Why and how should I track eye-movements during iEEG recordings?

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Abstract

We are visual animals. How we perceive, understand and interact with the world is intimately tied to our visual sense. Yet, the value of monitoring ocular activity in neuroscientific experiments is often overlooked. In this chapter, we set out to highlight how a whole host of ocular phenomena relate to brain function and human cognition, with a special focus on intracranial electroencephalogram (iEEG) recordings. We begin by describing key ocular events, such as saccades and fixations, before discussing the extensive impact these ocular events have on common neural phenomenon and measurable behaviour. Lastly, we provide practical recommendations for combining eye tracking and intracranial EEG in neuroscientific research.

Anatomy and activity of the human eye:

Our eyes serve to receive incoming light, transform said light into tangible information, and project this information towards the central nervous system. The process begins with light hitting the pupil, which is then projected onto a small area of the retina called the fovea. The fovea is capable of extracting a highly-detailed image of whatever the eye is fixated upon (though the size of this image is very small due to the small size of the fovea [~1.5mm; 0.25mm at its most sensitive area]). Complementing the highly-detailed foveal image is a coarser surrounding image generated by the parafovea (a region of the retina that surrounds the fovea). Together, the information extracted by the fovea and parafovea is projected to the central nervous system via the optic nerve. From here, the signal is passed to the occipital cortex via the thalamus, where an image is constructed and then passed across a wide range of brain regions for additional action (e.g., interpretation, response).

Given the limited diameter of the fovea, ocular movements are essential for building a comprehensive image of our immediate environments. Such exploration is principally achieved through rapid, ballistic eye movements known as saccades. Saccades are exceptionally brief (~20-50ms) and involve a ~2-5-degree rotation of the eye from one target to another. Once the eye has made its saccade, it will fixate upon the visual target, allowing key visual details to be extracted by the fovea. The duration of these fixations will vary according to a whole host of factors, including attention, stimulus complexity and current goals, but typically last between 150 and 300ms. Aside from saccades and fixations, the eye can execute other movements, such as smooth pursuits, and fixational eye movements, like tremor, and drift, and microsaccades (see table 1 for details). For the rest of this chapter however, we will principally focus on the influence of saccades and fixations on electrophysiology and cognition.

Table 1. Description of common ocular phenomena [1, 2]

Name	Description
Saccade	A rapid ballistic eye movement that orients the fovea towards the target.
Fixation	A prolonged moment in which the fovea is focused upon a stationary target.
Smooth pursuit	A smooth movement which allows the fovea to follow a moving target.
Vestibular ocular reflex	A movement of the eye that counteracts the movement of the environment incurred by events such as head rotation.
Vergence	Opposing movements of the left and right eyes as a stimulus approaches / moves away.
Drift	A smooth, slow movement incurred during periods of fixation.
Tremor	A small, oscillating movement (~90Hz) incurred during periods of fixation
Microsaccade	A small, rapid jump in eye position incurred during periods of fixation (which may serve to compensate for the drifts described above).

The neural correlates of ocular activity

There are very few aspects of iEEG activity that do not, in some way, shape or form, correlate with oculomotor activity. Whether a researcher is interested in evoked responses, changes in spectral power, phase-locking, rhythmic fluctuations in neural excitation, inter-area coherence or single unit activity, it is essential to account for oculomotor activity induced by our innate tendency to visually explore the local environment. In this section, we will describe how electrophysiological activity changes when a saccade is executed, when this saccade stops and a fixation begins, and when the preparation for the next saccade begins.

The onset of a saccade is accompanied by a rapid spike in electrophysiological activity that is attributable to neural activity associated with the saccade [e.g., 3–5], as well as muscular activity relating to the physical movement of the eyeball [6, 7] (see "*The electro-muscular correlates of oculomotor activity*" below). The neural correlates of saccadic activity arise ~50ms after the saccade onset [3, 8], and are readily observable in measures of local field potential, broadband power, inter-trial coherence, and single unit firing rate [e.g., 3–5, 8–10]. The magnitude of these effects scale with the size of the saccade [8, 9] and appear to be lateralised, with the ipsilateral hemisphere showing a greater saccadic spike potential than the contralateral hemisphere [3]. Importantly, these effects are not only observed in early visual regions; they extend across the entire visual hierarchy, from V1 [e.g., 4] to the hippocampus [5, 9, 10]. Functionally speaking, this spike in neural activity is thought to originate from a corollary discharge (a copy of motor output signals sent across the brain) and serves to reset the ongoing phase of oscillatory signals within the visual system so that incoming information falls upon the most excitable phase for stimulus processing [11, 12]. Moreover, by resetting phase across the entire visual hierarchy (which inherently synchronises neural activity across this network), properties of the viewed stimulus can be readily transferred between regions [13, 14] (this is discussed further in the next section).

At the offset of the saccade, a second ubiquitous electrophysiological phenomenon occurs: the lambda potential [15]. Much like the neural correlates of saccades, this lambda potential arises around ~50ms after saccade offset/fixation onset, and can be observed across the visual hierarchy using a number of different electrophysiological metrics including amplitude, inter-trial phase coherence, and single unit firing rate [12, 16–19]. This response is thought to be related to the influx of visual information [8, 17] - a theory supported by the absence of a

lambda potential when saccades are made in the dark [15], and the fact that the lambda potential appears to be highly similar to the visually-evoked P100 ERP component [20].

