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KEEP AN EYE ON IT: REPRESENTATION OF EYE MOVEMENTS IN THE SENSORIMOTOR CORTEX

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ABSTRACT: The Utrecht NeuroProsthesis system is a fully implanted electrocorticographic (ECoG) Brain-Computer Interface (BCI) that aims to provide independent control of a computer to people with locked-in syndrome. An incidental finding of the study showed that goal-oriented eye movements generated patterns of activity in the primary motor cortex (M1) that were similar to those elicited by attempted hand movement. In order to examine the overlap between eye and hand representation in M1 we compared responses elicited by both movements using ECoG and electrical cortical stimulation in epilepsy patients, and functional magnetic resonance imaging in healthy volunteers. Results from all modalities showed indications of eye movement-related activity in M1, but not consistently across subjects. Even though this overlapping representation is not a universal feature, the occurrence of eye-movement related activity in the M1 hand area bears relevance for refining the user-specific accuracy of BCI applications in people with severe paralysis, especially in cases where eye movements are (also) used to communicate.

INTRODUCTION

The aim of the Utrecht NeuroProsthesis (UNP) project is to develop viable BCI implants that provide individuals with locked-in syndrome (LIS) with a means of independent communication (www.neuroprosthesis.eu). The UNP implant employs electrocorticography (ECoG) arrays placed directly on the surface of the cortex. The first UNP participant was implanted with electrode strips over the hand region of the sensorimotor cortex (SMC) as well as over the dorsolateral prefrontal cortex [1]. By attempting to move her right hand, the participant is able to generate reproducible patterns of brain activity in the SMC. These activity patterns are used to extract signal features for generating ‘brain clicks’, which the participant uses to independently control a spelling program.

The participant has been successfully using the UNP BCI system for communication at home, supplementing and at times replacing the eye tracker she uses for communication as well. Interestingly, it was found that during the use of the eye tracker the goal-directed eye movements generated unintentional brain clicks in the UNP system. While there are several cortical areas associated with eye movements, such as the frontal eye field (FEF), supplementary eye field (SEF) and the parietal eye field (PEF), none of these are conventionally described to involve the primary motor cortex (M1) [2]. The observation of these ‘false positives clicks’ raised, therefore, the questions *whether the representation of eye movements in the M1 is a universal feature* and *if there is an overlap between the cortical representations of the eyes and hand in this region.* Answering these questions is important for understanding the mapping of cortical activity and refining the UNP system in order to improve its accuracy by reducing interference. Hence, in this study we used three neural signal recording modalities to address these questions, namely ECoG, electrical cortical stimulation (ECS) and functional magnetic resonance imaging (fMRI), all with a separate group of participants.

MATERIALS AND METHODS

All participants gave informed consent to participate in this research, which was approved by the Medical Ethical Committee of the UMC Utrecht in accordance with the Declaration of Helsinki (2013).

ECS and ECoG

The clinical ECS records of 34 epilepsy patients (14 female, mean age 28.4 ± 11.7) were investigated. Reports of eye movement responses elicited by electrical stimulation of the SMC using ECoG electrode arrays were collected. Mapping was performed by applying brief currents to neighboring pairs of electrodes using an IRES 600 CH electrical stimulator, with similar clinical settings to those described in [3]. For each electrode pair, all behavioral responses to the stimulation were noted by a trained clinician. Only data of patients with an electrode grid coverage that included the SMC was used. For the cases where eye movement responses were found in or close to the M1 region of interest, the associated electrodes were plotted on a

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reconstruction of the cortical surface and compared to the location of ECS *hand* responses. The localization of the electrodes was determined using a combination of cortical surface reconstructions based on pre-operative structural MRI scans and post-operative CT (computed tomography) scans, as described in [4-5]. Additionally, in order to provide a comparison and assess the degree of overlap between eye and hand representations on M1, the ECS results were compared with ECoG activity elicited during a hand motor task performed by the same patients. For that, ECoG data acquired during the hand motor task was filtered to remove 50 Hz noise. Channels with extremely poor-quality signal were excluded from the analysis. Signed R^2 values for the active versus rest condition in the high-frequency range 60-130 Hz were plotted on the cortical surface reconstructions. The high-frequency band (HFB) was chosen as a target for the analysis due to it being part of the control signal of the UNP participant [1] as well as for its known relevance for cortical activation [6-7].

