructed to realize a cued action with the BMI and was provided with movement-related sensory feedback using visual (via VR) and/or somatosensory (via NMES) stimulation. Critically, this feedback was either congruent or incongruent with respect to the motor commands decoded from M1: half of the trials, in which the decoded action corresponded to the cued action (e.g., open hand), were associated with congruent feedback (e.g., open hand), while the other half were associated with incongruent feedback (e.g. the opposite action: close hand). For each BMI action, we asked the participant whether he felt in control of that action and to rate his confidence about this judgement, allowing us to (1) gauge the sense of agency for BMI actions and how this was modulated by the congruency between motor commands and sensory feedback. Next, neural data from the M1 implant were analyzed to measure how (2) the sense of agency and (3) sensory feedback were encoded in the activity of M1 neurons, quantified as multi-unit (MU) firing rates and local field potentials (LFP). Finally, we investigated (4) how visual and somatosensory feedback, and the associated sense of agency, affected the performance of the BMI system by changing the pattern of response of M1 neurons. By investigating what it feels like to control actions mediated by an intracortical BMI, our data show neural patterns in M1 activity (MU and LFP) reflecting the processing of agency for BMI actions, as generated by the congruency between intention and sensory feedback. Importantly, we show that the nature of somatosensory feedback (and the related sense of agency) affected the

efficiency of the BMI system by modulating the response properties of M1 neurons, underlining the clinical relevance of sensory feedback and agency for the BMI field.

During the experiment, the participant was cued to execute one of four target actions (hand opening, hand closing, thumb extension, thumb flexion) using a validated BMI neuroprosthesis. Neural activity corresponding to each target movement was recorded via a 96-channel microelectrode array in M1 and a nonlinear support vector machine classifier was applied to decode the participant's chosen action from MU activity (see [6] for full description). On each trial, the classifier provided the likelihood of each target action (on a -1 to +1 range, in 100 ms bins), thus decoding one of the four target actions from the participant's M1 activity. In three different experiments, visual, somatosensory, or visual-somatosensory feedback about the BMI action was provided (Figure 1). In Experiment 1, VR was used to provide visual feedback, consisting of a life-size virtual arm on a monitor superimposed over the participant's right arm, matching the location and dimensions of the participant's real arm, which was occluded from view. In Experiment 2, NMES was used to provide 'somatosensory' feedback: the patient's upper limb muscles were electrically stimulated so he could feel, but not see the selected movement. Experiment 3 combined VR and NMES to provide 'visual-somatosensory feedback' (see below). In half of the trials, sensory feedback was congruent with the cued action, while in the other half it was incongruent (i.e., the opposite, action was executed) (see Figure 1B). At the end of each trial, we gauged the participant's sense of agency (0 or 1; Q1) and confidence (rating between 0 and 100; Q2). Importantly, the amount of sensory information was kept constant across experiments, by providing non-informative sensorimotor feedback in Experiment 1 (i.e., a pattern of NMES triggering no BMI action) and non-informative visual feedback in Experiment 2 (i.e., a static visual hand performing no action).

Results

Sensory feedback determines agency and confidence. Agency ratings were collected in a total of 844 trials (155, 243 and 448 trials for Experiments 1, 2 and 3, respectively; for Experiment 3 see below and Supplementary Information) and

compared across feedback conditions using permutation tests. A null distribution of the mean agency rating was created by shuffling the condition labels over 10'000 iterations. P-values (2-sided) were estimated by counting the proportion of shuffled samples exceeding the observed average difference across conditions. As expected, and as shown in Figure 2A, we were able to manipulate agency and confidence for BMI actions. Thus, congruent visual (Experiment 1, 93.8% (bootstrapped 95% confidence interval 93.4% - 94.2%) and 5.2% (4.8% - 5.6%) of positive responses to Q1 for congruent and incongruent trials, respectively, $p<.0001$) and congruent somatosensory (Experiment 2, 97.5% (97.3% - 97.6%) and 8.8% (8.4% - 9.1%) of positive responses for congruent and incongruent trials respectively, $p<.0001$) feedback resulted in more frequent agency responses versus incongruent conditions. Analyzing the role of feedback for confidence ratings (irrespective of the agency ratings), we found that confidence was modulated by somatosensory congruency (Experiment 2, Q2 ratings were higher for somatosensory congruent [M = 74.0 (73.9 - 74.2)] than incongruent [M = 65.0 (64.8 - 65.2)] feedback; $p < 0.001$). The effect of visual congruency on confidence ratings was not significant (Experiment 1, mean Q2 rating = 70.9 (70.6 - 71.1) for congruent, 73.4 (73.1 - 73.6) for incongruent trials; $p = 0.28$).

In order to disentangle the role of visual and somatosensory cues for agency and confidence, Experiment 3 combined VR and NMES including combinations of congruent and incongruent visual and somatosensory feedback (Figure 1). Most relevant are the comparisons between feedback conditions in which visual (V) and somatosensory (S) signals were both congruent (+) or both incongruent (-) (V+/S+; V-/S-) or when feedback was congruent in one modality and incongruent in the other modality (V+/S-; V- /S+). Results revealed that somatosensory congruency was more effective in driving the sense of agency and the associated confidence: ratings were higher not only when both feedback signals were congruent (Q1 = 100% "Yes", mean Q2 = 83.98 [83.7 - 84.0]) as compared to both being incongruent (Q1 = 7.6% "Yes" [7.2% - 7.9%], mean Q2 = 72.4 [72.2 - 72.6)], both p-values < 0.001), but also in the V- /S+ (Q1 = 68.9% "Yes" [68.4% - 69.4%], mean Q2 = 59.4 [59.3 - 59.6] as compared to the V+/S- condition (Q1 = 52.2% "Yes" [51.5% - 52.8%], mean Q2 = 54.6 [54.4 - 54.8]; $p = 0.0035$ and $p = 0.036$, for agency and confidence respectively) (Figure 2). Collectively, these data from

Experiments 1-3 show that the congruency between decoded actions and sensory feedback, especially for the somatosensory modality, alters the sense of agency and confidence for actions mediated by an intracortical BMI.

The sense of agency has been traditionally studied by presenting participants with different visuo-motor couplings[2,12–15]. In comparison, the role of somatosensory signals remains poorly understood[16], notably because it is normally impossible to decouple motor commands, somatosensory feedback and visual feedback, with extremely rare exceptions as in deafferented patients. Here we were able to contrast feedback cues that were congruent in one modality (e.g., visual) and incongruent in the other modality (e.g., somatosensory; and vice versa) with respect to the motor command and demonstrate that somatosensory cues dominate the sense of agency and the associated confidence for BMI-NMES actions. Of note, this effect cannot be due to the presence of somatosensory cues alone, as BMI actions in the visual condition were always associated with non-informative NMES stimulation producing somatosensory sensations without generating any actions (i.e., pseudo random somatosensory feedback, see Supplementary Information). Collectively these psychophysical data in a BMI expert reveal that agency for BMI actions depends on visual and somatosensory feedback (tactile and proprioceptive input) with somatosensory cues being more relevant.

Cortical signatures of sensory feedback in M1. We next investigated how such sensory feedback, that modulated the sense of agency, was encoded in M1 activity. We first analyzed the LFP amplitude in the different feedback conditions across the three experiments, using a regularized generalized linear model (ridge regression) and input signals from each individual channel at every time point (see Supplementary Information). As shown in Figure 3A (left), the analysis distinguished congruent vs. incongruent visual feedback (maximum Cohen's Kappa $K = 0.40$, t-sum = 219.4, $p < 0.001$) within a single period of a positive potential that lasted from ~700-1200 ms after the BMI action classification onset (Experiment 1). We could also distinguish congruent vs. incongruent somatosensory feedback (maximum Cohen's Kappa $K = 0.64$, t-sum = 979.8, $p < 0.001$) during two time periods: an early period characterized by a negative

potential (stronger for incongruent feedback), starting at ~200 ms after BMI classification onset, followed by a later persistent differentiation lasting almost until the end of the trial. These results were further corroborated by data from Experiment 3: congruent trials in both modalities were clearly distinguished from incongruent trials in both modalities, lasting from ~250-1900 ms after BMI classification onset (maximum K = 0.66, t-sum = 958.8, $p < 0.001$). In addition, V+/S- trials were different from V-/S+ trials from ~300-1400 ms from BMI classification onset (maximum K = 0.31, t-sum = 256.7, $p < 0.001$) (Figure 3B left). These findings show that visual and somatosensory feedback were both encoded by LFPs in human M1 and that such M1-LFP coding started earlier and was more stable over time for somatosensory feedback.

Applying the same decoding algorithm as for LFPs, we next determined if sensory feedback was also encoded by the spiking rate of MU in M1 (for methods see Supplementary Information). As shown in Figure 3A (right), in Experiment 1, MU activity distinguished between congruent and incongruent visual feedback from ~400-900 ms from BMI classification onset (max K value = 0.41, t-sum = 56.2, $p < .001$). Extending LFP findings, an earlier and more stable differentiation between congruent and incongruent somatosensory feedback was found in MU activity in Experiment 2, with an effect as early as ~200 ms from the BMI classification onset (max K value = 0.66, t-sum = 390.7, $p = < .001$) and then persisted from 800 to 2000 ms. Similar results were found in Experiment 3 (Figure 3B, right), where MU activity distinguished between trials congruent and incongruent in both modalities (max K value = 0.68, t-sum = 271.8, $p = < .001$) and between V+/S- and V-/S+ trials from ~160 ms from BMI classification onset (max K value = 0.55, t-sum = 151.2, $p = < .001$). These data show that LFP and MU activity reflects visual and somatosensory feedback during actions driven by a BMI neuroprosthesis, with M1 activity early reflecting somatosensory feedback starting ~200 ms after NMES activation (~150 ms after BMI classification onset, ~200 ms before M1 activity encoding visual feedback) and persisting for a longer period.

The role of somatosensory and visual information is an important topic in motor control, with robust evidence showing how perturbations of sensory feedback impact motor

execution and adaptation[17]. The present data show that the congruency between an intended action and somatosensory/visual feedback is encoded by M1 neurons at different latencies. Previous studies in non-human primates described responses in M1 related to tactile and visual input[18,19], during active and passive movements[20] and during visual feedback of a pre-recorded movement[21,22]. The present results are consistent with proposals that suggest that M1 activity codes both for movement types and their sensory consequences, in line with recent works describing how M1 neurons encode different movement parameters (see [19,23,24] for reviews). Here we report that, at the population level, human M1 activity in addition discriminates between arm movements that were congruent or incongruent with the motor command, as defined by somatosensory and visual feedback, with higher accuracy, earlier and more consistent processing for the former type of sensory information. Thus, neural coding in M1 contains, at the population level, information not only about the movement itself, but also about sensory consequences of actions, involving somatosensory-motor and visuo-motor loops. These results are important to explain how sensory feedback affects the proficiency of the BMI system as described below.

Cortical signatures of the sense of agency in M1. It is known that sensory-motor congruency is a key mechanism of agency for able-bodied actions[2,3]; here we have shown that this also applies to agency and confidence for BMI-mediated actions and that LFPs and MU activity in human M1 distinguishes congruent vs. incongruent BMI actions. Next, we investigated to what extent LFP and MU activity in M1 also discriminate actions with and without an accompanying sense of agency. For each trial, we sorted LFP responses as a function of whether the participant reported agency or not. As seen in Figure 4A (left), LFP activity starting ~270 ms after BMI classification onset was found to code for agency and reached a maximum information value (Max K = 0.41, t-sum = 1258.3, $p < 0.001$) at ~1000 ms after BMI movement onset. Thus, BMI actions for which the participant felt to be the agent were characterized by a different LPF pattern compared to BMI actions for which he did not. This was corroborated by MU activity analysis (Figure 4A, right). The MU firing rate was higher for trials with versus no agency; this discrimination started at ~300ms after BMI classification onset,

until 500 ms, and peaked at ~400 ms (max K = 0.45, t-sum = 232.5, $p < 0.001$). Later on, MU activity also differentiated for agency, with higher firing rate for trials with no agency (800-1600 ms after BMI classification). The same decoding was also able to discriminate trials with high vs. low confidence, based on a median split of Q2, from LFPs (max K = 0.296 at ~1200 ms, t-sum = 8449.3, $p < 0.001$) and MU (max K = 0.225 at ~400 ms, t-sum = 214.9, $p < 0.001$).

