Human Time Data

Working with iEEG Data

An Introduction

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Introduction

Electroencephalogram (EEG) studies the electrical activity of the brain produced by neurons firing in tandem via the scalp. EEG is particularly well-suited to studies that examine functional or effective connectivity and research where temporal resolution is important (da Silva, 2013). Intracranial electroencephalogram (iEEG), scalp-recorded EEG's close relative, is an invasive technique usually performed in a clinical context. iEEG involves the surgical implantation of electrodes and is most often used for the mapping of epileptic foci (areas of focused seizure activity) prior to surgical interventions when epilepsy medications fail to work. Employed for decades in animal studies, human iEEG offers exciting new possibilities for examining cognition that cannot be observed in animal studies (Mukamel & Fried, 2012; Parvizi & Kastner, 2018).
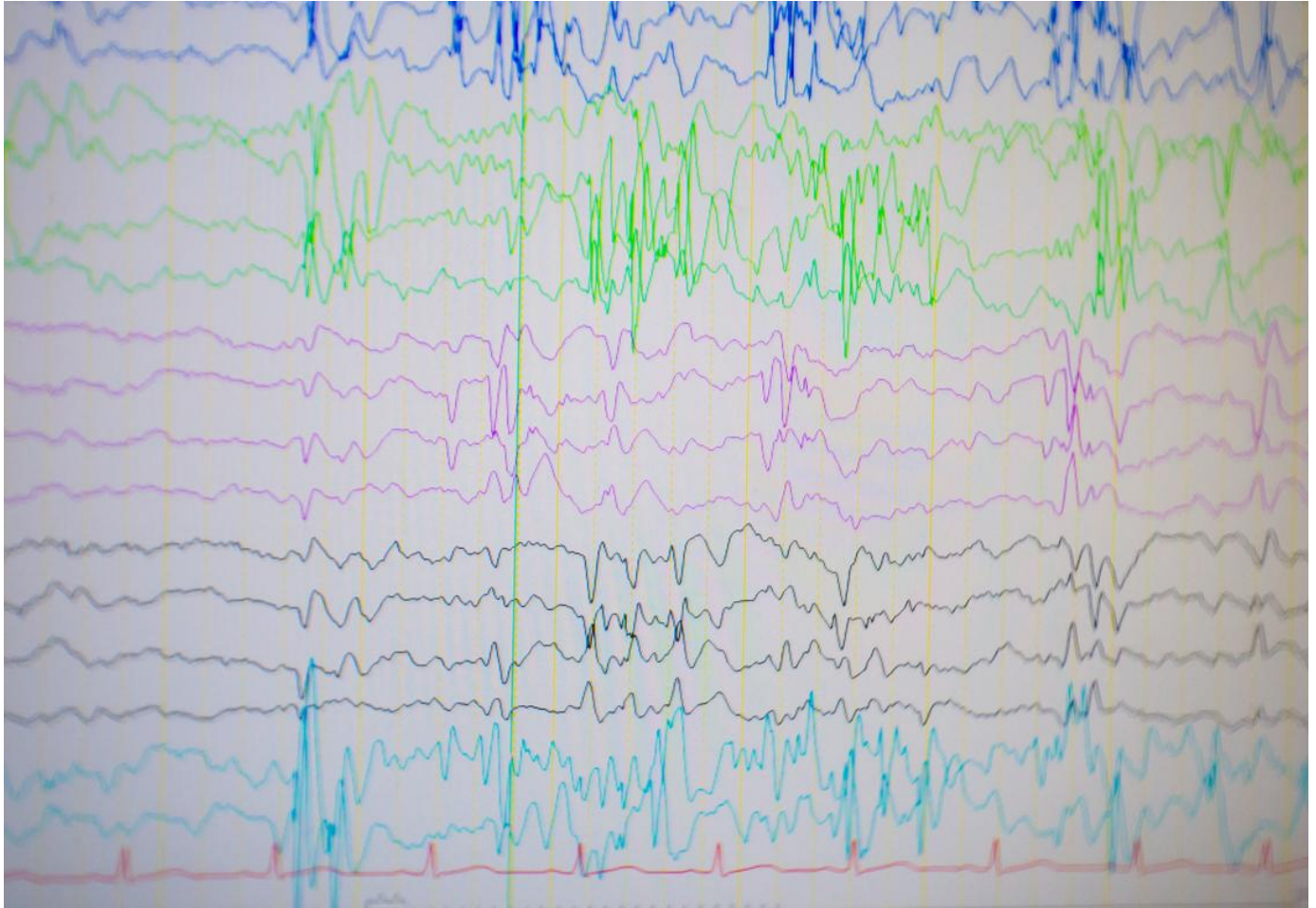
One advantage of iEEG is that it permits direct recording of electrical activity at the individual cell or cellular cluster-level. Other modalities like PET and fMRI rely upon signals from the biproducts of neural activity such as the blood oxygen level dependent (BOLD) signal in fMRI, which is a metabolic response to neurological activity. Another advantage to iEEG is its extremely high spatial and temporal resolution, as well as its high signal to noise ratio (Mukamel & Fried, 2012). This can be seen in contrast to EEG, which has low spatial accuracy due to physiological barriers which are not present with iEEG. Studies using iEEG can provide data about neuronal activity on the millimeter scale in terms of localization and can capture temporal-related activity at the millisecond scale (Parvizi & Kastner, 2018). iEEG can also help us understand the nature of functional activity between different networks or regions of the brain and determine causality through neural electrical stimulation (ibid).