In addition to onset and offset potentials, there is evidence to suggest that a number of regions engage in preparatory processes that precede saccades. These pre-saccadic effects present as fluctuations in amplitude, spectral power and phase clustering over the visual cortex [8, 21–23] as well as in frontal regions [24, 25]. Typically, this is thought to be related to motor planning, shifts in attention and a suppression of visual processing prior to this upcoming saccade in order to ensure perceptual stability across the saccade [26, 27]. This suppression, in conjunction with the post-saccadic excitation described above, has been interpreted as a cyclic modulation of excitability across the saccade-fixation cycle [11].

Based on the evidence above, it is clear that the brain is highly sensitive to eye movements, but the neural-ocular link is also observable in the absence of major eye movements. For example, microsaccades correlate with very similar neural responses to the saccades described above, albeit with a smaller magnitude [e.g., 28]. Moreover, pupil dilation that arises when fixating upon emotionally salient stimuli has been linked to fluctuations in amplitude and alpha/beta power [29]. In other words, even in absence of major oculomotor activity, the eyes continue to exert a noticeable influence over electrophysiological activity.

In sum, there is an extensive link between ocular and electrophysiological activity that can be observed across the brain, using many different signal processing techniques, and are sustained (in one way or another) across the fixation-saccade cycle. Given that patterns of ocular activity cannot be fully suppressed (that is, even the most well-trained participant will occasionally make a saccade), it is wise to assume that ocular activity will influence iEEG recordings under almost any circumstance. As such, one needs to consider how to account for this, and how it may interact with other variables of interest, such as behaviour.

A note on the electro-muscular correlates of oculomotor activity

Unlike scalp EEG and MEG recordings, iEEG recordings are thought to be largely unaffected by muscular artefacts induced by eye movements, owing to the local, intracerebral nature of iEEG recordings. However, this is not always the case. Saccade-related muscular artefacts can be observed in intracranial recordings taken from numerous brain regions [7]. These effects are most prominent in the temporal pole, which neighbours extraocular muscles (namely, rectus lateralis [30]). While some of these effects have been attributed to the choice of re-referencing (with a scalp-based reference producing the greatest artefact), even bipolar-referenced recordings used in conjunction with independent components analysis cannot fully correct for such artefacts [7]. Consequently, researchers should be aware of saccade-related artefacts in intracranial recordings when interpreting their results and, wherever possible, use direct measurements of ocular activity to address the possibility of such a confound.

The functional roles of eye movements for brain function and behaviour

As alluded to above, the neural correlates of ocular activity are not epiphenomena; rather, they exert a profound influence over brain function and behaviour. In this section, we give two examples of how eye movements influence brain function and behaviour, and then highlight several key resources relating these eye movements to various psychological constructs.

Eye movements map visual space

Eye movements can be viewed as a window to cognitive processes [31] and accounting for them has been shown to reveal valuable insights into fundamental cognitive processes. One

particularly impressive example pertains to the neural correlates of spatial navigation across different species, and the implications different exploration strategies in these species might have for the coding of space. Seminal research in rodents discovered place cells, head directions cells and grid cells and identified them as the major pillars underlying navigation and memory [32–34]. The quest to discover cells in primates that show analogous spatially tuned firing patterns has long been difficult (but see [35, 36]). Instead, what has been consistently found in primates are cells that code for visual space. That is, neurons in the monkey hippocampus fire with respect to where the animal is looking, rather than where the animal is located in space [e.g., 37]. A variety of gaze dependent firing patterns have been found in neurons located in the primate medial temporal lobe, some of which closely resemble their rodent counterparts (e.g., visual grid cells, saccade direction cells and visual border cells), but also cells that code for multiple aspects of visual and other spaces [38–40]. Considering the primacy of vision among primates' senses and the extent to which primates use vision to explore their environment, it seems clear that cells code essential features of visual space to build a cognitive map. In humans, single neurons coding for visual space have not yet been identified, but brain activity exhibiting grid-like coding of visual space has been shown with fMRI, MEG and iEEG [41–43].

Eye movements align brain rhythms

While exploring the visual environment, we rapidly move our eyes, shifting the fovea centralis from one location to another. During saccadic eye movements, neural activity is suppressed and perception is reduced, while during fixation periods in between saccades, neural activity is enhanced [44]. Saccades typically occur at a frequency of 3-4 Hz during visual exploration (with slight variations depending on the task). Each saccade interrupts the flow of visual input, making our perception of the visual world rhythmic rather than continuous. Our brains, however, compensate for the perceptual gaps during saccades and create the illusion of a continuous stream of visual input [e.g., 45, 46]. The quasi-periodicity of saccades thus produces temporal windows during which novel visual input arrives in the brain and excites both visual and non-visual areas. The brain itself also relies on temporal windows during which neural processing is favourable, located between periods when processing is impeded or even impossible which can range from a few milliseconds (e.g., refractory periods in neurons) to several hundreds of milliseconds (e.g., down-states during slow wave sleep). Brain oscillations are a prominent example of these rhythmic temporal windows, or duty cycles, defined by the phase of the oscillation. Much of the functionality ascribed to brain oscillations lies in the very fact that they provide a window of opportunity for (ensembles of) neurons to fire coherently and, thus, enable coordinated processing and communication of information [47]. Therefore, an optimised strategy to process and communicate incoming visual information would be to align one temporal window to the other, such that new input arrives during the duty cycle. At least two steps are necessary to achieve this: (1) The system needs to be able to predict upcoming temporal windows, and (2), the system needs to adjust one (or both) of the temporal windows according to the prediction.