In the experimental design, sensory feedback congruency was used to modulate the sense of agency and this may have influenced these agency findings. Accordingly, we next tested whether LFP and MU contained information related to the sense of agency per se, after controlling for the effect of sensory feedback. For this we built a continuous measure of sense of agency and confidence allowing us to regress out the effect of sensory feedback. This new index was computed by recoding confidence ratings (Q2) as -Q2, for trails with no agency (as indicated in Q1) and +Q2 for trials with agency (from Q1). This index was then orthogonalized with respect to congruency in order to regress out this effect from the agency scores. As M1 signals also varied as a function of the different cued actions (see SI), the index was also orthogonalized for the type of action. We then used the same decoder to predict orthogonalized agency scores from LFP and MU activity over time. This analysis shows that LFPs predicted the sense of agency starting at ~450 ms after BMI classification onset (max $R^2 = 0.03$, t-sum = 69.8, $p = 0.017$) (see Figure 4B left). A similar pattern was found when considering MU activity, although the peak failed to reach significance after cluster-based correction for multiple comparisons (Figure 4B right). These data show that M1 activity encodes the sense of agency and associated confidence level and was modulated by the congruency between motor commands and sensory feedback. Thus, subjective mental states associated with BMI actions and control are encoded by M1 activity at the LFP level (and to a minor extent at MU), independent of the neural processing associated with sensory feedback (see Supplementary Information for single channel analyses).

Somatosensory feedback modulates BMI classifier accuracy. Given the strong role of sensory congruency in determining agency and its coding in M1, we finally asked

whether sensory feedback has any impact on the BMI classifier. To this aim, we tested whether the congruency between the decoded motor commands and sensory feedback (visual, somatosensory) affected the accuracy of the BMI classifier, defined as the summed suprathreshold activation values across a 4s window. In Experiments 1 and 2 we found that congruent somatosensory feedback improved classifier accuracy ($t(241) = 9.29$, Cohen's $d = 1.238$, $p < 0.001$) (Figure 5B right). There was no effect due to visual feedback ($t(153) = 1.523$, Cohen's $d = -0.245$, $p = 0.14$) (Figure 5A). Moreover, incongruent somatosensory feedback was associated with lower classifier accuracy for the cued movement (Figure 5B left), and even increased classifier accuracy for the opposite movement (Figure 5B left). Thus, only somatosensory feedback congruency affected BMI accuracy in the present participant. This was extended by the results of Experiment 3, where we found a significant main effect of sensory feedback condition ($F(3,444) = 15.83$, $\eta^2 = 0.097$, $p < 0.001$; Figure 5C). Further post-hoc corrected tests showed that the BMI classifier's accuracy was higher when feedback was congruent, than incongruent, in either modality (Tukey corrected $t = 4.966$, Cohen's $d = 0.666$, $p < 0.001$). More interestingly, when feedback was congruent for the somatosensory modality and incongruent for the visual modality (V-/S+) BMI accuracy was higher than in the opposite feedback condition (S-/V+) ($t = 4.558$, Cohen's $d = 0.612$, $p < 0.001$). Figure 5 also shows the modulation of the BMI decoder as function of sensory feedback over time during the trial. Significant change of the decoder's output is visible from 430 ms from somatosensory feedback.

These data from Experiments 1-3 show that BMI performance is affected by the congruency between the decoded motor commands and the somatosensory feedback induced by the action actuated by NMES. This finding is also coherent with the more reliable (i.e., earlier, more long-lasting and better decoded) processing of somatosensory feedback from M1 activity (LFP, MU). The fact that the same action as actuated by NMES (e.g., open hand) increased or decreased the BMI classifier performance, depending on whether somatosensory feedback was congruent (open hand) or incongruent (close hand) with the cued action, excludes that this effect was a generic artifact of NMES stimulation affecting the input to the BMI classifier independently from sensory information.

In order to better understand how somatosensory feedback affected the accuracy of the BMI classifier, we analyzed time point by time point changes in multiunit activity for the whole array. We computed the average Euclidean distance between firing patterns of trials with a given cued movement and either congruent or incongruent somatosensory feedback. For a given cued movement (e.g., movement hand open) at congruent feedback (hand open), we computed its distance either with the same movement (cued: hand open) at incongruent feedback (hand close) or with the opposite movement (hand close), at its relative incongruent feedback (hand open). This way, we compared cases with the same motor intention, but opposite sensory feedback, and trials with the opposite motor intention, but the same sensory feedback. As shown in Figure 6, trials from Experiment 2 with opposite somatosensory feedback, but the same motor intention, diverge after sensory feedback, whereas trials with opposite motor intention, but the same sensory feedback, seem to even Otheconverge slightly with respect to baseline. This shows that M1 activity after feedback reflects the movement implemented via NMES more than the intended movement, thus explaining the modulation of somatosensory feedback in BMI proficiency (see Figure 6B). As a control, we also analyzed trials with opposite motor intention and congruent somatosensory feedback. We found the activity patterns to differ only slightly with respect to trials with same somatosensory feedback, but opposite motor intention, further showing that somatosensory feedback is prevailing over motor intention after movement onset. In the case of visual feedback (Experiment 1), instead, there was no divergence of activity patterns after the feedback, while trails with different motor intention clearly diverged before the movement onset (see Figure 6A).

In order to better display the effect of somatosensory feedback on M1 activity for each type of movements, we computed a 2D multidimensional scaling of neural activity as a function of intended movement and congruency of somatosensory feedback. This technique aims at representing the high dimensional spatio-temporal pattern of neural activity in 2D plane, while maximising the fraction of retained variance. As shown in Figure 6C, both for hand (opening/closing) and thumb (flection/extension) movements, before sensory feedback (in the window between -650 and -150 ms before sensory feedback onset), M1 neural activity is clustered solely as a function of the intended

movement. After somatosensory feedback (between 0 and 600 ms from sensory feedback onset, Figure 6D), trials with congruent somatosensory feedback and a given intended movement are clustered more with trials coding for the opposite movement, but receiving the same sensory feedback rather than with trials coding for the same movement.

No prior study in humans and only few studies in monkeys directly tested the effects of sensory feedback on BMI performance[21,25]. Here we show, for the first time, an effect of feedback congruency on BMI performance, and the underlying role of M1 in this process. Our findings indicate that the recorded M1 units processed motor signals for the trained BMI actions, for sensory and sensory-motor signals reflecting the type and congruency of the sensory feedback. Importantly, these processes were found to change across time, as a function of the sensory feedback provided. In particular, our results show that, after somatosensory feedback, the pattern of neural activity from M1 reflected more closely the type of movement realized by the NMES (i.e., the pattern of somatosensory feedback) rather than the intended and decoded movement. This re-writing of the encoded M1 movement as a function of the NMES-implemented movement directly relates to the improvement of BMI efficiency based on congruent somatosensory feedback that we observed and was absent in visual feedback trials.

This effect might be mediated by mutual connections between the primary motor and the primary somatosensory cortices, which have been extensively documented in non-humans primates[26] and in humans[27]. In addition, this effect might also depend on direct somatosensory inputs reaching M1 neurons likely from the dorsal columns via the ventrolateral thalamic nucleus[28]. This is an important finding, considering that original BMI approaches for severely motor-impaired patients generally provide visual feedback only[5,29] or somatosensory feedback by directly stimulating primary somatosensory cortex[30–32] (see [31] *for a review*). Although from a single tetraplegic participant, the present data show that non-invasive somatosensory feedback via NMES not only enables higher subjective feeling of being in control (agency and confidence), but also leads to better actual control of the patient's BMI actions.

Agency covaries with BMI classifier. We finally investigated whether agency has an impact on BMI efficiency and thus tested whether the sense of agency covaried with BMI classifier accuracy. We found that trials with agency versus trials without agency were associated with higher classifier accuracy when somatosensory feedback was modulated (Experiment 2; $t(241) = 8.91$, Cohen's $d = 1.199$, $p < 0.001$), as confirmed from analysis of data from Experiment 3 ($t(446) = 6.256$, Cohen's $d = 0.601$, $p < 0.001$). We found no statistically significant difference between trials with agency and trials without agency in classifier accuracy when visual feedback was modulated (Experiment 1; $t(153) = 0.690$, Cohen's $d = 0.111$, $p = 0.49$). In addition, there was a significant correlation across all three experiments between BMI classifier accuracy and confidence (See Supplementary Table 1 for multiple regression analyses). Thus, agency and confidence were both directly related to the performance of the present BMI system, but only when somatosensory feedback was involved. In order to confirm the role of agency on BMI performance, while controlling for other potential factors, we compared the BMI performance between trials in which the BMI user reported high and low agency, within conditions at equivalent sensory feedback, that is V-/S+ and V+/S- from Experiment 3 (which resulted in a balanced and sufficient numbers of trials with "Yes" and "No" responses to Q1). As shown in Figure 5D, BMI accuracy varied as a function of subjective agency judgments, in conditions of equivalent sensory feedback. BMI accuracy was significantly higher in trials with high agency as compared to trials with low agency from 300 ms in the V-/S+ condition. The same pattern is visible in the V-/S+ condition, although the comparison was not significant (i.e., did not survive to correction for multiple comparisons). The same analysis run on confidence ratings (by sorting high and low confidence ratings by means of a median split) did not show any significant difference in BMI accuracy due to confidence at equivalent conditions of sensory feedback (see Supplementary Figure S6). These results suggest that the sense of agency, and not confidence (see Supplementary Table 1 for further analyses), has an effect on BMI accuracy beyond the prominent role of sensory feedback, and impacts BMI accuracy at a later time point. Since agency judgments and confidence ratings reflect two different processes of subjective experience, the present data suggest that

pre-reflexive, rather than post-decisional agency components more strongly affect the proficiency of a BMI decoder in M1.

Discussion

By combining techniques from neurophysiology, neuroengineering, and VR with psychophysics of agency, we were able to study the sense of agency for actions enabled by a BMI-based intracortical neuroprosthesis and found that congruent sensory feedback boosted agency and confidence when controlling BMI actions. Moreover, we showed that human M1 processes not only motor and sensory information, but also different levels of congruency between sensory and motor signals and the resulting sense of agency. The present data are also of clinical relevance, because our NMES-based BMI approach, by providing congruent somatosensory feedback (without direct S1 stimulation) to a tetraplegic patient, improved the ability of the BMI classifier in decoding the patient's motor commands. Interestingly, such higher BMI proficiency was associated with a stronger sense of agency, suggesting that, beyond supporting close-loop systems and M1 feedback in general, somatosensory feedback and signals related to subjective aspects of motor control (i.e., agency) are important input for improving BMI proficiency. Quantifying subjective action-related mental states and including controlled motor and sensory feedback may therefore provide new levels of comfort and personalization and should be considered for the design of future BMIs.