With both EEG and iEEG, fluctuations in the voltage of ionic currents produced by neurons are recorded through electrodes (St. Louis & Frey, 2016). Electrodes are the physical sensors or transducers that perform the analogue recording. They are connected to amplifiers, which not only amplify, but also filter the iEEG activity. iEEG data is represented by channels for each electrode, with voltages represented on the x-axis, and time represented on the y-axis. Event codes (which signal at what point periods of interest in an experiment occur) may be found at the bottom of the data graph along the y-axis (Acheson, 2019), depending upon the acquisition system used.

This guide will focus on data collection and management issues specific to iEEG and aims to be particularly useful to the new beginner. We additionally provide resources that can add additional depth as to the understanding of iEEG data, what iEEG records and iEEG analysis that go beyond the scope of this guide.
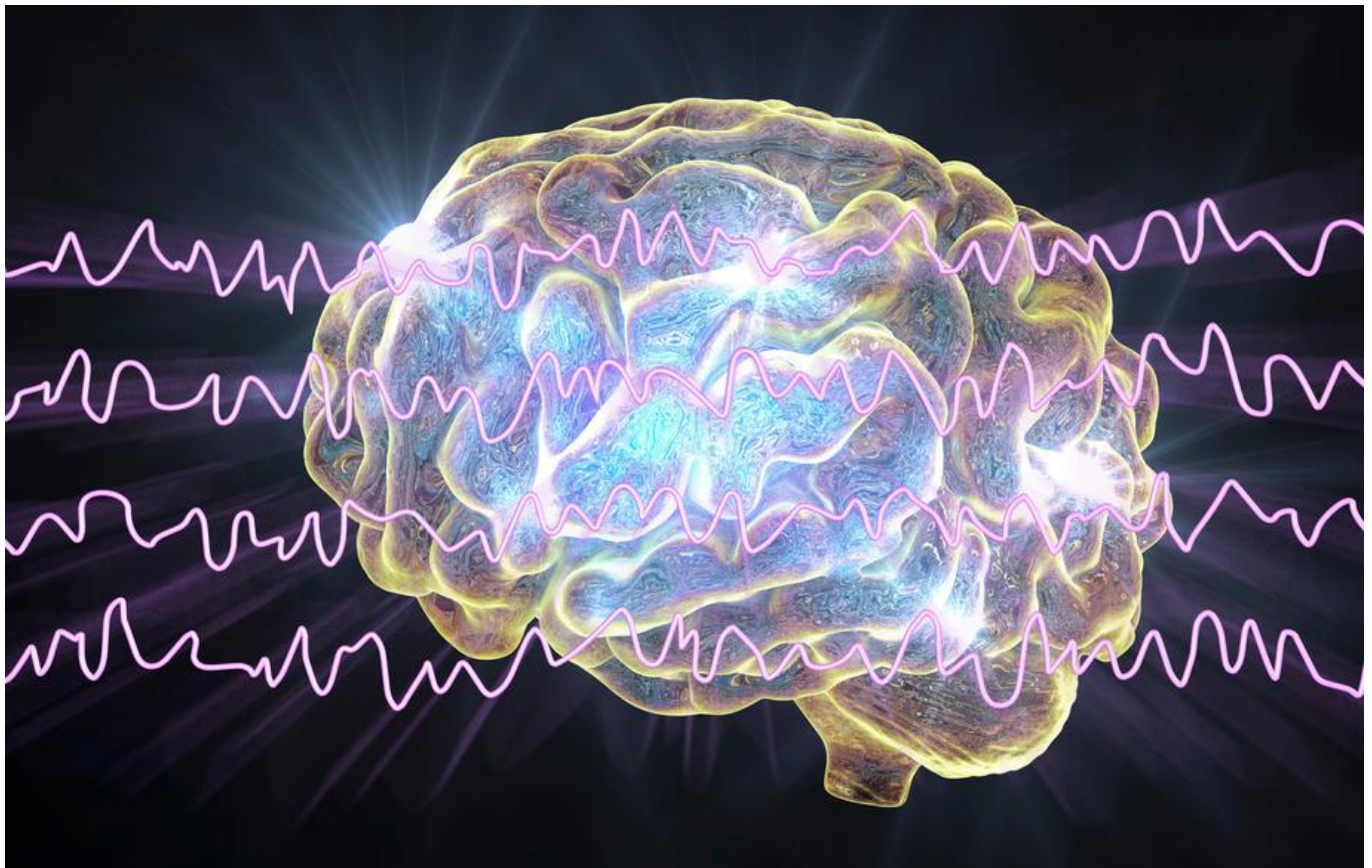
Terminology

- **Electrodes** are the sensors which form the "point of contact" between the acquisition system and the brain (Holdgraf et al, 2019). See the section on electrodes for more information on the specific types of electrodes used in iEEG.

- **Channels** are the digital signals recorded by the amplifiers. It is important to distinguish them from the sensors. Channels consist of two electrodes whose activity is referenced to another more distant electrode to form the signal (referential montages).

- **Signals** are voltages at a given site at a given timepoint. The signal consists of different frequencies that can be derived/calculated via a time-frequency analysis. Delta waves range from 1-3 cycles per second (Hz), theta are 4-7 Hz, alpha are 8-12 Hz, and beta waves include those 13 Hz and higher. These can reveal the state that the participant is in, for example, wakefulness or sleep (St. Louis & Frey, 2016).

- A **session** is a grouping of neuroimaging and behavioral data consistent across participants. A session includes the time involved in completing all experimental tasks. This begins when a participant enters the research environment and continues until they leave it. One session would typically start with informed consent procedures followed by participant preparation (i.e., electrodes placement procedure) and ends when the electrodes are removed but can also include a number of pre- or post-EGG observations and measurements (e.g., additional behavioral or clinical testing, questionnaires, structural MRI). Defining multiple sessions is appropriate when several identical or similar data acquisitions are planned

and performed on all (or most) participants, often in the case of some intervention between sessions or for longitudinal studies.

- A **run** is an uninterrupted period of continuous data acquisition without operator involvement.