A temporal prediction of when windows for novel visual input will occur can be made on the basis of efference copies. Efference copies are copies of the motor commands that the brain sent to produce the movement (also called corollary discharge). Whenever the brain sends a motor command towards the periphery to execute a movement, a copy of this command is kept within the system. The information about the imminent movement can then be used to prepare the brain and potentially modulate the state of a network such that it is optimised for when the predicted movement happens. Consequently, efference copies usually target brain circuits interpreting sensory inputs and are particularly important for distinguishing self-generated movements from changes in the external world. In the case of saccades, this is particularly striking: whenever we move our eyes, the image on our retinas moves in the opposite direction. However, the brain predicts and compensates for the movement in the physical world to provide a stable internal representation [27]. The neural foundations of eye movement related efference

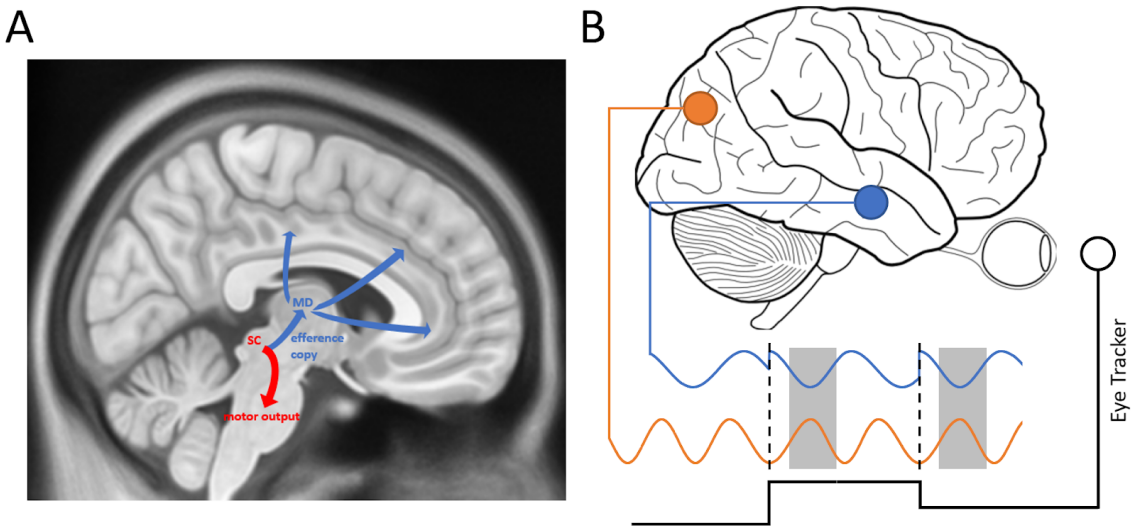


Figure 1. Saccade-triggered phase alignment of brain rhythms. (A) Superior colliculus (SC) neurons send a motor command which is branched off to the mediodorsal thalamus (MD), signalling an upcoming saccade (efference copy). (B) Sketch of the proposed model. Simultaneous recording of eye movements (black lines) and iEEG from multiple brain areas (blue, orange). To prepare for processing and communication of the incoming stimulus, the phases of brain areas are aligned to the saccade (but it is also plausible to suggest that saccades align to brain rhythms). Shaded areas depict duty cycles of the respective brain rhythms. Dashed lines depict saccade onsets. Specific phase angles and brain areas are chosen for clarity purposes and not based on real data.

copies have principally been investigated in non-human primates [e.g., 48]. Cortical areas, in particular the frontal eye fields, send a motor command to the superior colliculus which is conveyed downstream to lower motor areas. An efference copy is sent from the superior colliculus to the mediodorsal thalamus, which holds information about the onset and direction of the upcoming saccade (see figure 1a). This information is provided to the frontal eye fields via thalamocortical neurons. Providing essential information about impending (motor) behaviour has been suggested to be one of the fundamental roles of thalamocortical loops [49] and could be a fundamental mechanism to predict an upcoming temporal window during which new input arrives.