The present data demonstrate that M1 activity contains information specifically linked to subjective aspects of motor control, in particular the sense of agency and confidence that our participant associated with his BMI actions. It is known that agency likely involves a network of multiple brain areas from which we did not record in the present study (e.g., posterior parietal cortex[33] and angular gyrus; anterior insula[34,35]; supplementary motor cortex[36]; premotor cortex[37]; for reviews see [3,38]). However, our findings – even if coming from a single tetraplegic patient - directly demonstrate that M1 activity contains sufficient information to decode actions for which a human participant feels to be in control. The present BMI findings extend previous research that investigated the sense of agency for non-invasive BCI, as based on scalp

electroencephalography (EEG). They add important information about the underlying neural underpinnings based on M1 multiunit activity of the sense of agency in humans. In keeping with a prominent line of research on the role of visuo-motor (and visuo-tactile) cues in boosting or modulating body ownership for artificial and real limbs[39–42], previous BCI studies also demonstrated that coherent visual feedback results in a higher sense of agency for BCI actions[14]. This effect is associated with stronger activations in a cortical-subcortical network, recruited during motor imagery used to control the BCI, consisting of posterior parietal cortex, insula, lateral occipital cortex, and basal ganglia[13]. Another study[10] further demonstrated that a stronger sense of agency for BCI-mediated actions is associated with stronger activity in sensorimotor areas during motor imagery based BCI. The present data on the sense of agency when using an intracortical BMI, although from a single, highly proficient BMI user (see below), demonstrate that this relationship can be tracked down even at the level of multi-unit activity from M1 neurons, and it is further associated with higher BMI proficiency.

Moreover, the present findings offer a mechanistic explanation for the relationship between sensorimotor activity, sensory feedback and the resulting sense of agency, by showing that M1 activity before movement execution codes for the intended movement, while activity after movement execution encodes the sensory feedback associated with the implemented movement. By showing that somatosensory feedback in particular affects the performance of the BMI classifier, these analyses provide insights into the sensorimotor mechanisms of BMI proficiency. We note that this last finding was possible only due to the combination of a SCI lesion and the present intracortical BMI, which allowed us to decode efferent signals and manipulate afferent signals, not only as visual reproductions of body movements (via VR, as in previous studies), but also as physical movements of the real body (via NMES). In order to highlight the dynamic, multiscale brain mechanisms underlying the sense of agency in humans, future studies should combine insights that can be gained from invasive BMI - with ultra-high spatial resolution, but limited coverage in a handful of subjects – and non-invasive BCI – with limited resolution, but recording from the entire brain in larger subject samples.

Finally, our results can be of interest not only within the field of neuroprosthetics and its clinical application, but also for basic neuroscience as well as current ethical and legal debates about the subjective sense of agency and responsibility when applying neurotechnology solutions for human repair or enhancement[38,43,44].

Limitations of the study

Because of the uniqueness of the present experimental setup, generalization of the present findings to the general population should be done carefully. First, we tested a single participant, who is an extremely trained BMI user, who could have developed an extraordinary capacity of controlling his BMI system. This could have in turn impacted the associated sense of agency and the discovered links with BMI proficiency. Second, in order to enable movements of his upper limb, we used an NMES system that provides a series of somatosensory cues, which are only partially comparable to those associated with natural movements. For example, the intensity and temporal activation of somatosensory fibers as well as of the recruited motor fibers (antidromic) differs from sensorimotor activation during natural movements. We also note that although our participant suffered severe somatosensory loss (following damage at the C5-C6 level), he may have "learned" to associate some patterns of cutaneous sensations with the specific type of NMES stimulation used to enable specific movements. Indeed, outside of the experimental tasks described here, he was able to identify NMES-implemented movements even without seeing his arm. Finally, given the long-term spinal cord lesion suffered by this participant, we cannot exclude that some plastic changes have occurred in his motor representations in M1, his somatosensory representations in S1, or the connectivity between the two. There is still no consensus about plasticity following spinal cord injury, with some evidence of preserved network organization, some possible changes in grey matter density[45,46] or activation in the sensorimotor cortices[47,48]. It is also not clear how these results at the population level of SCI patients are predictive of changes at the single patient level. Thus, at the moment, it is not possible to exclude that some of the present results are idiosyncratic to this particular clinical case.

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References

1. Blakemore, S. J., Wolpert, D. M. & Frith, C. D. Abnormalities in the awareness of action. *Trends Cogn. Sci.* **6**, 237–242 (2002).
2. Jeannerod, M. *Motor cognition : what actions tell the self*. (Oxford University Press, 2006).
3. Haggard, P. Sense of agency in the human brain. *Nat. Rev. Neurosci.* **18**, 196–207 (2017).
4. Hochberg, L. R. *et al.* Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature* **485**, 372–375 (2012).
5. Collinger, J. L. *et al.* High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet* **381**, 557–564 (2013).
6. Bouton, C. E. *et al.* Restoring cortical control of functional movement in a human with quadriplegia. *Nature* **533**, 247–250 (2016).
7. Ajiboye, A. B. *et al.* Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. *Lancet* **389**, 1821–1830 (2017).
8. Lebedev, M. A. & Nicolelis, M. A. L. Brain-Machine Interfaces: From Basic Science to Neuroprostheses and Neurorehabilitation. *Physiol. Rev.* **97**, 767–837 (2017).
9. Donoghue, J. P. Connecting cortex to machines: recent advances in brain interfaces. *Nat. Neurosci.* **5**, 1085–1088 (2002).
10. Nierula, B. *et al.* Agency and responsibility over virtual movements controlled through different paradigms of brain−computer interface. *J. Physiol.* **0**, 1–16 (2019).
11. Nierula, B. & Sanchez-Vives, M. V. Can BCI Paradigms Induce Feelings of Agency and Responsibility Over Movements? in (2019). doi:10.1007/978-3-030-05668-1_10.
12. Sato, A. & Yasuda, A. Illusion of sense of self-agency: Discrepancy between the predicted and actual sensory consequences of actions modulates the sense of self-agency, but not the sense of self-ownership. *Cognition* **94**, 241–255 (2005).
13. Marchesotti, S. *et al.* Cortical and subcortical mechanisms of brain-machine interfaces. *Hum. Brain Mapp.* **38**, 2971–2989 (2017).
14. Evans, N., Gale, S., Schurger, A. & Blanke, O. Visual Feedback Dominates the Sense of Agency for Brain-Machine Actions. *PLoS One* **10**, e0130019 (2015).
15. Knoblich, G. & Sebanz, N. Agency in the face of error. *Trends Cogn. Sci.* **9**, 259–261 (2005).
16. Tsakiris, M., Prabhu, G. & Haggard, P. Having a body versus moving your body: How agency structures body-ownership. *Conscious. Cogn.* **15**, 423–432 (2006).
17. Scott, S. H., Cluff, T., Lowrey, C. R. & Takei, T. Feedback control during voluntary motor actions. *Curr. Opin. Neurobiol.* **33**, 85–94 (2015).

18. Shokur, S. *et al.* Expanding the primate body schema in sensorimotor cortex by virtual touches of an avatar. *Proc. Natl. Acad. Sci.* **110**, 15121–15126 (2013).

19. Hatsopoulos, N. G. & Suminski, A. J. Sensing with the motor cortex. *Neuron* **72**, 477–487 (2011).

20. Hatsopoulos, N. G., Xu, Q. & Amit, Y. Encoding of movement fragments in the motor cortex. *J. Neurosci.* **27**, 5105–14 (2007).

21. Suminski, A. J., Tkach, D. C., Fagg, A. H. & Hatsopoulos, N. G. Incorporating Feedback from Multiple Sensory Modalities Enhances Brain-Machine Interface Control. *J. Neurosci.* **30**, 16777–16787 (2010).

22. Tkach, D., Reimer, J. & Hatsopoulos, N. G. Congruent activity during action and action observation in motor cortex. *J. Neurosci.* **27**, 13241–50 (2007).

23. Churchland, M. M. & Shenoy, K. V. Temporal Complexity and Heterogeneity of Single-Neuron Activity in Premotor and Motor Cortex. *J. Neurophysiol.* **97**, 4235–4257 (2007).

24. Schwartz, A. B. Movement: How the Brain Communicates with the World. *Cell* **164**, 1122–1135 (2016).

25. O'Doherty, J. E. *et al.* Active tactile exploration using a brain–machine–brain interface. *Nature* **479**, 228–231 (2011).

26. Stepniewska, I., Preuss, T. M. & Kaas, J. H. Architectionis, somatotopic organization, and ipsilateral cortical connections of the primary motor area (M1) of owl monkeys. *J. Comp. Neurol.* **330**, (1993).

27. Eickhoff, S. B. *et al.* Anatomical and functional connectivity of cytoarchitectonic areas within the human parietal operculum. *J. Neurosci.* **30**, (2010).

28. Fetz, E. E., Finocchio, D. V., Baker, M. A. & Soso, M. J. Sensory and motor responses of precentral cortex cells during comparable passive and active joint movements. *J. Neurophysiol.* **43**, (1980).

29. Hochberg, L. R. *et al.* Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* **442**, 164–171 (2006).

30. Tabot, G. A. *et al.* Restoring the sense of touch with a prosthetic hand through a brain interface. *Proc. Natl. Acad. Sci. U. S. A.* **110**, 18279–84 (2013).

31. Flesher, S. N. *et al.* Intracortical microstimulation of human somatosensory cortex. *Sci. Transl. Med.* **8**, 361ra141 LP-361ra141 (2016).

32. Bensmaia, S. J. & Miller, L. E. Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. *Nat. Rev. Neurosci.* **15**, 313–325 (2014).

33. Desmurget, M. *et al.* Movement intention after parietal cortex stimulation in humans. *Science* **324**, 811–3 (2009).

34. Farrer, C. & Frith, C. D. Experiencing Oneself vs Another Person as Being the Cause of an Action: The Neural Correlates of the Experience of Agency. *Neuroimage* **15**, 596–603 (2002).

35. Chambon, V., Wenke, D., Fleming, S. M., Prinz, W. & Haggard, P. An online neural substrate for sense of agency. *Cereb. Cortex* **23**, 1031–1037 (2013).

36. Fried, I., Mukamel, R. & Kreiman, G. Internally Generated Preactivation of Single Neurons in Human Medial Frontal Cortex Predicts Volition. *Neuron* **69**, 548–562 (2011).

37. Fornia, L. *et al.* Direct electrical stimulation of the premotor cortex shuts down awareness of voluntary actions. *Nat. Commun.* **11**, 1–11 (2020).

38. Sperduti, M., Delaveau, P., Fossati, P. & Nadel, J. Different brain structures related to self- and external-agency attribution: A brief review and meta-analysis. *Brain Struct. Funct.* **216**, 151–157 (2011).

39. Blanke, O., Slater, M. & Serino, A. Behavioral, Neural, and Computational Principles of Bodily Self-Consciousness. *Neuron* **88**, 145–166 (2015).

40. Makin, T. R., Holmes, N. P. & Ehrsson, H. H. On the other hand: Dummy hands and peripersonal space. *Behav. Brain Res.* **191**, 1–10 (2008).

41. Rognini, G. *et al.* Multisensory bionic limb to achieve prosthesis embodiment and reduce distorted phantom limb perceptions. *J. Neurol. Neurosurg. Psychiatry* **90**, 833–836 (2019).

42. Sanchez-Vives, M. V., Spanlang, B., Frisoli, A., Bergamasco, M. & Slater, M. Virtual hand illusion induced by visuomotor correlations. *PLoS One* **5**, e10381 (2010).

43. Yuste, R. *et al.* Four ethical priorities for neurotechnologies and AI. *Nature* **551**, 159–163 (2017).

44. Fried, I., Haggard, P., He, B. J. & Schurger, A. Volition and Action in the Human Brain: Processes, Pathologies, and Reasons. *J. Neurosci.* **37**, 10842–10847 (2017).

45. Wang, W. *et al.* Specific Brain Morphometric Changes in Spinal Cord Injury: A Voxel-Based Meta-Analysis of White and Gray Matter Volume. *J. Neurotrauma* **36**, (2019).

46. Melo, M. C., Macedo, D. R. & Soares, A. B. Divergent Findings in Brain Reorganization After Spinal Cord Injury: A Review. *Journal of Neuroimaging* vol. 30 (2020).