- An **event** is an isolated occurrence of a stimulus being presented, or a response being made. It is essential to have exact timing information in addition to the identity of the events, synchronized to the iEEG signals. For this, a digital trigger channel with specific marker values and timing information is used.

- The term **epoch** designates the outcome of a data segmentation process. Typically, epochs in event-related designs (for analysis of event related potentials - ERPs) are time locked to a particular event (such as a stimulus or a response). Epochs can also include an entire trial, made up of multiple events, if the data analysis plan calls for it.

- A **trial** is a period of time that includes a sequence of one or more events with a prescribed order and timing, which is the basic, repeating element of an experiment. For example, a trial may consist of a cue followed after some time by a stimulus, followed by a response, followed by feedback. Trials of the same type belong to the same condition. Critical events within trials are usually represented as **"triggers"** stored in the iEEG data file, or documented in a marker file.

- **Source space** refers to iEEG expressed at the level of estimated neural sources that gave rise to the measured signals. Each signal maps onto a spatial location that is readily interpretable in relation to individual or template-based brain anatomy.

- **Anatomical landmarks** are well-known, easily identifiable physical locations on the head (e.g., nasion at the bridge of the nose; inion at the bony protrusion on the midline occipital scalp) that have been acknowledged to be of practical use in the field.

- **Acquisition parameters** are the reported **reference and ground electrodes** used in data acquisition. Similarly, reference electrode(s) used in data analysis are also reported. Additional electrodes are sometimes applied to the face to measure eye movement, and their exact spatial positions are specified, preferably with reference to well-known anatomical landmarks (e.g., outer canthus of the eye).

Experiments Using iEEG

An EEG study typically follows several specific steps. First one sets up the experiment itself, using various software, then pre- and pilot testing may be followed by the actual data acquisition and finishing with the analysis.

Experiment Setup → Pre-Test → Pilot → Data acquisition → Analysis
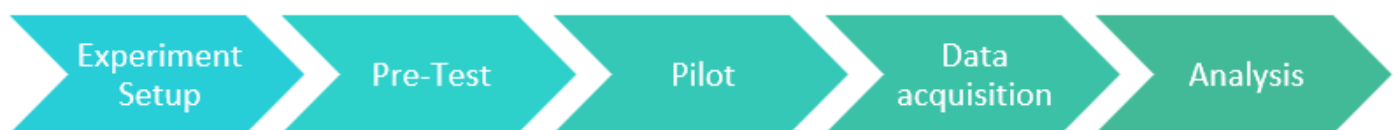
Experiment Setup

Some limitations must be considered when designing a study around this modality. Because of the invasive nature of iEEG, only patient groups with serious pathology (usually epilepsy) may be sampled, which may limit the generalizability of the findings (Parvizi & Kastner, 2018). The brains of people with epilepsy may present with anatomical and functional differences that must be accounted for, and the use of various medications must also be considered (Mukamel & Fried, 2012). For an overview of how these issues have been dealt with in other studies see Lachaux et al., 2012. It is also not possible to provide coverage of the entire brain and study time is often limited to a period in which the participant is admitted to a hospital for observation, often prior to resectioning surgery, which removes the part of the brain responsible for seizure activity. Additionally, the type of electrode used
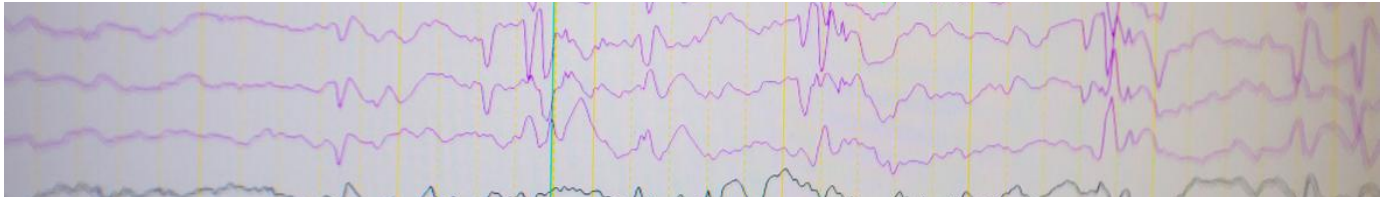
relates to clinical necessity and not to the aims of a research project (Parvizi & Kastner, 2018). For reasons that should be obvious, it is not possible to include a control group in iEEG studies.