With the system primed for an upcoming eye movement, neural activity now needs to be modulated to synchronise peak excitability with the eye movement. A potential mechanism to adjust windows of excitability according to the prediction based on an efference copy is the alignment of low frequency oscillatory phase. Such low-frequency phase-alignment has been demonstrated to co-occur with saccades in humans as well as non-human primates [9, 10, 17, 50] and linked to prioritised cognitive processing [5, 51]. Phase alignment is not necessarily limited to a single ensemble of neurons, but might, instead, be a feasible tool to organise functional networks across many brain areas [52]. In order to make this work, efference copies would need to be distributed to and induce phase alignment in multiple brain regions (which is feasible considering the widespread projections of the thalamocortical system). A coordinated alignment of low-frequency phase on a global level could set the stage for efficient neural communication [13, 47]. Recent findings combining intracranial recordings and eye tracking support this idea by showing enhanced connectivity related to saccade onset [51] (see figure 1b).

The role of eye movements in various psychological constructs

There are numerous other examples of exciting research lines investigating the relationship between cognitive processes and oculomotor behaviour. Since a comprehensive review of all these findings would be sufficient to form it's very own book, we list suggestions for

the interested reader on a selection of topics: memory [e.g., 53, 54], navigation [e.g., 55, 56], attention [57, 58], perception [59], reading [60, 61] and 'active sensing' [62, 63].

Accounting for ocular activity in cognitive neuroscience research

The previous two sections demonstrate that eye movements are intimately linked to a wide range of electrophysiological phenomena, and quite possibly mediate the interaction between this neural activity and cognition [e.g., 54]. Consequently, it is essential to account for ocular activity when exploring the links between electrophysiological activity, cognition and behaviour. In this section, we discuss how best to account for ocular activity when studying brain-behaviour correlations, and their relative strengths and weaknesses.

The first approach, which is perhaps the default for those who are unaware of the ubiquity of ocular influence over the brain and cognition, is to simply 'prevent' eye movements. This could include designing a paradigm that uses simple stimuli, presented at the centre of the screen and instructing participants to avoid making eye movements during the task. We place 'prevent' in quotes, because this 'prevent eye movements' approach does not really prevent eye movements at all. The eyes are never completely still. While these design choices may reduce the number of major saccades made in the experiment, some of these larger saccades will remain, and smaller movements (i.e., microsaccades, tremors) will continue to be prevalent. Impeding all eye movements is, on the other hand, not practical in most experimental settings anyway. If one were successful in preventing their participants' eye movements completely (including miniature ones), they would soon realise the drawback of this unnatural condition: visual perception fades when all eye movements are suppressed [64]. One can experience a mild version of this in the so-called Troxler's effect: when fixating upon the centre of a display, peripheral stimuli will start to fade after only a short period of time. The effect vanishes immediately when the eyes are moved. Neurally, this can be explained by adaptation processes during fixation, which are counteracted by micro-saccades [64]. Moreover, such an approach lacks ecological validity - in daily life, eye movements are not suppressed, and if they do indeed serve to facilitate cognition [54, 65], suppression of eye movements may lead to peculiarities in cognitive processes that undermine the experimental question at hand. Ultimately, this approach is not fit-for-purpose, and experimenters who take such an approach must accept the fact that eye movements may be acting as a latent variable that mediates the experimenter's observed link between the brain and cognition.

The second approach, which involves a deep dive into ocular activity, is to embrace "free-viewing" paradigms and employ simultaneous eye tracking-iEEG recordings. By allowing participants to fully explore the stimuli presented to them, the neural data and behaviour recorded will be most representative of what occurs in daily life, substantially boosting the ecological validity of the data. Of course, such an approach also requires careful analysis of data, focusing not only on what happens when a stimulus is presented, but also what happens when saccades and other eye movements occur (details on how to handle such analyses can be found in the next section). However, these additional analyses may be off-putting to researchers who are not focused principally on the influence of eye movements on the brain and/or behaviour, and they may prefer the third approach.

The third approach sits somewhere between the first and second approaches, in that it acknowledges the importance of eye movements in cognitive electrophysiology, but does not wish to focus a study on them. Like the second approach, simultaneous eye tracking and intracranial recordings would be taken, but in a paradigm that serves to minimise eye movements (e.g., by presenting simple stimuli at the centre of the screen). The nature of eye movements could then be calculated on a trial-by-trial level (e.g., number of saccades, length of fixations) and included as covariates in the main analyses (see the section '*"eye movements-as-covariates" analysis'* below*)*. This approach may be best suited to those researchers who simply wish to factor out the contributions of eye movements from their experimental questions.

A “how-to” of eye tracking and intracranial EEG

The sections above have highlighted the influence that ocular activity exerts over neural activity, but a question remains: what practical steps can researchers take to measure the interactions between the eyes, brain, and behaviour? Here, we provide an overview on how to conduct simultaneous iEEG-eye tracking experiments, from the practicalities of recording in the clinic to descriptions of the myriad of analytical possibilities. Given the breadth and depth of eye tracking as a research topic, this section should not be viewed as a comprehensive guide to eye tracking, but rather an introduction to the key issues in relation to intracranial recordings. For the interested reader, we have provided a number of references to other detailed guides at relevant moments which go deeper into various aspects of the methodology.

Recording ocular activity in the clinic

It would be fair to say that most eye trackers have not been designed with iEEG patients in mind, and many lab-based eye tracking solutions have their drawbacks when brought to the patient’s bedside. In this section, we aim to highlight the relative strengths and weaknesses of different eye tracking solutions when used in the clinic (discussed further later in the book).