47. Freund, P. *et al.* MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: A prospective longitudinal study. *Lancet Neurol.* **12**, (2013).

48. Henderson, L. A., Gustin, S. M., Macey, P. M., Wrigley, P. J. & Siddall, P. J. Functional reorganization of the brain in humans following spinal cord injury: Evidence for underlying changes in cortical anatomy. *J. Neurosci.* **31**, (2011).

49. Mallat, S. *A Wavelet Tour of Signal Processing*. *A Wavelet Tour of Signal Processing* (2009). doi:10.1016/B978-0-12-374370-1.X0001-8.

50. Humber, C., Ito, K. & Bouton, C. Nonsmooth Formulation of the Support Vector Machine for a Neural Decoding Problem. *arXiv* (2010).

669 51. Colachis, S. C. *et al.* Dexterous control of seven functional hand movements
670 using cortically-controlled transcutaneous muscle stimulation in a person with
671 tetraplegia. *Front. Neurosci.* **12**, 1–14 (2018).
672 52. Colachis, S. C. I. Optimizing the Brain-Computer Interface for Spinal Cord Injury
673 Rehabilitation. (2018).
674 53. Zhang, M. *et al.* Extracting wavelet based neural features from human intracortical
675 recordings for neuroprosthetics applications. *Bioelectron. Med.* **4**, 11 (2018).
676 54. Quiroga, R. Q., Nadasdy, Z. & Ben-Shaul, Y. Unsupervised Spike Detection and
677 Sorting with Wavelets and Superparamagnetic Clustering. *Neural Comput.* **16**,
678 1661–1687 (2004).
679 55. Hoerl, A. E. & Kennard, R. W. Ridge Regression: Biased Estimation for
680 Nonorthogonal Problems. *Technometrics* **12**, 55–67 (1970).
681 56. Kuhn, M. R Package: caret, Ver. 6.0-80. *CRAN* (2018).
682 57. Maris, E. & Oostenveld, R. Nonparametric statistical testing of EEG- and MEG-
683 data. *J. Neurosci. Methods* **164**, 177–190 (2007).
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Figure legends

Figure 1. **Experimental setup.** A. Events during trials. One (out of four possible movements) was cued, following a "Go" signal to initiate the movement. The BMI classifier decoded the movement from M1 activity and sensory feedback was given. The patient answered two questions: Q1. "Are you the one who generated the movement?", by saying "Yes" or "No"; and Q2. "How confident are you?", by indicating a number ranging from 0 (absolutely unsure) to 100 (absolutely sure). B: Example of sensory feedback for one type of movement. The chosen movement was realized as a visual feedback, via virtual reality (VR – Experiment 1), as a somatosensory feedback, via NEMS (Experiment 2) or both (Experiment 3). In different congruency conditions, either the cued and correctly decoded movement (Congruent) or the opposite movement (Incongruent) was realized for the different modalities. The location of the electrodes array in the M1, with respect to the pattern of activity for upper limb attempted movement from fMRI is also shown (from [6]).

Figure 2. **Agency judgements and confidence depends on sensory feedback.** A. Proportion of "Yes" and "No" answers (Q1) to congruent and incongruent trials for the visual (Experiment 1) somatosensory (Experiment 2) and the combination of the two modalities (Experiment 3). B-C-D: Confidence about agency judgments. Distribution of Q2 responses as a function of the congruency of visual (B), somatosensory (C) or both (D) sensory feedback.

Figure 3. M1 activity depends on sensory feedback. Sensory feedback as encoded by Local field potentials (LFP; left panel) and Multiunit firing rates (MU; right panel). LFP and MU modulation for congruent and incongruent visual (Experiment 1) and somatosensory (Experiment 2) feedback (A) and for the combination of the two (Experiment 3, B). Colored lines represent averaged signal across all channels (shaded areas indicate SEMs); black lines report the time-related k-values of the multivariate decoder distinguishing between congruent and incongruent feedback; the underlying thick segments indicate k-values significantly higher than chance level from cluster-based permutation analyses.

Figure 4. Sense of agency in M1. Sense of agency as coded by LFP (left) and Multi-unit firing rates (right). A. Left and right panels respectively show averaged LFP and Multi-unit modulation for high (green) and no (grey) agency response to Q1 (shaded areas indicate SEMs); black lines report the time-related k-values of the multivariate decoder distinguishing the two conditions; the underlying thick segments indicate k-values significantly higher than chance level from cluster-based permutation analyses. B: Results of the decoder discriminating between high vs. low orthogonalized agency scores from LFP (left) and MU (right) after regressing out for the effects of the congruency of sensory feedback and type of movements.

Figure 5. Performance of BMI classifier as a function of sensory feedback and sense of agency. A-B-C. The left panels (A, B, C) show the modulation in time of the performance of the BMI classifier for the 4 types of movements indicated for the cued movement (filled line) and the opposite (dashed line), as a function of feedback (i.e. black dots indicate time points with significant difference). The right panels show the area under the curve taken as an index of global performance of the BMI. The performance of the BMI classifier does vary not as a function of visual feedback (Experiment 1, A), but it is significantly better when somatosensory feedback is congruent both in Experiment 2 (B) and in Experiment 3 (C). D. BMI accuracy in time as a function of sense of agency. Blue/red curves represent the BMI classifier output for the cued movement as a function of agency judgements (Q1: 1=high agency; 0=low agency) in conditions of equal sensory feedback.

Figure 6. Somatosensory feedback changes firing rates of M1 neurons. A-B. Euclidean distance in time between trials with same motor intention and opposite feedback (red), same feedback and opposite intention (blue), or opposite congruent feedback and intention (green), for experiment 1 (A) and 2 (B). In Experiment 1, neural activity diverged as a function of motor intention before the movement, as shown by the increase in Euclidean distances between the green and blue curves. In Experiment 2, neural activity diverged as function of sensory feedback after NMES activation. **C-D.**

Multidimensional scaling of neural activity before (-650/150 ms; C) and after (0/500 ms; D) sensory feedback. The plots show a 2D dimensionality reduction of population activity in the target period, in order to represent it on a plane. As in a principal component analysis, Dimensions 1 and 2 can be seen as the two abstract coordinates explaining most variance in the data. Movements are separated by classes of hand (open/close; right) and thumb (extension / flection; left) movements.

Materials and Methods

Participant

The participant in this study was enrolled in a pilot clinical trial (NCT01997125) of a custom neural bridging system (Battelle Memorial Institute) to reanimate paralyzed upper limbs after C4-6 spinal cord injury. The system consisted of a Neuroport data acquisition system (Blackrock Micro, Salt Lake, Utah), custom signal processing and decoding algorithms (Battelle), and a NeuroLife Neuromuscular Stimulation System (Battelle). The trial received investigational device exemption (IDE) approval by the US Food and Drug Administration and Institutional Review Board approval through the Ohio State University (Columbus, Ohio). The study conformed to institutional research requirements for the conduct of human subjects. The site of the experiments was the Ohio State University NeuroRehabLab (Bockbrader, PI) and data was analyzed at Ohio State (Columbus, Ohio) and École polytechnique fédérale de Lausanne (EPFL, Switzerland). The participant provided informed consent at the time of enrollment and also provided written permission for photographs and videos.

The study participant was a 22 year-old male at the time of study enrollment. He had complete C5 ASIA A, non-spastic tetraparesis from cervical spinal cord injury associated with a diving accident 3 years prior. On neurological exam, he had full motor function bilaterally for C5 level muscles (e.g., biceps and shoulder girdle muscles), but no motor function below the C6 level. He had 1/5 strength on the right and 2/5 strength on the left for wrist extension (C6 level) on manual muscle testing. His sensory level was C6 on the left and C5 on the right, although he had sensation for pressure on his right thumb. He had preserved proprioception for shoulder, elbow and wrist joint position, but was at chance level for distinguishing digit joint positions (flexion/neutral/extension) for the thumb and fingers. He had mild finger flexor contractures bilaterally, limiting finger extension at the proximal and distal interphalangeal joints of digits 2-5.

He was implanted with a 4.4 x 4.2mm intracortical silicon Neuroport microelectrode array (Blackrock Microsystems) in the dominant hand/arm area of his motor cortex on 4/22/2014, as previously described[6]. The implant site was determined by preoperative functional neuroimaging obtained while the participant visualized movements of his right

hand and forearm. He began using cortically-controlled transcutaneous neuromuscular electrical stimulation (NMES) on his right forearm on 5/23/14. Data for this study was collected over 13 sessions (45 hours) from 11/16/2016 - 2/20/2017, corresponding to post-implant days 939-1035. One session with visual and NMES feedback was used for practice (5 blocks of 32 trials on post-implant day 939). At the time of data collection, the participant was an expert brain-machine interface (BMI) user with over 800 hours of study participation.

The participant underwent cognitive testing approximately one year after Utah array implantation (January – July, 2015). He scored with superior verbal abilities, attention, and working memory (ranging between 92nd - 99th percentile for his age).

Cortical Signal Acquisition and Classification

Neural data (96 channels) were acquired from the left motor cortex Utah array through the Neuroport data acquisition system (Blackrock Micro). Raw data were processed using analog hardware with 0.3Hz 1st order high-pass and 7.5kHz 3rd order Butterworth low-pass filters, then digitized at 30,000 Hz. Data were divided into 100ms bins and passed into Matlab (version 2014b), where signal artifact was removed by blanking over 3.5ms around artifacts (defined as signal amplitude >500μV at the same time on 4 of 12 randomly-selected channels). Signals were decomposed into mean wavelet power (MWP) using the 'db4' wavelet over 100ms[49]. Coefficients within the multiunit frequency bands (234–3,750Hz, coefficients of scales 3, 4, 5, 6) were averaged across the 100ms window and normalized by channel (by subtracting the mean and dividing by the standard deviation of each channel and scale, respectively). Normalized coefficients for each channel were averaged across scales 3-6, creating 96 MWP values (one for each channel) per each 100ms. MWP values were fed as features into a real-time, nonlinear support vector machine (SVM) classifier[50] with five classes (hand open, hand closed, thumb extension, thumb flexion, and rest). Classifier activation values were computed for each 100ms bin and ranged from -1 to 1. Classifier output represented the movement pattern (hand open, hand closed, thumb extension, thumb flexion) with the highest activation greater than threshold (zero). If no movement classes had activation

greater than zero, the classifier was in the “rest” state. If multiple output classes exceeded threshold, only the one with the highest score was used to provide feedback. Signal quality was stable[51] during the interval of data collection; but represented about a 30% decline in MWP normalized to post-implant 87[52]. (See below for single unit statistics.) Average impedance was approximately 200 kΩ, a decline of 40% of its initial value. Average signal-to-noise was approximately 17.5dB, a decrease of about 10% of its initial value[53]. Most of the decline in signal quality occurred in the first 400 days post-implantation.

Classifier Training and Neurally Controlled Hand Movements

Before each session, the SVM classifier was trained in an adaptive manner over 5 blocks. Each block consisted of 3 repetitions of 4 movements (hand open, hand closed, thumb extension, thumb flexion) presented in a random order. Movements were cued for 3-4s (4-5s inter-cue interval) using a small, animated hand in the corner of the video display. Feedback was given with both NMES and the feedback hand on the video screen. During the first training block, scripted feedback was provided simultaneously with the cued movements. In subsequent blocks, appropriate movements were activated when an output class for a given movement exceeded threshold (>0). Training took approximately 10-15 minutes per session.

Neuromuscular Electrical Stimulation

The NMES system was used to evoke hand and finger movements by stimulating forearm muscles. The system consisted of a multi-channel stimulator and a flexible, 130-electrode, circumferential forearm cuff. Coated copper electrodes with hydrogel interfaces (Axelgaard, Fallbrook, CA) were 12mm in diameter, spaced at regular intervals in an array (22mm longitudinally X 15mm transversely), and delivered current in monophasic, rectangular pulses at 50Hz (pulse width 500μs, amplitude 0-20mA). Desired hand/finger movements were calibrated at the beginning of each session by determining/confirming the intensity and pattern of electrodes required to stimulate intended movements. This took 5-10 minutes per session.