High-Density ECoG

Data from one patient (E1, female, 31 years old) temporarily implanted with subdural ECoG grids for removal of the focus of epilepsy was used. The subject was also implanted with a high-density (HD) ECoG grid over the sensorimotor cortex (PMT Corporation, MN, USA; 4 mm inter-electrode spacing, sampled at 2000 Hz). We defined an ROI for the M1 hand region based on anatomical landmarks. E1 performed one eye movement and one finger movement localizer task with 15 s blocks of rest and active conditions (10 trials in total). In the active condition of the eye localizer the subject was asked to follow a red circle moving along the edges of a square with her eyes. The target circle could start in any of the corners of the square and move in either clock- or counter-clockwise direction. The active trials of the finger localizer consisted of continuous finger tapping movements. Data were processed in similar way as described in the previous section.

fMRI

Ten healthy (F1-10), right-handed volunteers participated in the study (6 female, mean age 26.9 ± 10.7). The fMRI scanning was carried out using a 7 Tesla Philips Achieva MRI system (Philips Healthcare, Best, Netherlands). Participants performed an eye-movement task while fMRI data was acquired using an Echo Planar Imaging (EPI) sequence. The fMRI task employed a different paradigm than the ECoG tasks, in that an event-related design was used instead of a block design. The participants were instructed to fixate on a target at the center of the screen. Once every 10.5 s, the target moved upwards, downwards, to the left or to the right (32 trials in total). When this happened, the subject had to execute a saccade to fixate on the target at the new position. Additionally, the subjects performed a hand localizer task, from which movement of all fingers (against rest) was used to look for overlap between hand and eye activation. fMRI data was preprocessed using standard protocol and co-registered to the T1-weighted anatomical scan of the participant. FreeSurfer (https://surfer.nmr.mgh.harvard.edu/) was then used to create a surface reconstruction based on the anatomical images. First level statistics were carried out using SPM12. A custom procedure called CGRID was employed to visualize the results and facilitate between-subject comparisons [8]. CGRID transforms the flattened surface reconstructions of the SMC into a grid of 84 x 28 tiles with standardized x- and y-coordinates. In this grid an ROI corresponding to the M1 hand area which consisted of 210 tiles.

RESULTS

ECS and ECoG

Eye responses to stimulation of M1 were present in some subjects. Of the 34 clinical ECS records available for analysis, 10 contained reports of eye-related motor or sensory responses. Of these, only 3 reports described eye-related responses in the proximity of the region of interest (Figure 1). One individual had eye responses close to M1 but with no overlap with hand movement. Two individuals had eye-responsive electrodes exactly on M1 and partly overlapping with electrodes that elicited hand movement during stimulation. One of these subjects (S3) also showed overlapping with electrodes that showed significant HFB power changes during the finger tapping localizer task.

High-Density ECoG

For subject E1, multiple electrodes on M1 responded to the eye task with high and significant signed R^2 values (Figure 2). Many of these electrodes were located on M1, even partly overlapping with electrodes that showed increases in HFB activity in response to a hand movement task. A total of 7/42 electrodes in the M1 ROI with signed R^2 values > 0.25 ($p < 0.05$) in response to the eye task also had HFB increases in response to the hand task with at least $R^2 > 0.25$ ($p < 0.05$).

fMRI

Movement of the fingers elicited clear and recognizable patterns of activity in the contralateral SMC, with the majority of activity increases in M1 being observed in the hand area, located relatively high on M1 (Figure 3). While the responses to eye movements were variable, in most subjects increases in activity were observed in either the hand region or very near it. Furthermore, in some subjects, such as F1, F3 and F7, more than 20% overlap between the eye and hand activation was present, measured as the number of tiles with both eye and hand activity out of all active tiles. Even in the case of F2, F5 and F6, who had little or no actual overlap, distinct regions of eye and hand activation in the ROI were present in close proximity to each other. On average, out of the total active tiles in the ROIs of all participants, 12% had overlap, while 25% were exclusively eye-responsive (Figure 4).