Eye tracking systems can be divided into two broad categories: desk-mounted systems and wearable systems. Desk-mounted systems tend to be large units that are placed on the desk in front of a participant, either as large towers sitting directly between participants and the computer screen (e.g., Tower Mount EyeLink 1000 Plus) or smaller, remote devices that sit beneath/beside the computer screen (e.g., Tobii Pro Spectrum, Eyelink Portable Duo, TrackPixx 3). These desk-mounted systems tend to provide a more accurate and higher-sampled recording (up to 2000 Hz) of ocular activity than wearable systems, but they do have their drawbacks. Due to their weight and a lack of dedicated work surfaces available to the patient in the clinic, tower systems are not a practical option for combined iEEG-eye tracking recording. The remote systems, in contrast, can be used in the clinic settings, but care is required. For example, remote systems can be set up on the patient bedside table if this does not interfere with the patient responding to a computer task. However, the remote system is still heavy, meaning some tables will struggle to hold the weight of the system. Moreover, the system may become a hazard should the patient experience a seizure. As with other research equipment brought to the hospital ward, one needs to be careful not to block medical staff access to the patient. One solution for this particular issue is to use downscaled versions of some manufacturers’ high-end products (e.g., Tobii Pro Fusion), that can be attached directly to a monitor or a laptop and are, consequently, easier to set up and more mobile. Usually, these systems come with less sampling rate than their high-end siblings. Beyond size, it is also important to consider how tolerant the eye tracker would be to head movements. Research with iEEG patients will in most cases be conducted while the patient is in their hospital bed, and fixing their head position using a chin-/forehead rest or a bite bar will be very hard to accomplish and potentially unpleasant for the patient. A visualisation of how iEEG and eye tracking can be combined at the patient’s bedside is provided by Wang and colleagues [66]. Researchers aiming to track eye movements intraoperatively (e.g., when Parkinson’s patients are awake during placement of deep brain stimulation lead) will face additional challenges. The setup and access to the patient needs to be arranged in close consultation with surgeons and other medical staff, and the time available for experimental procedures during surgeries is usually very little, restricting the range of suitable tasks. However, in contrast to patients outside the operating room, head movements are less problematic since patients’ heads are restricted in a head frame (though this may obscure the patient’s field of view). Nonetheless, should the researcher manage to navigate these issues, remote systems can provide a robust and reliable measure of ocular activity in the clinic.

Wearable eye trackers provide a light-weight alternative to desk-mounted options. Typically, wearable eye trackers train one camera (or more) on each eye, and point an additional camera outwards to capture the participant's frame of view (e.g., Tobii Pro Glasses 3; Pupil Core, Eyelink II). As these eye trackers are worn by the participant, researchers needn't worry about additional desk space to hold the system, which may allow for more flexibility in the tasks which participants complete. However, these eye trackers also have their drawbacks. For example, the maximum sample rate tends to be smaller than desk-mounted alternatives (often <120Hz), meaning analysis of saccades can become difficult. Furthermore, depending on where intracranial electrodes have been implanted and/or where bandages have been placed, the patient may not be able to wear these eye trackers.

Ultimately, the question of which type of eye tracker to use boils down to the experimental question at hand. If researchers are interested in fixation-related analyses (which do not require high sampling rates), or have limited space, wearable eye trackers may be more appropriate, but if researchers are focused on saccadic activity, desk-mounted options with high sampling rates are more suitable.

Regardless of which system is used however, researchers need to consider how they will synchronise the eye tracking recordings with the iEEG recordings as this is paramount to exploring the interactions between ocular activity, neural activity and behaviour. Fortunately, many systems will have the capability to receive a trigger much like how iEEG recording systems do. This means researchers may be able to send a single trigger from the experimental computer to both the iEEG and eye tracking systems, allowing the two data streams to be aligned during subsequent analysis. If the eye tracking system is not built to receive such triggers, however, researchers will need to synchronise the clocks of the experimental, iEEG-recording and eye tracker-recording computers so that timestamps are consistent across all hardware elements of the experiment (as clocks have a tendency to drift over time [67]). One popular synchronisation solution is 'Lab Streaming Layer' (LSL; https://github.com/sccn/labstreaminglayer), which can synchronise clocks up to every five seconds. While LSL may take a little additional work to set up in comparison to a simple trigger cable, it may be more effective in situations where recordings occur across multiple sites and researchers wish for a single, common means of synchronisation rather than bespoke solutions for each site.

If eye tracking equipment is unavailable, researchers may still benefit from the use of electrooculography (EOG). Depending on the position of the patient's bandages, researchers can place horizontal EOG pairs (one left of the left eye, and one right of the right eye) and vertical EOG pairs (one above the eye and one below the same eye). EOG recordings can be used to identify when a saccade or fixation occurred, as well as amplitude and direction of these ocular phenomena [68]. Moreover, EOG recordings are often directly fed into the iEEG recording system, avoiding the issues relating to synchronisation described above. However, much like the wearable eye trackers, the placement of EOG electrodes may be difficult for some patients depending on bandage placement. Nonetheless, EOG provides a feasible alternative for measuring ocular activity when eye tracking equipment is not available.