During the experiment, the participant's view of NMES-evoked movements was obscured from view by the video display. During Experiment 1, non-informative NMES feedback was given (current at an intensity equivalent to what was used for movement calibration patterns, but that did not evoke movement). During Experiments 2 and 3, NMES feedback was provided that evoked hand and finger movements.

Virtual Reality Animation

A non-immersive virtual reality system (i.e. without a head-mounted display or head-tracking) was used to provide visual feedback. This was done in order to adopt a previous setup that the participant was already familiar with to the present experiments and also facilitated the calibration procedure to train the BMI classifier. A physics-based animated hand was used to provide visual feedback of classifier activation. During training, two animated hands were displayed, a small cue hand at the bottom left and a larger centrally-placed feedback hand (Figure 1 main text). During the experiment, the display was oriented over the participant's forearm, a single, centrally-placed feedback hand was displayed to match the size and location of the participant's right hand (the cue hand was not displayed). During Experiments 1 and 3, feedback was provided using the virtual hand. During Experiment 2, non-informative visual feedback was given (the feedback hand remained in a neutral, rest position).

Feedback Congruency

In half of the trials across Experiments, the visual and/or somatosensory feedback was covertly manipulated to be incongruent with the cue. In incongruent trials, when the participant correctly activated the classifier associated with the cue, he received feedback opposite to the cue (i.e., hand closed for "hand open", thumb extension for "thumb flex", etc.). In congruent trials, he received feedback consistent with the cue (i.e., hand open for "hand open", thumb flexion for "thumb flex", etc.).

Agency Assessment

All experimental trials began with a verbal cue ("hand open", "hand closed", "thumb extend", "thumb flex"), followed by a 2 second delay, then a verbal cue ("go"). During the next 4s, the participant was given feedback based on classifier activation levels, and

then was told to “stop”). Over the next 5-5.5s, the participant reported whether he felt in control of the movement (“yes” or “no”) and his degree of certainty (0-100). The next trial began at the end of this 5-5.5s interval. There were 32 trials per block in Experiments 1 and 2 and 26 trials per block in Experiment 3.

Trial Selection and Time-locking

To ensure that the participant was successfully activating the classifier for the cued movement, and the signal can be meaningfully time-locked to movement onset, we applied the following selection criteria on the trials. We consider it as a correct imagined movement when the participant is able to maintain the classifier of the cued movement above the threshold for at least 600 ms (6 classifier output bins). We retain trials in which at least one correct movement happens between the GO cue and 1.5 seconds before the STOP cue. Epochs are then constructed by time-locking every trial with respect to the onset of such imagined movements. In case several correct movements occurred during the same trial, the time-locking is relative to the first movement. Furthermore, we excluded 128 trials from the session on which the participant systematically reported problems with controlling the BMI system and absent subjective agency. Globally, we retained 846 out of 1408 trials (60%).

Note that, since we define the onset as the beginning of the 100 ms bin of neural activity that is fed to the classifier, and around 50 ms are required to compute the output, the corresponding feedback is received about 150 ms after the onset of the imagined movement.

Experiment 1: Agency Assessment with Virtual Hand Feedback and Non-informative NMES

Twelve blocks of 32 trials were collected on post-implant days 953 (4 blocks), 988 (4 blocks), and 1035 (4 blocks). In each trial, the participant received a verbal cue to perform a movement (“hand open”, “hand closed”, “thumb extend”, “thumb flex”). When a classifier crossed threshold during the 4 second feedback window, feedback was given by showing movement of the virtual hand and by activating non-informative NMES (radial wrist electrode activation that did not elicit movement, did not vary from trial to trial, and that the participant could feel and distinguish from real NMES feedback).

Feedback on half of the trials was randomly selected to be incongruent with the cue. His subjective sense of agency and level of certainty were recorded for each trial.

A total of 384 trials were collected across three days. After removing trials where the cued action could not be correctly decoded and the session on post-implant day 1035 (see trial selection paragraph), 83 congruent and 72 incongruent trials remained for behavioral and neural activity analysis.

Experiment 2: Agency Assessment with NMES Feedback and Non-informative Virtual Hand

Twelve blocks of 32 trials were collected on post-implant days 941 (5 blocks), 960 (3 blocks), and 967 (4 blocks). In each trial, the participant received a verbal cue to perform a movement (“hand open”, “hand closed”, “thumb extend”, “thumb flex”). When a classifier crossed threshold during the 4 second feedback window, feedback was given by activating movement of the participant’s hand and wrist through NMES and showing non-informative visual feedback (non-moving hand). The participant could not see his own hand/wrist, but could distinguish his hand state based what the stimulation patterns felt like to him. Feedback on half of the trials was randomly selected to be incongruent with the cue. His subjective sense of agency and level of certainty were recorded for each trial.

A total of 384 trials were collected across three days. After removing trials where the participant did not respond correctly by activating the classifier associated with the cue, 154 congruent and 89 incongruent trials remained for behavioral and neural activity analysis.

Experiment 3: Agency Assessment with Virtual Hand and NMES Feedback

Twenty blocks of 32 trials were collected on post-implant days 993 (3 blocks), 990 (5 blocks), 1007 (4 blocks), 1014 (3 blocks), and 1021 (5 blocks). In each trial, the participant received a verbal cue to perform a movement (“hand open”, “hand closed”, “thumb extend”, “thumb flex”). When a classifier crossed threshold during the 4 second feedback window, feedback was given by activating movement of the participant’s hand and wrist through NMES and showing movement of the virtual hand. The participant could not see his own hand/wrist, but could distinguish his hand state based what the

stimulation patterns felt like to him. Congruency with respect to the cue was manipulated independently in the visual and somatosensory modalities such that 25% of the trials were each: congruent for both visual and NMES feedback, incongruent for both visual and NMES feedback, congruent for visual but incongruent for NMES feedback, congruent for NMES but incongruent for visual feedback. His subjective sense of agency and level of certainty were recorded for each trial.

A total of 520 trials were collected across five days. After removing trials where the participant did not respond correctly by activating the classifier associated with the cue, the number of trials that remained for behavioral and neural activity analysis were: 117 congruent for both visual and NMES feedback, 103 incongruent for both visual and NMES feedback, 101 congruent for visual and incongruent for NMES feedback, and 127 congruent for NMES and incongruent for visual feedback.

Firing Rate Calculation and Single Unit Analyses

Single units were identified through offline data processing. For each block, raw voltage recordings at each channel were processed in a series of steps. First, FES stimulation artifact was removed using a 500μV threshold and 3.5ms artifact removal time window. The removed window was replaced with an interpolated segment to retain temporal information. Then, the raw signal with FES artifact removed was processed with a 300-3000Hz bandpass filter. The filtered data was fed into an automated spike detection and sorting algorithm, wave_clus[54] using the default optimization settings. A threshold was set to four times the standard deviation of the noise and used to detect spike locations. A wavelet decomposition was performed on the spikes to extract features and a superparamagnetic clustering algorithm was used to cluster the spikes into groups, representative of individual single units. The superparamagnetic clustering algorithm was used to eliminate spikes that were considered noise to ensure only single units were analyzed. As spike sorting was not performed before data collection, there was no way to match single units across days. Additionally, the number of single units detected at a given channel fluctuated between days, possibly due to micro-movement of the array and brain state changes. For this reason, all single units detected at a given channel were considered the same and pooled at the single channel level as multiunit activity in subsequent analysis.

Offline neural decoding

Sensory feedback congruency and subjective ratings (Q1 and Q2) were decoded offline both from LFPs and from multiunit activity. For LFP analysis, the signal amplitude for each channel was downsampled to 500 Hz, band-passed between 0.1 and 12 Hz with an IIR filter and smoothed using sliding averaging windows of 250 ms. Following multiunit spike times calculation (see above), multiunit firing rate was estimated at 20 Hz over a 250 ms sliding window.

We fed each channel's signal amplitude (LFP) or firing rate (multiunit) as predictors to a penalized linear decoder based on ridge regressions[55]. A separate model was trained to decode congruency (Q1) or confidence (Q2) on each signal timepoint, with a sampling rate of 20 and 500 Hz for multiunit and LFPs respectively. Decoding performance was evaluated by computing and averaging Cohen's k (logistic regression; Q1) or R2 (linear regression; Q2) values over 10 independent 10-fold cross validation runs. The regression was performed through the "train" function of the R "caret" package[56]. To evaluate the statistical significance of the decoding, we generated a null decoding performance distribution by applying the same decoding methods on the data after randomly shuffling Q1 and Q2 values. 1000 permutations were generated, and the decoding performance was evaluated for each of them. Then, a t-value was assigned to every time-point both in real and permuted data, by comparing its decoding performance to the null distribution of permuted data. Finally, the t-values were used to define significant decoding time windows based on a cluster-based permutation test on each epoch's largest cluster[57]. After checking that the t-value threshold used to define clusters was not significantly affecting the results, its value was set at 2.

Computation of distance between neural activity patterns

Since the neural activity recorded by the microelectrode array can change significantly between experimental sessions (i.e., days of recording) spanned by our analysis, Euclidean distances per each pair of conditions were computed separately within each day of recording and then averaged to obtain the final results. Confidence intervals were obtained through a bootstrapping technique, again applied within sessions. For each

session and condition, we extracted n random trials with replacement, where n is the number of trials for that condition/session, and the final Euclidean distance was obtained by averaging across sessions as described above. The procedure was repeated 100 times, and 95 % confidence intervals were obtained as 1.96 times the standard deviation of the surrogated distribution obtained as explained here.

Multidimensional scaling

In order to graphically represent the spatio-temporal patterns of neural activity, we performed a multidimensional scaling (MATLAB function mds) on correlation distances computed between spatio-temporal patterns of neural activity. Also, in this case, to avoid including sources of variances due to the change in signal between experimental sessions, the procedure was run within experimental sessions. In order to obtain correlation distances between trials we started by concatenating, for each trial, data from all channels and timepoints within the selected temporal window. Then, we computed the correlation coefficient of the resulting vector with the equivalent vector from all other trials within the same session and subtracted the obtained values to 1 to obtain values of the correlation distance. The first two dimensions of the multidimensional scaling were then aligned across sessions via the Procrustes analysis (MATLAB function Procrustes), using the means by conditions (combinations of movement/somatosensory feedback) in the first session as a reference.