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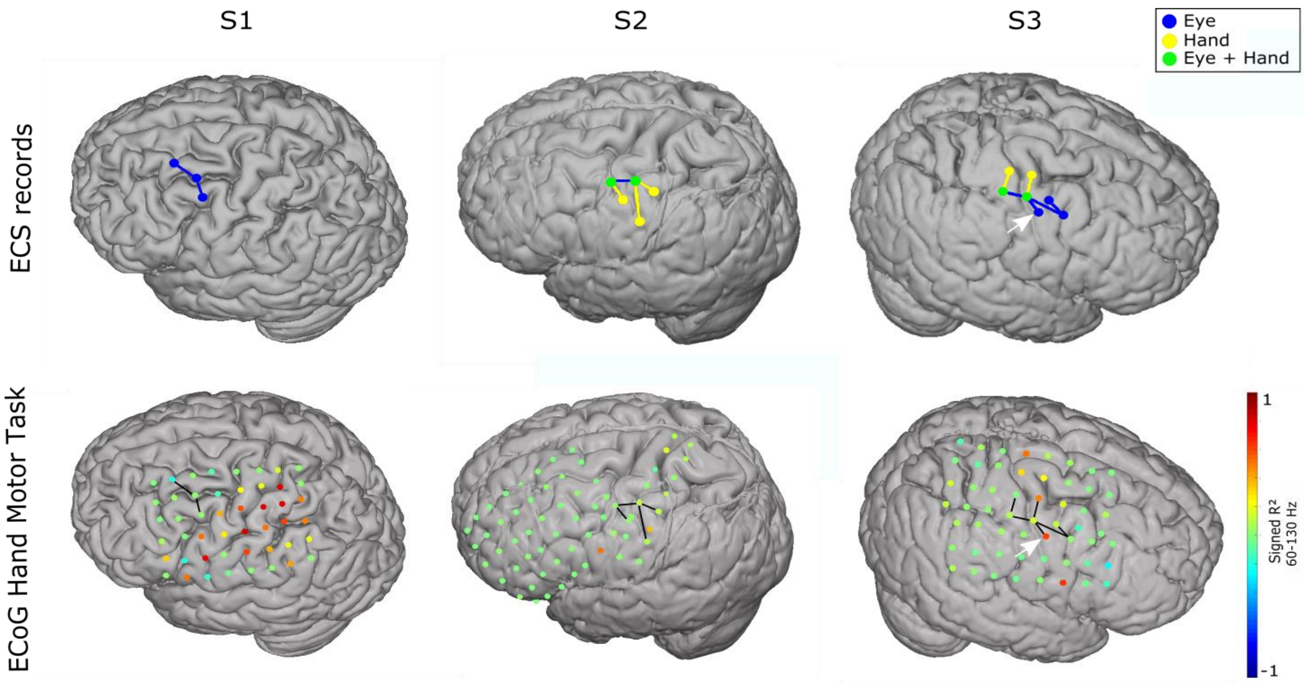

Figure 1: Top row - three of the investigated clinical ECS records (coded S1, S2 and S3) contained reports of eye responses (sensation for S1, movement for S2 and S3) in response to electrical stimulation of the SMC near the M1 hand region. These electrodes are plotted on the cortical surface reconstructions of the specific patients. Pairs of electrodes with eye-related responses are connected by blue lines, whereas yellow lines indicate pairs associated with hand responses. Electrodes that were associated with both eye and hand responses are coloured green. Bottom row - the signed R^2 values for the 60-130 Hz frequency band from an ECoG hand motor task of the same patients. The electrodes of interest (based on the ECS results) are connected by black lines. One electrode of S3 showed both eye ECS responses and ECoG responses to a hand task (white arrow).