Detecting ocular events

The detection of ocular events is key to any analysis focusing on the intersection of ocular activity, neural activity and behaviour. While large events such as saccades and fixations can be readily identified in the raw eye tracker trace, manually labelling every event can be a time-consuming approach that is difficult to replicate by others. Consequently, algorithms tend to be more popular when it comes to event detection. Here, we provide a brief overview of the two most common forms of event detection algorithm, and then describe how to handle common artefacts that may impair the performance of these algorithms.

Almost all event detection algorithms involve translating the gaze co-ordinates (i.e., the x- and y-positions of where the eye is focused on the computer screen) into key ocular events (e.g., saccades, fixations). Dispersion algorithms will set out to identify key ocular events based upon the range of the x- and y- gaze positions over a predefined period of time (that is: dispersion = [max(**x**) - min(**x**)] + [max(**y**) - min(**y**)], where **x** and **y** are vectors containing x- and y- gaze positions over the predefined time window). In the most basic of dispersion algorithms, if the dispersion measure falls below a predetermined threshold (either based on existing literature, or through visual inspection of the participant data), then that time period is considered to be a 'fixation' and the remainder of time periods are inferred to be 'saccades'. One of the most common examples of a dispersion algorithm is the 'identification by dispersion threshold' algorithm (I-DT [69]). While popular and widely-available, dispersion algorithms do have their drawbacks. For example, they are often distorted by ocular drifts, and tend not to function well when the sample rate of the eye tracker exceeds 50Hz.

An alternative is to use velocity-based algorithms [e.g., 57]. Many of these algorithms use a derivative of gaze position (i.e., velocity = change in visual angle / change in time) to identify saccades based upon a pre-defined velocity threshold. When the data exceeds this threshold, a saccade is marked, and anything that falls below the threshold is assumed to be a fixation (though some algorithms also include a minimum fixation threshold, where velocity must fall below the threshold for a set period of time). In their most basic form, velocity-based algorithms are simpler than dispersion algorithms, but they are often built upon to help minimise distortion by noise. For example, implausibly fast saccades may be discarded, or a two-pass procedure may be implemented in which approximate saccade windows are identified in the first pass, and then the onsets/offsets are concretely defined in the second pass. However, even with these modifications, defining events based solely on velocity can be unreliable. This has led to some incorporating acceleration into the algorithm (where acceleration = change in velocity / change in time; [e.g., 70]), which can help distinguish slow saccades from moments involving fast smooth pursuits. Both velocity and velocity-plus-acceleration algorithms tend to perform better when the eye tracking data has a high sample rate, as high sample rates allow for a more robust estimation of velocity/acceleration.

Of course, no event detection algorithm is perfect, and it is important to consider how to handle potential artefacts that distort the algorithm output. One of the most common artefacts comes from blinks; the moving of the eyelid can lead to a rapid change in the eye tracker-predicted gaze position, which in turn can lead to algorithms detecting an illusionary saccade. Some researchers tackle this issue by asking participants to refrain from blinking during the key moments of a task, and then discarding trials in which participants did blink, while others tackle this issue by ignoring any events that are detected just before (e.g., 100ms) or just after a blink. Stochastic noise can also be problematic for event detection, where momentary jumps in gaze position are erroneously defined as saccades. If these jumps are relatively small, smoothing or filtering the data will often attenuate these issues. However, in cases where these jumps are large, smoothing/filtering may make the situation worse as it may make these jumps appear more saccade-like to the automated algorithms. Visual inspection is perhaps the best approach to tackle these larger jumps, where artefactual trials are discarded in much the same way that artefactual trials are discarded when contaminated by an iEEG artefact.

In sum, many event detection algorithms are readily available for eye tracking research, each of which have their relative strengths and weaknesses. Dispersion-based algorithms search for fixations based on limited change in gaze position, and are better suited for low sample-rate data, while velocity-based algorithms detect saccades based upon changes in velocity (and also acceleration). If the reader is interested in exploring these approaches further, we can recommend Holmqvist & Andersson (2017) for a detailed review of many different forms of algorithm [1], and Nyström & Holmqvist (2010) for a description of how to build a bespoke, velocity-based, event detection algorithm [70].

Saccade-/fixation-locked analysis

For researchers looking to directly explore the impact of saccades and fixations on a particular brain-behaviour correlation, it can be highly informative to conduct a saccade- or fixation-locked analysis in which the intracranial data is re-epoched around these saccadic or fixation events. In order to do so, however, researchers should consider three factors: (1) what ocular event to lock the iEEG data to, (2) how to address trial imbalances, and (3) how to baseline correct the data. We will consider each issue in turn.

The decision about which ocular event to lock to should be driven by the question at hand. If researchers are focused on how the brain/behaviour responds to stimulus properties, fixation-locked analyses are more appropriate as this form to time-locking is more closely locked to the 'onset' of the visual stimulus, whereas saccade-locked analyses are more effective for questions relating to the preparation, execution, and response to eye movements themselves. In instances where researchers are unsure about which method to use, they could elect to do both (though of course this will effectively double the number of epochs that will need to be analysed, as well as double the number of statistical comparisons that will be made later down the line).