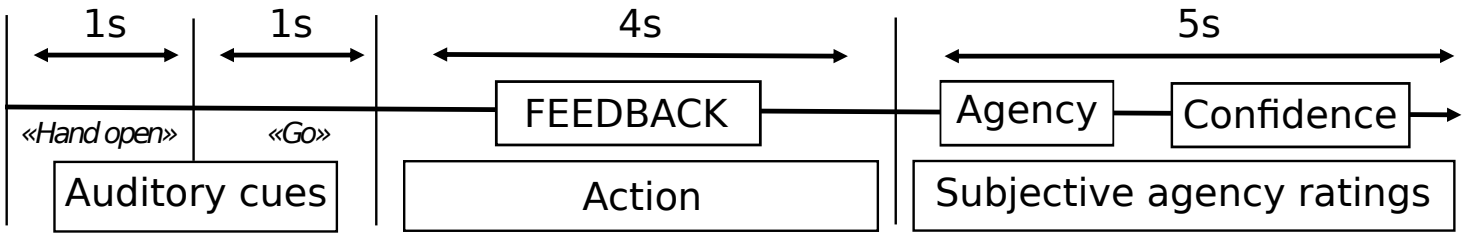
Data availability statement

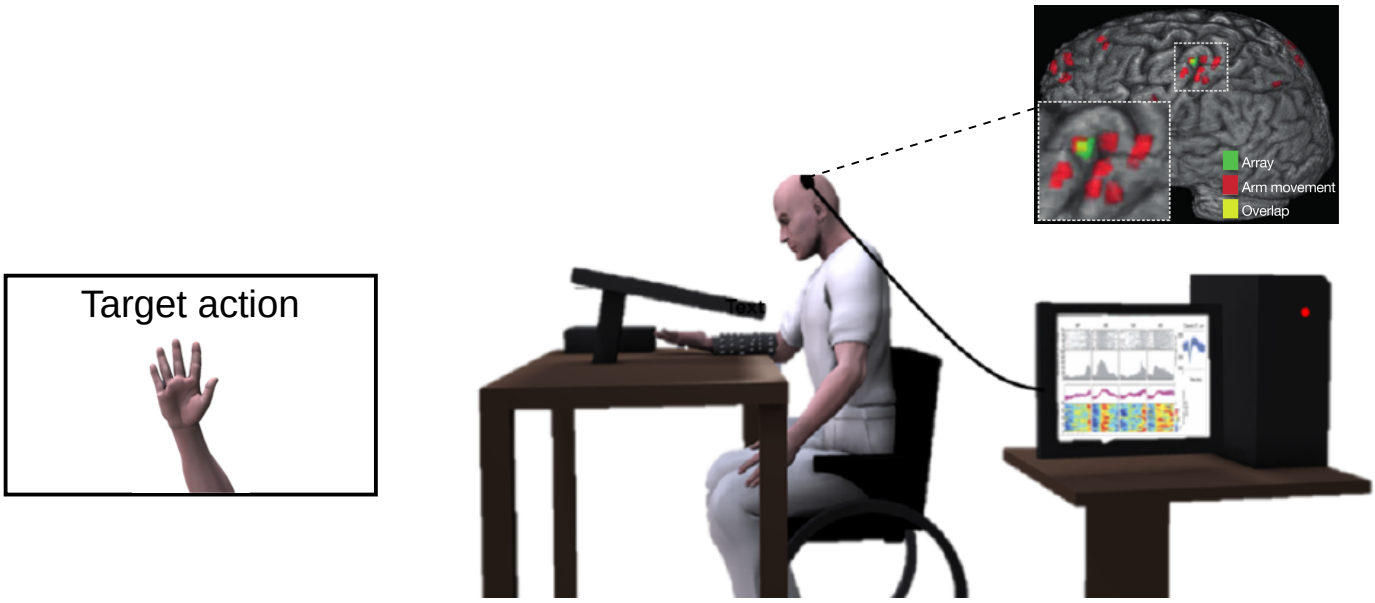
Behavioral data and processed data necessary to reproduce the figures in the main text can be found in the OSF repository accessible at:
https://osf.io/7rma5/?view_only=9928bd8e32a748828f7ecfdbeb1f8baa.
Neural data and code for BMI control can be made available to qualified individuals for collaboration via a written agreement between Battelle Memorial Institute and the requester's affiliated institution. Such inquiries or requests should be directed to: ganzer@battelle.org.

Code availability statement

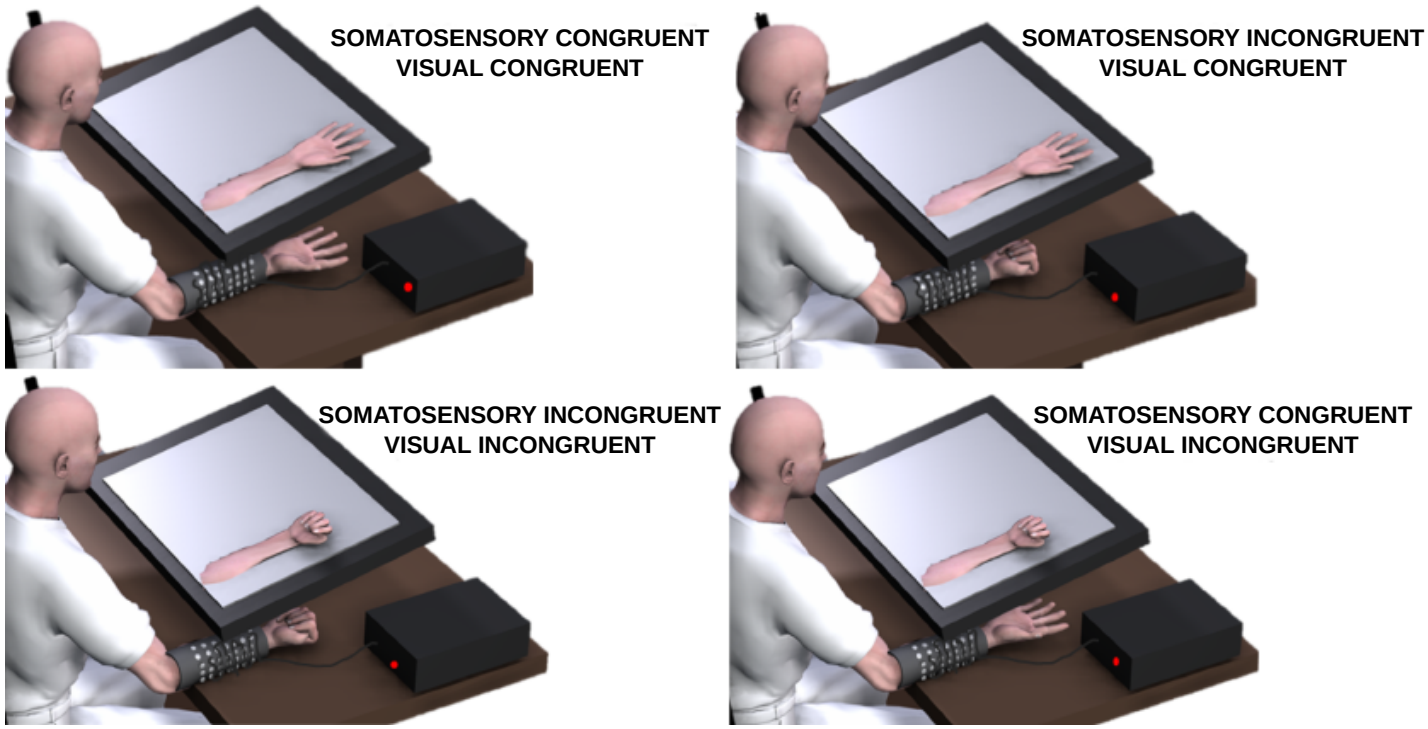
Custom code for neural data analysis and BMI control can be obtained following a written agreement between Battelle Memorial Institute and the requester's affiliated institution. Such inquiries or requests should be directed to: ganzer@battelle.org. Inquiries or requests concerning custom analysis code used for this study should be directed to AS.

A


1s
1s
4s
5s
«Hand open»
«Go»
FEEDBACK
Agency
Confidence
Auditory cues
Action
Subjective agency ratings