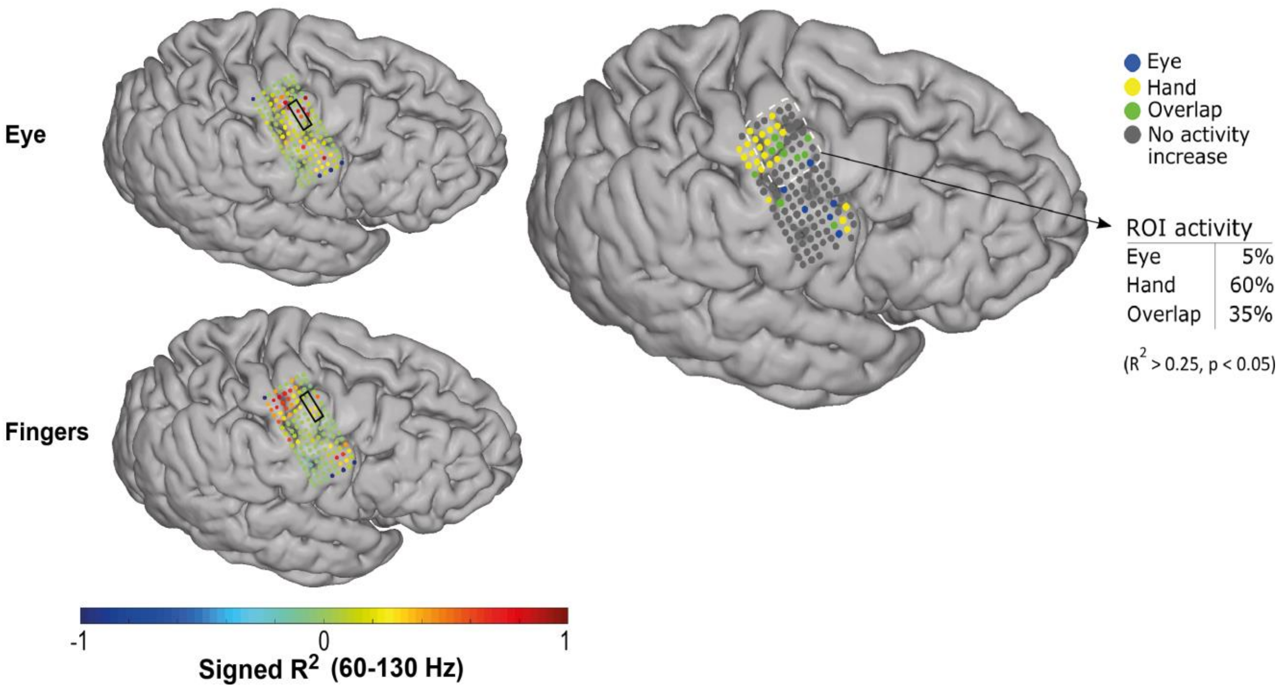

Figure 2: HD-ECoG grid plotted on a surface reconstruction of the cortex of E1 (Left column). Each electrode is color-coded with its signed R^2 values (HFB; 60-130 Hz) during an eye movement task (top-left) or a finger movement task (bottom-left). Electrodes that had a significant $R^2 > 0.25$ for the eye task, finger task or both were plotted onto the surface reconstruction of the subject's cortex (right). The hand region ROI is outlined by white dashed lines and contained 42 electrodes. Of the 20 active electrodes, 35% contained overlap between eye and hand responses. 60% were activated exclusively by the hand task, while one electrode (5%) showed an activity increase only during the eye task.