After deciding which ocular event to lock to, researchers need to consider balancing trials between conditions. As described earlier, the size and direction of saccades [e.g., 8, 9] and duration of fixations [e.g., 11] can have a large impact on neural activity. If there are differences in saccadic or fixation-related activity between conditions, this has the potential to drive neural differences between conditions. So, if researchers are not interested in the effects of differences in saccadic/fixation-related activity, these parameters should be matched as best as possible between conditions. For example, researchers could, for every trial of one condition, find the most similar trial of the second condition (e.g., in terms of saccade distance, fixation duration), and use these two matched conditions for subsequent analysis.

After balancing trials, the choice of baseline needs to be considered for a range of iEEG analyses (e.g., event-related potentials or changes in amplitude / power). Typically, baselines can either be common across all saccades/fixations of a trial/recording, or individual to each saccade/fixation event. Common baselines typically take data from before the beginning of the trial and correct epochs based on this signal. Such an approach is useful if the researcher is interested in exploring how neural responses change over the course of a trial (e.g., increase in memory load, change in attentional resources). However, for long trials, or continuous recordings (e.g., movie-viewing), drifts in activity between the pre-trial baseline and later saccades can become problematic. Individual baselines are less likely to be swayed by such drift, as the baseline signal comes directly before the event of interest. It also helps control for factors such as shifts in attentional resources if this is not a variable of interest. However, individual baselines also have their drawbacks. For example, these baselines are easily swayed by differences in preceding saccadic/fixation-related activity (e.g., saccade size, fixation duration), which means greater effort is required when it comes to matching trials between conditions. This issue can also become exacerbated if the two conditions have inherent differences in saccadic-/fixation-related activity; in such instances, a common baseline may be more appropriate. Ultimately however, the decision sits with the researcher, and they should select the method they feel is most appropriate for the question at hand.

After completing these steps, researchers can proceed with their iEEG analyses as if the data were locked to a stimulus trigger. However, it is always worth remembering that for saccade-/fixation-locked recordings, the data immediately preceding the event may correspond to some other ocular activity (e.g., the offset of a fixation, saccade execution), and methods that involve temporal smoothing (e.g., wavelet-based time-frequency decomposition approaches) may lead to this preceding activity obscuring the effects of interest. For the interested reader, a deep dive into the various decisions involved in saccade-/fixation-locked analyses has been presented by Nikolaev and colleagues [8].

Most of the information provided above pertains to the analyses of local field potentials. Only a few studies have related human single cell recordings to eye movement behaviour [e.g., 50, 51, 71]. As a general approach, firing rates of putative single units can be analysed during time windows related to saccades or fixations. For example, a single cell could be classified as being visually selective if its firing rate was modulated by the category of fixated image in a defined time window after fixation onset. Obviously, a plethora of single unit analyses and approaches could be used in a similar way, the interested reader is referred to the publications cited above for inspiration (discussed later in the book).

Encoding models

There has been a rapid expansion in the use of multivariate methods to analyse neuroimaging data in the last decade. One approach that is particularly relevant to studying the link between eye movements and the brain is the *forward encoding model* (FEM).

A FEM aims to model neural activity at any given electrode/sample point as a function of the properties of a stimulus, be that visual stimuli [e.g., 72, 73], auditory stimuli [e.g., 74], or ocular activity [e.g., 75]. This is achieved by breaking the stimulus down into its constituent parts. In the case of ocular activity, breaking this down into constituent parts can be done in a myriad of ways. For example, one could simply use eye position on the x- and y-axes as two predictors in the encoding model, or one could push the boat out and model eye position as a series of circular–Gaussian kernels covering all possible ocular angles as has previously been done for virtual head direction [76]. Ultimately, the decision on how to break down the patterns of ocular activity depends on the research question at hand.

Whatever the approach used, the next step of the FEM analysis involves building a general linear model to estimate activity at a given intracranial electrode based upon the consistent parts of a stimulus (each of which will act as a separate predictor variable in the linear model). The linear model is constructed such that the outcome variable (y) reflects a vector of iEEG activity from a single iEEG channel, where every row of the y reflects a separate sample point of this iEEG activity. The predictor matrix (X) contains all the predictor variables which make up the stimulus, with every column of X representing a different stimulus feature. The beta weights (β) are then estimated using the conventional equation: $y = \beta X$.

To validate the performance of the FEM, the estimated beta weights are then applied to a second, hold-out dataset. By multiplying the beta weights with the predictor matrix of the hold-out dataset, a predicted time-series of iEEG activity is produced. This predicted time-series can then be correlated with the observed iEEG time-series of the hold-out dataset. If there is a significant correlation (or one that significantly deviates from a surrogate distribution), one can conclude that the stimulus (in this case, ocular activity) can predict neural activity at a given iEEG electrode. Beyond predicting iEEG activity, the beta weights of the FEM can be inspected to identify which parts of the stimulus best predict iEEG activity (though see [77], for a cautionary note on the interpretation of weights in multivariate models), or the weights can be inverted to allow researchers to predict stimulus properties based on iEEG activity.