Array
Arm movement
Overlap
Target action

B


SOMATOSENSORY CONGRUENT
VISUAL CONGRUENT
SOMATOSENSORY INCONGRUENT
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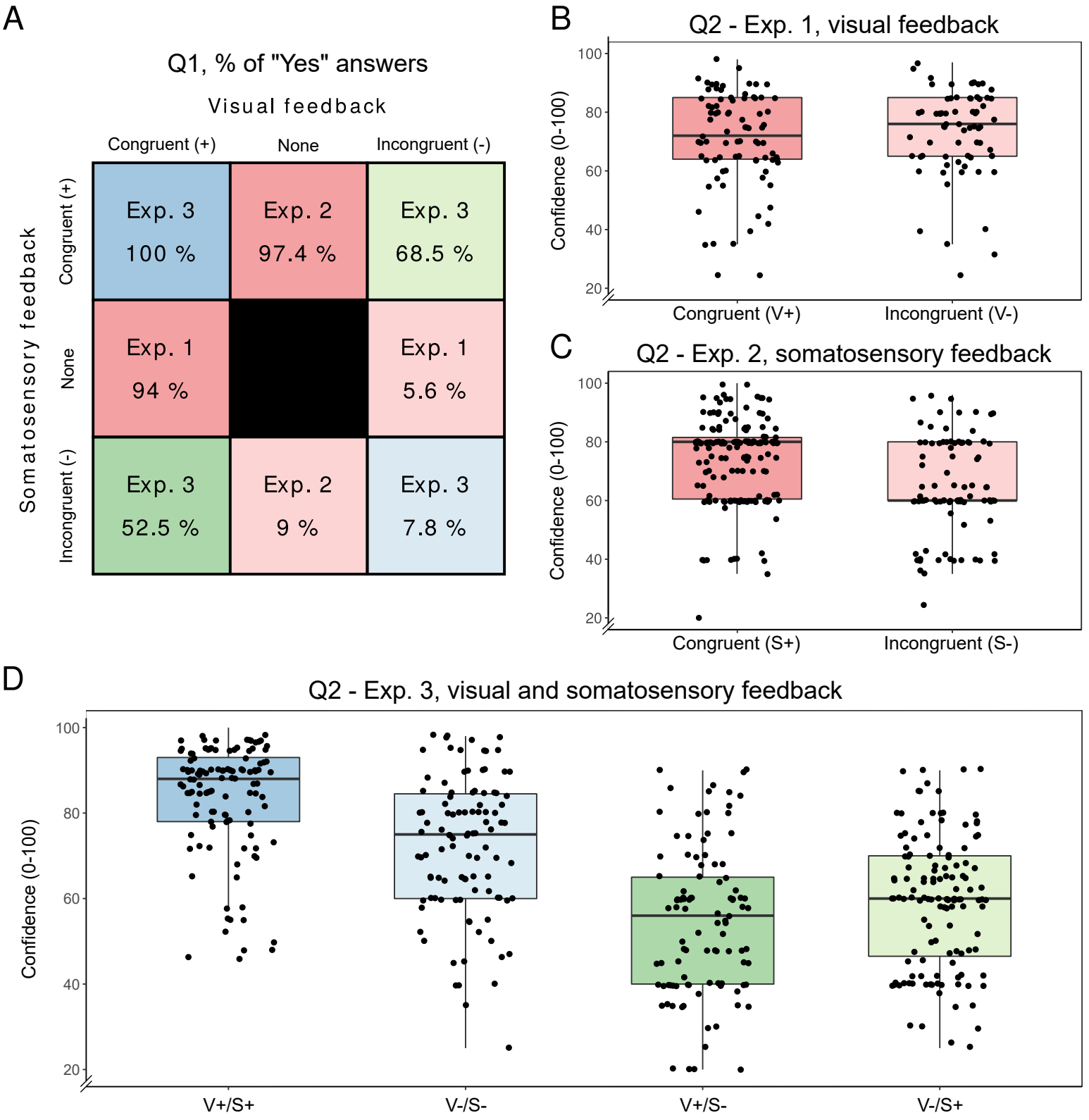
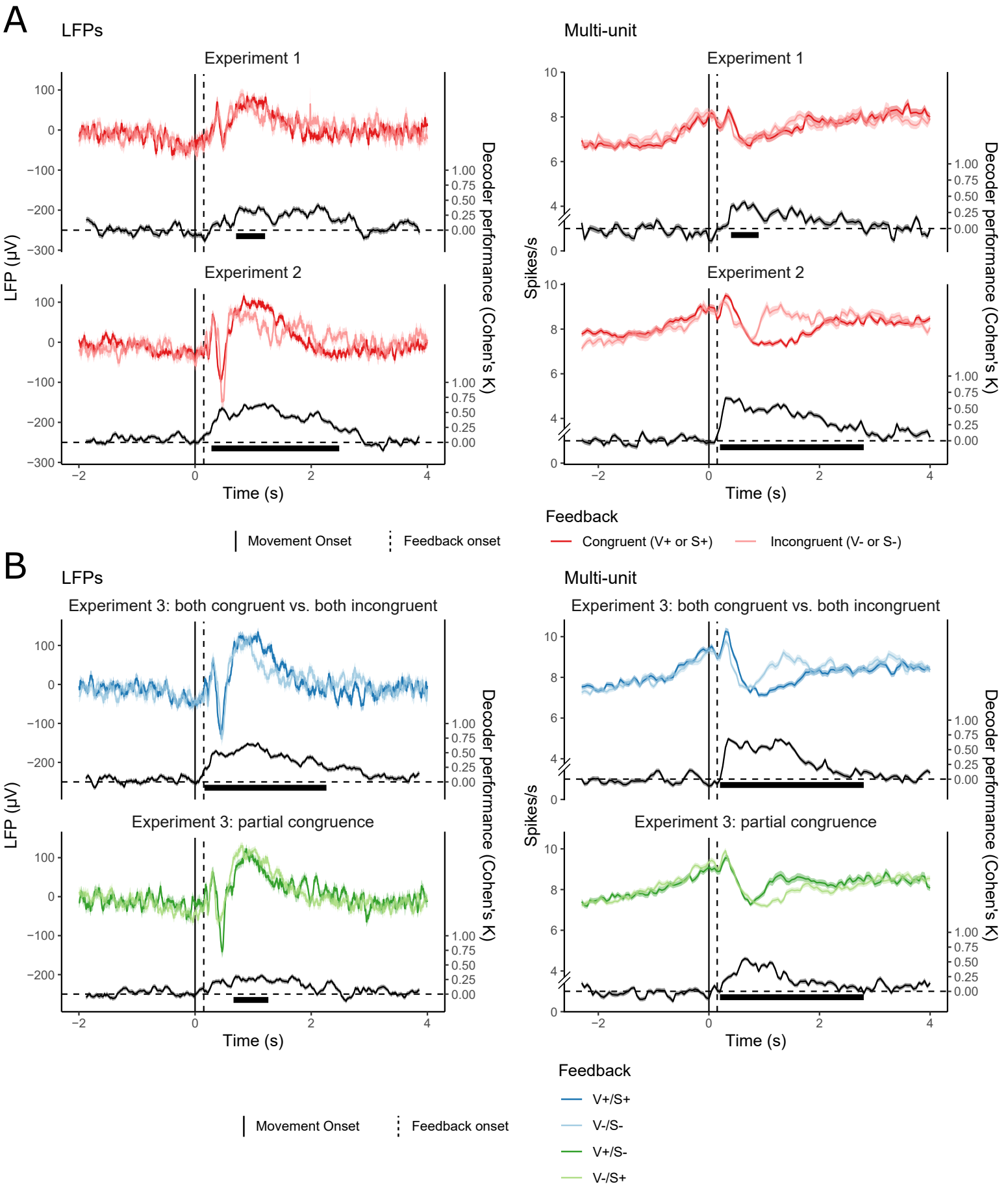
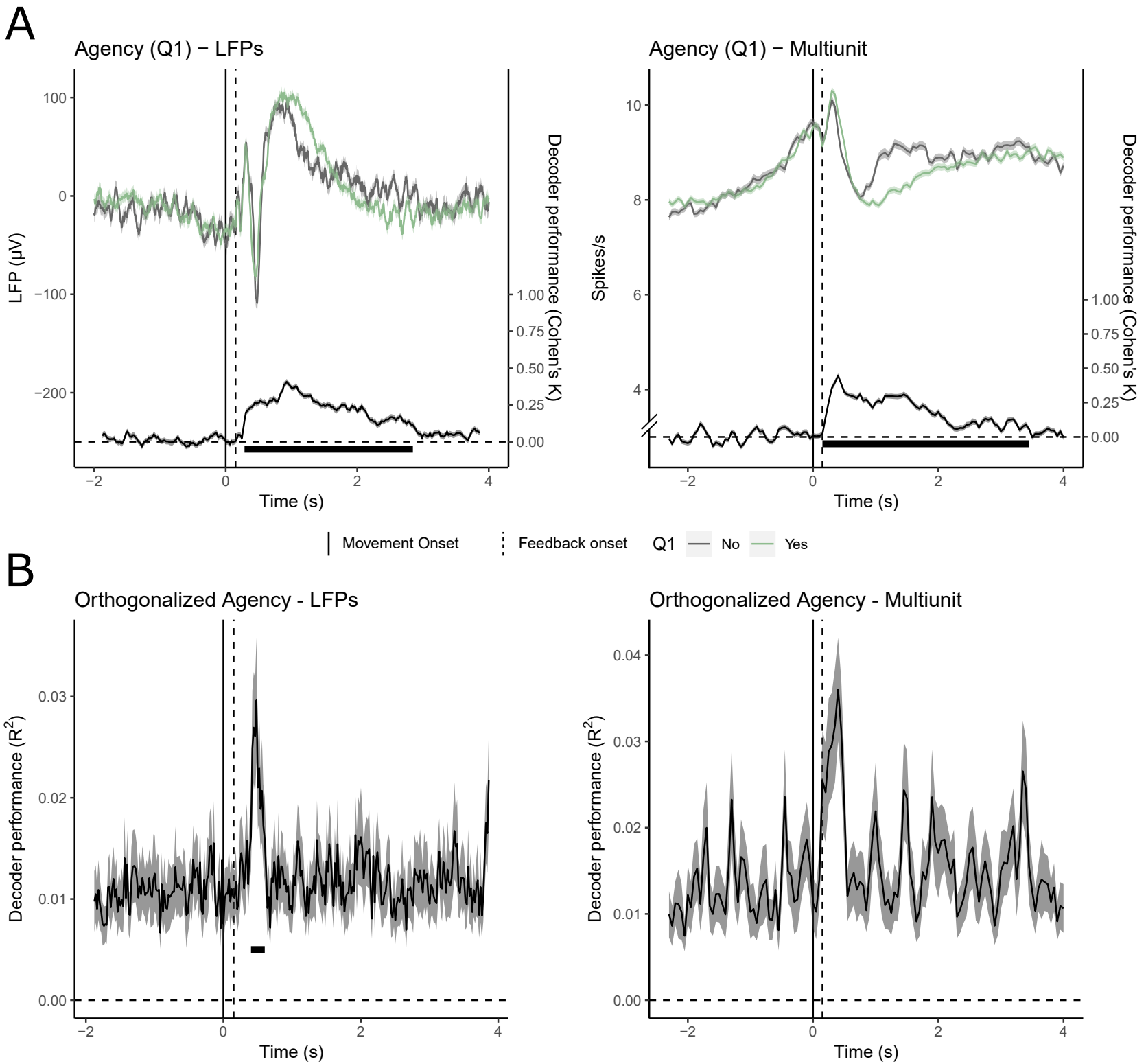
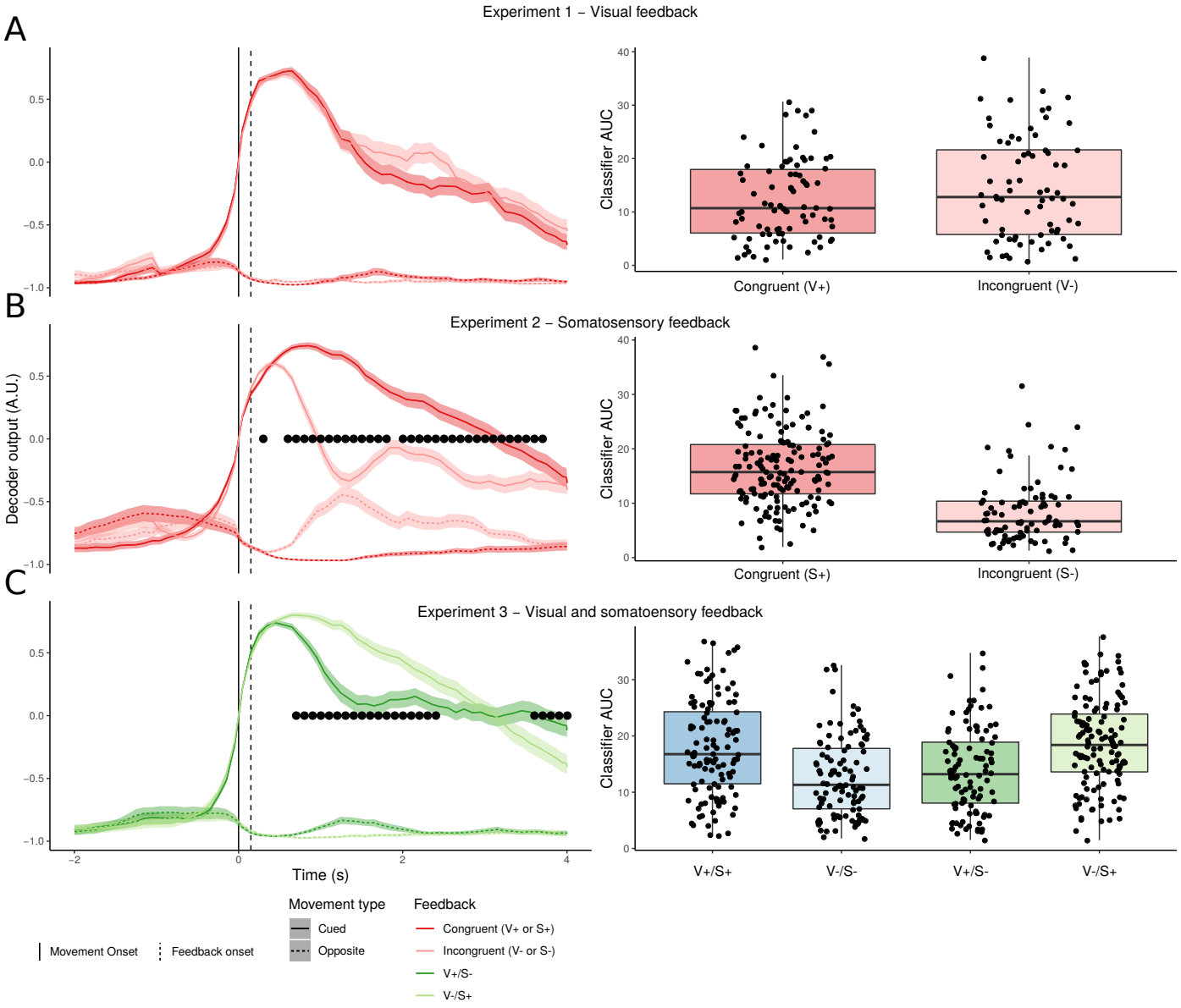
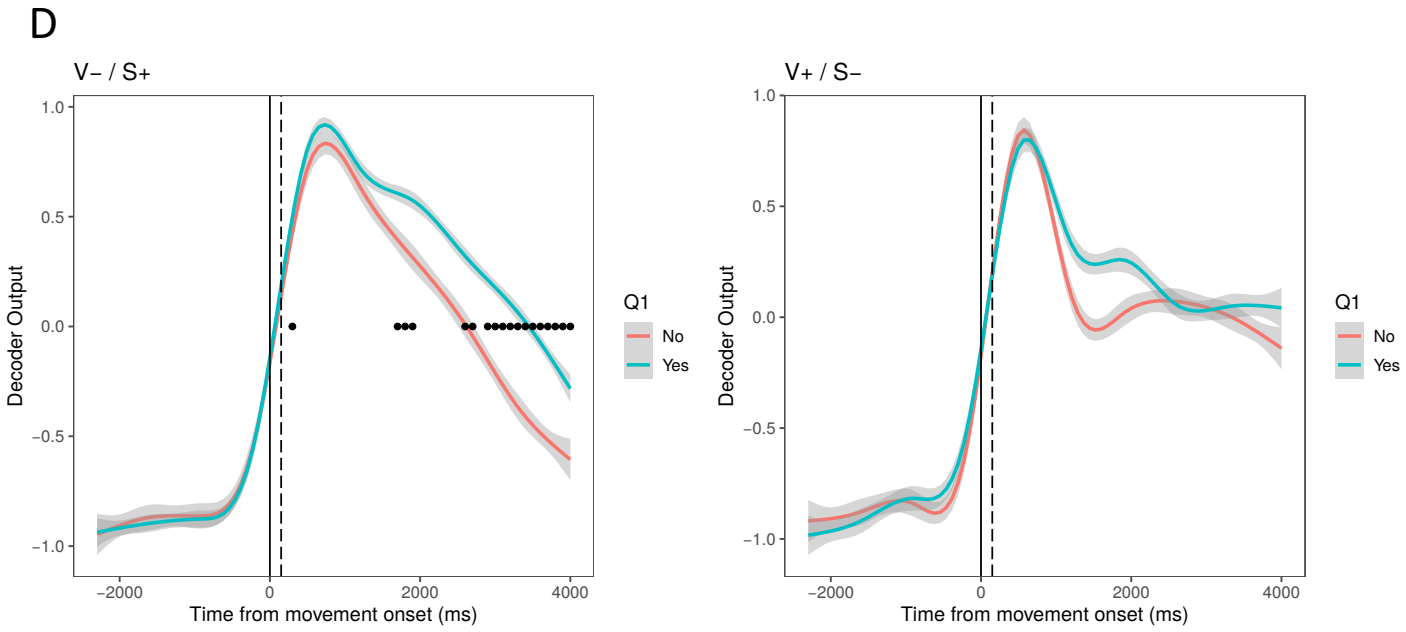
VISUAL INCONGRUENT