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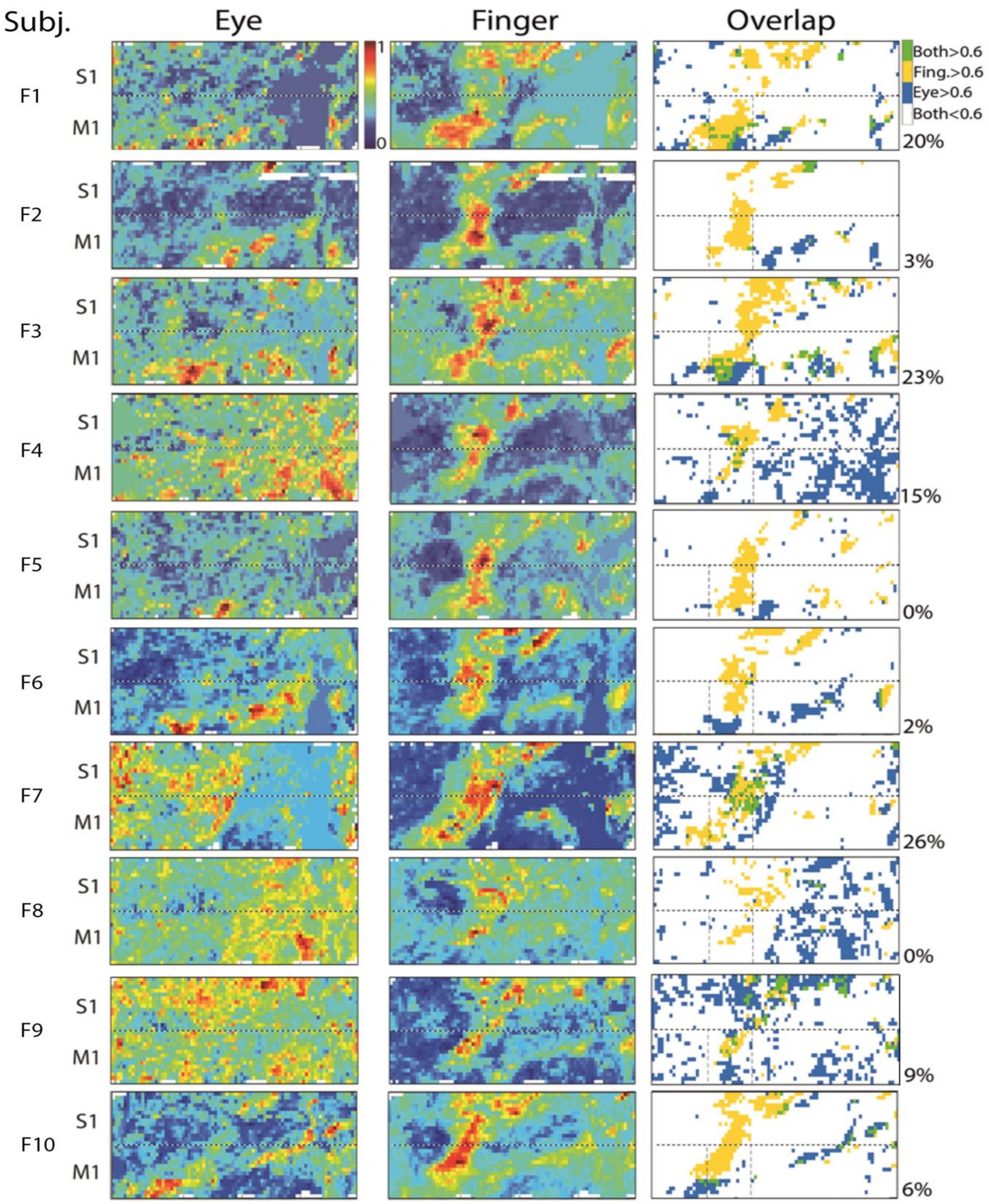