FEMs are a powerful technique for probing the link between ocular and electrophysiological activity. For example, they allow for the simultaneous modelling of multiple stimulus features, which many univariate analyses cannot easily do. However, this also has drawbacks. The relative complexity of the FEM makes the analysis computationally expensive, sometimes prohibitively so. Moreover, it is sometimes unclear what parts of the stimulus feature it is best to model. This can lead to researchers having to build and compare several models, which incurs issues with multiple comparisons. Nonetheless, so long as the researchers have a clear research question in mind, and have the computational means to run the analyses, FEMs could prove to be a fruitful venture when exploring the link between ocular and electrophysiological activity.

FEMs are a complex topic in their own right, and the interested reader may wish for more detail than what is provided here. Fortunately, there are a number of great primers on the topic out there which can be explored in more detail [e.g., 78] (see also later in the book).

"Eye movements-as-covariates" analysis

If the research question does not focus on the role of ocular activity, but the experimenters wish to control for the potential mediating effect of such activity on the brain, behaviour and cognition, the experimenters can consider ocular activity as a covariate. There are many ways to analyse brain-behaviour relationships while controlling for covariates, and here we provide two suggestions, one simple and one more sophisticated.

Perhaps the most straightforward solution is the median split, whereby the dataset is split into two based on a covariate, and analysis is conducted on the two groups separately: One could divide participants into two groups based on, say, the mean number of saccades they made per trial, and run the brain-behaviour correlation separately for the two groups. If the correlation remains significant in both groups, and there is no significant difference in the correlation coefficient between the groups, one could conclude that saccade count does not exert a substantial influence over the brain-behaviour correlation. If, however, the correlation disappears for one group, or a significant difference in the correlation coefficient is observable between the two groups, then one could conclude that saccade count mediates the brain-behaviour correlation. While this approach is easy to implement, it does have a number of drawbacks. First, by splitting the data in two, the sample size for each test is halved, substantially limiting statistical power. Second, one needs to test whether there is a difference between the two groups (i.e., a between-samples comparison) which may be difficult to robustly implement given the inconsistent placement of intracranial electrodes across participants. Third, one can only address one covariate at a time. If, for example, one wished to also explore the impact of saccade count and fixation duration on the brain-behaviour correlation, a second median split analysis using fixation duration as the criterion for dividing the groups needs to be conducted. Critically, this prevents one from simultaneously accounting for two covariates (i.e., number of saccades, fixation duration), meaning both median split analyses may still contain influence from the other covariate.

An alternative approach which does not impact statistical power, and can handle multiple covariates simultaneously, involves linear modelling. Here, a linear model would be constructed in which iEEG activity (the outcome variable) is modelled as the weighted sum of behaviour and the saccade count (the predictor variables) on a trial-by-trial level. The resulting regressor (i.e., beta) weight for behaviour can then be viewed as the link between behaviour and iEEG activity after regressing out the influence of saccade count. These beta weights can then be statistically appraised in one of two ways. The first option involves running a linear model separately for each participant, pooling the resulting beta weights and then testing whether they consistently differ from zero in a one-sample t-test. The alternative is to create a single linear mixed-effects model, which includes iEEG activity, behaviour and saccade count for every trial of every participant as well as additional random effects to account for influences of individual participants (see also later in the book). The linear mixed model can then be statistically appraised in a myriad of ways, including likelihood ratio tests or permutation testing (for more details, see [79]). Unlike median split analyses, linear modelling approaches preserve statistical power, which may aid in the detection of smaller effects. Moreover, multiple covariates can be inserted into the same model, allowing for the simultaneous control of several potentially-mediating factors. However, the analyses are more computationally intensive, which may cause difficulty for analytical approaches that already require large amounts of computational resources.

Eye movement artefacts in intracranial EEG

As discussed throughout this chapter, treating eye movements as nothing more than artefacts is a highly problematic practice. That said, some parts of the ocular-induced change in electrophysiological signal (namely, the electromuscular component) should be suppressed prior to analysis [7, 30] as these signals do not reflect true brain activity. For example, intracranial electrodes that are proximal to the extraocular muscles are likely to pick up electrical signals generated by these muscles during saccadic activity. The magnitude of these effects depends on the referencing montage used, with bipolar montages perhaps being the most effective in suppressing the artefact [30]. However, even bipolar referencing is not sufficient to fully remove the artefact. Independent components analysis has also been proposed as a means to suppress these artefacts, and can do a good job in suppressing the electromuscular artefact [7], although this too does not totally remove the artefact. In conjunction, bipolar referencing and independent components analysis acts as perhaps the most effective means to remove electromuscular artefacts from intracranial data, but even after applying these analytical steps, researchers would be wise to view eye movement artefacts as “suppressed" rather than fully subtracted from the recordings.

Conclusion

With this chapter, we hope to convince the reader that recording eye movements and iEEG simultaneously will benefit their research. We argue that eye movements are more than just artefacts, and ignoring oculomotor behaviour in iEEG research will impede our understanding of brain processes underlying cognition. Eye tracking in clinical settings is challenging, but by pointing out several options on how to combine and analyse eye tracking and iEEG recordings, we hope to mitigate these concerns and inspire new avenues of research.

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