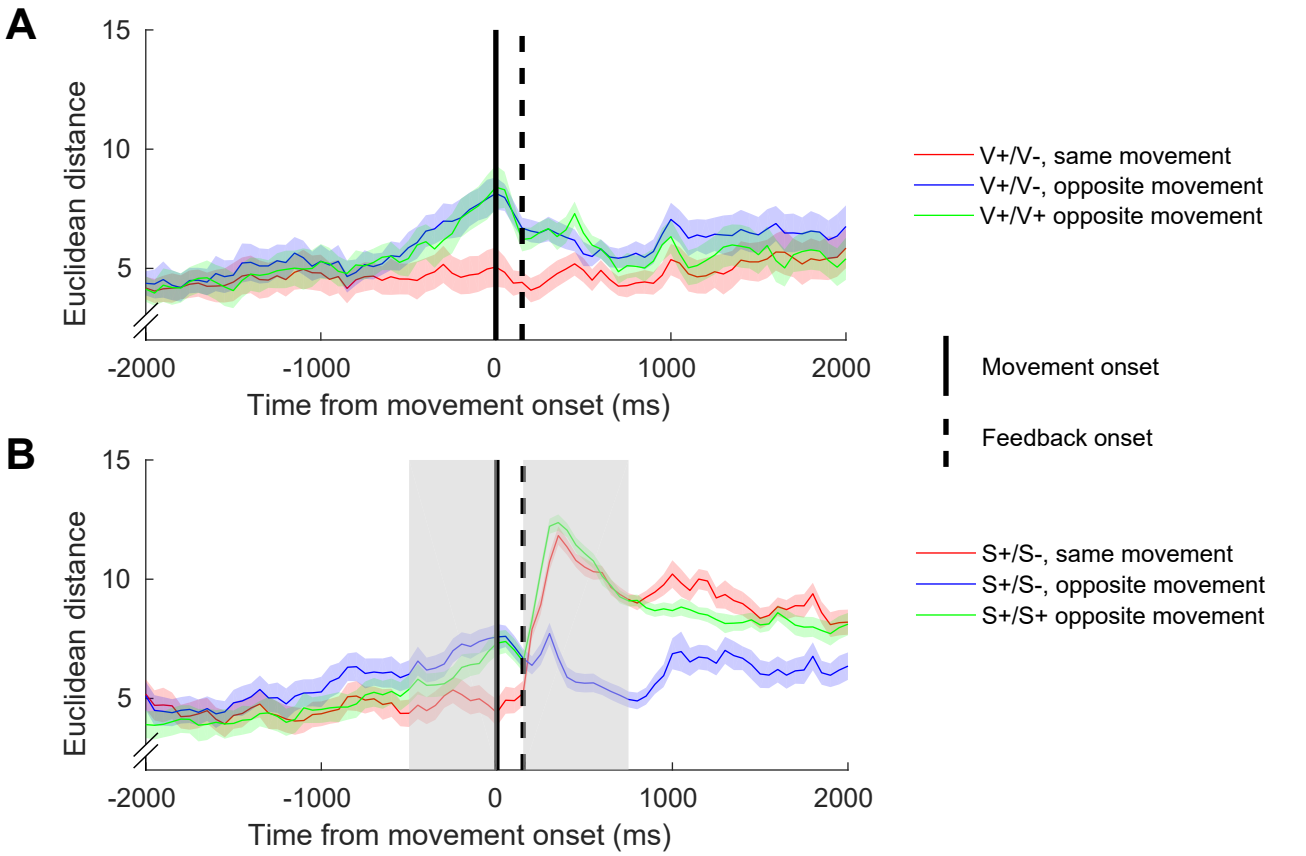

A
Q1, % of "Yes" answers
Visual feedback
Congruent (+)
None
Incongruent (-)
Somatosensory feedback
Congruent (+)
None
Incongruent (-)
Exp. 3
100 %
Exp. 2
97.4 %
Exp. 3
68.5 %
Exp. 1
94 %
Exp. 1
5.6 %
Exp. 3
52.5 %
Exp. 2
9 %
Exp. 3
7.8 %
B
Q2 - Exp. 1, visual feedback
Confidence (0-100)
100
80
60
40
20
Congruent (V+)
Incongruent (V-)
C
Q2 - Exp. 2, somatosensory feedback
Confidence (0-100)
100
80
60
40
20
Congruent (S+)
Incongruent (S-)
D
Q2 - Exp. 3, visual and somatosensory feedback
Confidence (0-100)
100
80
60
40
20
V+/S+
V-/S-
V+/S-
V-/S+

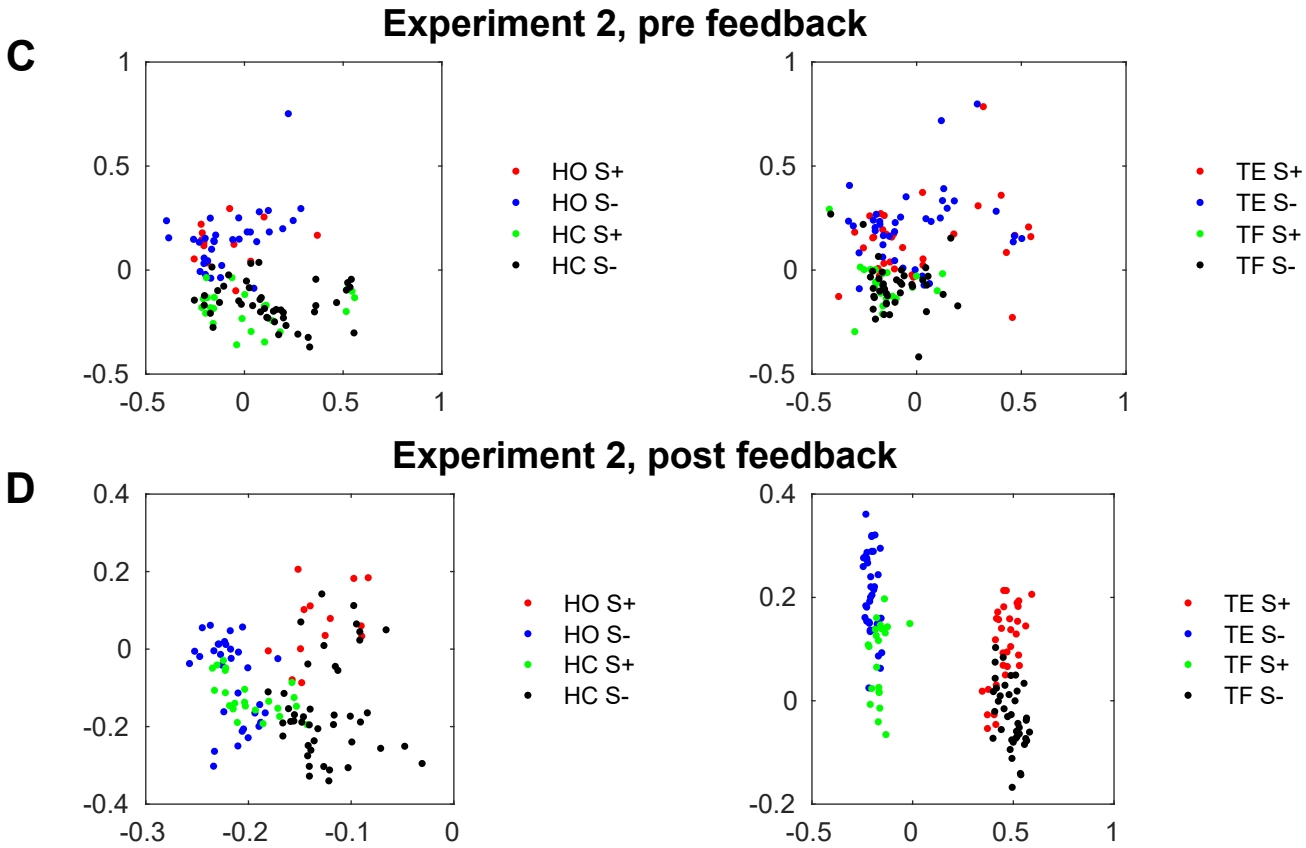

A
LFPs
Multi-unit
Experiment 1
Experiment 2
LFP (μV)
Spikes/s
Decoder performance (Cohen's K)
Time (s)
Movement Onset
Feedback onset
Feedback
Congruent (V+ or S+)
Incongruent (V- or S-)
B
LFPs
Multi-unit
Experiment 3: both congruent vs. both incongruent
Experiment 3: partial congruence
Feedback
V+/S+
V-/S-
V+/S-
V-/S+


A
Agency (Q1) − LFPs
Agency (Q1) − Multiunit
LFP (μV)
Spikes/s
Decoder performance (Cohen's K)
Time (s)
Movement Onset
Feedback onset
Q1
No
Yes
B
Orthogonalized Agency - LFPs
Orthogonalized Agency - Multiunit
Decoder performance (R^2)
Time (s)


A
Experiment 1 – Visual feedback
Classifier AUC
Congruent (V+)
Incongruent (V-)
B
Experiment 2 – Somatosensory feedback
Decoder output (A.U.)
Classifier AUC
Congruent (S+)
Incongruent (S-)
C
Experiment 3 – Visual and somatoensory feedback
Classifier AUC
V+/S+
V-/S-
V+/S-
V-/S+
Time (s)
Movement type
Cued
Opposite
Feedback
Congruent (V+ or S+)
Incongruent (V- or S-)
V+/S-
V-/S+
Movement Onset
Feedback onset


D
V– / S+
V+ / S–
Decoder Output
Time from movement onset (ms)
Q1
No
Yes


A
B
Euclidean distance
Time from movement onset (ms)
V+/V-, same movement
V+/V-, opposite movement
V+/V+ opposite movement
Movement onset
Feedback onset
S+/S-, same movement
S+/S-, opposite movement
S+/S+ opposite movement


Experiment 2, pre feedback
C
HO S+
HO S-
HC S+
HC S-
TE S+
TE S-
TF S+
TF S-

Experiment 2, post feedback
D
HO S+
HO S-
HC S+
HC S-
TE S+
TE S-
TF S+
TF S-