Figure 3: The complete CGRID maps of all 10 fMRI subjects. Dorsal direction is to the left on the panels. The three columns visualize the maps of eye movement activation, contralateral hand movement activation and the overlap between the two, respectively. The t-maps to be mapped on the CGRID were normalized between 0 and 1, and 0.6 was set as a threshold for a tile to be considered active. Blank tiles in the actual CGRID maps are tiles that were excluded in order to conform to the shape of the CGRID. In the overlap maps, the ROI is outlined by dashed lines. The percentage of overlapping tiles out of the total number of activated tiles within the ROI is given as a percentage to the right of the overlap maps.

DISCUSSION

Overlap between hand and eye activity

An incidental finding in the first participant of the UNP project showed that goal-directed eye-movements elicited similar activity to that elicited during attempted hand movement. Here, we used three neural signal recording methods to assess whether this finding was an isolated case or a general feature of the SMC. Overall, we found evidence of eye movement-related activity in the M1 hand area, although not consistently across subjects.

The results of the fMRI study were likely the most

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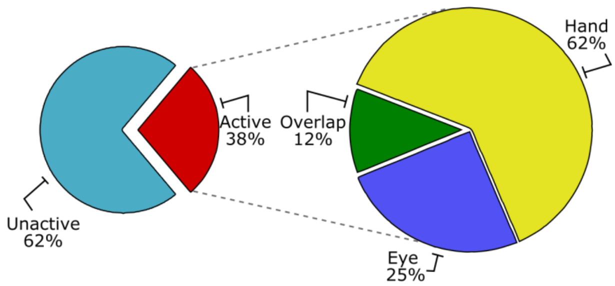

Figure 4: Percentage of tiles inside the ROI that were active during both eye and hand task (out of 210) averaged across subjects. From the active tiles, 25% were activated by eye movement only and 12% were activated during eye and hand movement.

convincing of the three methodologies and were able to demonstrate eye movement-related activity in M1 in multiple subjects. However, for a few of the subjects the peak t-values for the activity increases in response to the eye task were somewhat lower than might be expected, resulting in more scattered activation maps, likely due to noise. This is largely explained by the fact that event-related designs elicit shorter neuronal activation and result in lower t-values than block designs due to the intrinsic slow temporal resolution of the fMRI recording. In the future, a block design may be an interesting consideration that may further increase the robustness of the results obtained. The limited ECS outcome could be explained by the fact that the records that were investigated were diagnostic recordings, not experimental ones. The clinicians making the records may not have focused on the eyes as much as, for example, on the movement of the limbs. The number of subjects implanted with HD-ECoG grids covering the region-of-interest and who performed the eye localizer task was very limited (one subject). In the future, the results of the ECS and ECoG measurements should be replicated in more subjects in order to establish the prevalence of this finding.

The functional boundary of the FEF

Literature typically associates the frontal eye fields (FEF) with the generation of eye movements. The FEF is generally located around the intersection of the superior frontal sulcus and the precentral sulcus, which is in the proximity of M1. As an area, it is defined by its capacity to generate eye movements in response to stimulation or to display activity increases during the execution of eye movements [9]. Due to this functional definition, it does not have strict anatomical boundaries. In humans, it is generally described to be located frontal to the SMC, with some studies also describing it extending to M1 [10-12]. The high degree of variability in the localization of eye movement-related responses around the area of interest reported by the diverse studies (Figure 5) is in line with the results here found with ECS, ECoG and fMRI.

Inter-individual variability

While the small sample size in the current study prevents measuring the prevalence of overlap between eye and hand representation in M1, the results so far strongly indicate that such overlap is present in some individuals. If, indeed, the degree of eye representation on M1 is something that varies greatly from one person to another, it could help explain why it is not discussed in literature at large, but it also begs the question why such inter-individual variation exists. While disease-related neurophysiological phenomena and neural plasticity induced from BCI feedback training could help explain the results of the UNP participant, especially when considering that ALS is known to influence the arrangement of cortical representations [13], the fact that similar results were also found in subjects without the condition make this explanation insufficient. As such, the presence of eye-hand overlap found on the motor cortex in the UNP participant could not be explained solely by disease-related changes in cortical function representation.

CONCLUSION

In this study, we investigated the possible overlap between the eye and hand representations in the primary motor cortex using three methodologies. Results show that eye movements activate patches of M1 very close to or overlapping with the hand region. Due to the variability of the results, it is proposed that such overlap exists in the overall population but its presence and extent vary greatly on an individual basis. Based on existing literature it is likely that the eye representation in question belongs to the FEF extending beyond its conventionally defined borders. Further research into the phenomenon is encouraged in order to gain an understanding of its localization as well as the potential effects of eye movements on BCI signal acquisition from the SMC. This will help inform the implantation procedure for BCI systems in order to avoid false positives caused by interference in the signal, therefore improving overall accuracy and usability of its applications.

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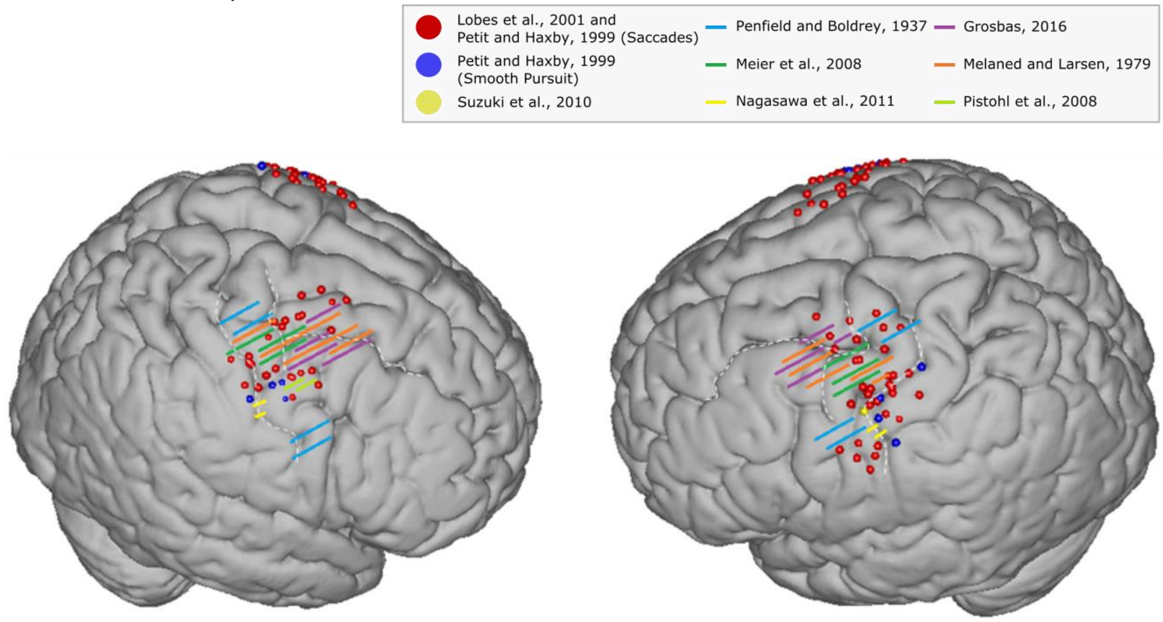

Figure 5: Reports of eye movement-related activity in the vicinity of the SMC found in the literature mapped onto a standardized MNI brain. Spheres correspond to specific coordinates reported in studies, with red coding for saccades, blue coding for smooth pursuit movements and yellow coding for closing and opening of the eye. Striped regions correspond to areas reported in the figures or descriptions of each study. The white dashed lines indicate the central sulcus as well as the precentral sulcus and superior frontal sulcus.

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