Because iEEG studies are mostly carried out on patients with epilepsy, the regions studied frequently mirror the focal areas that tend to be common among such patients: the temporal and frontal lobes. Studies on the subcortical regions are rare as a result (Parvizi & Kastner, 2018). Because the research takes place in a hospital, the ability to carry out elaborate research paradigms is often limited (ibid) and trials must be timed according to the participant's condition and length of time since implantation of the electrodes (Lachaux et al., 2012). Thus, researchers may not be able to meticulously plan for subject participation in the same way that one can with other studies. This also means that studies can take much longer to obtain enough data (Parvizi & Kastner, 2018) and frequently, iEEG research involves far fewer participants than studies utilizing non-invasive methods of data acquisition (Lachaux et al., 2012). A typical study conducted by researchers at UiO varies, ranging from 2-3 days of access to the participant to almost a week in some cases.

Posing an additional challenge is the clinical environment itself. For example, interference from electrical devices can be controlled for in an EEG lab at a university but are often not able to be controlled for in a hospital setting. There is also the chance that participants may be distracted by sounds and events outside of the researcher's control because of the limited control over the setting (Lauchaux et al., 2012). Lastly, access to this modality is rare and requires the involvement of clinicians trained in iEEG, as well as access to a neurologist to determine where seizure activity has occurred, so that those channels or sessions can be removed from analysis (Parvizi & Kastner, 2018).

While setting up a psychology experiment that requires it, one must decide which software to use for stimulus presentation. Mobility is also an issue to consider with presentation in iEEG studies, but thankfully laptops now allow for the movement of software-based experiments into the clinical setting. It is also important to keep in mind that experiments for iEEG study may need to be simplified or shorter in duration due to the clinical limitations presented by iEEG studies in a hospital setting.

At UiO, researchers have the choice between several options for presentation software with the most popular being E-prime, MATLAB/Psychtoolbox and Python/PsychoPy. The following table gives a short overview of these programs.

|	E-Prime	MATLAB/Psychtoolbox	Python/PsychoPy
GUI/ Script	Yes/Limited	No/Yes	Yes/Yes
Price	Free at UiO; otherwise ~$1000	MATLAB free at UiO; otherwise $50-500;	Free/ open source
Ease of use	Easy	Moderate	Moderate
Flexibility	Moderate	High	High
Timing control	Moderate	High	High
Connection to EEG system	Can be difficult; own scripting required	Easy; several functions available	Easy; several functions available
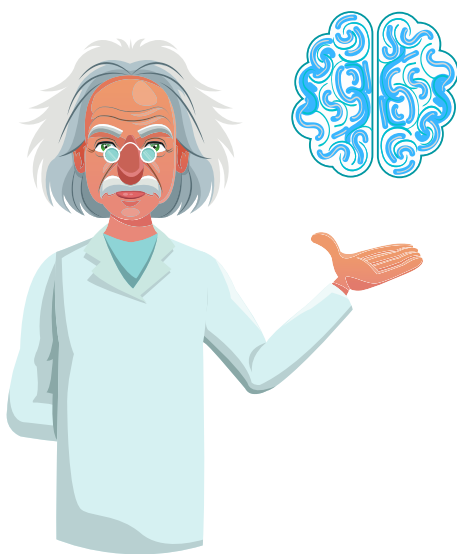
Pre-tests

In a regular neuroimaging study, pre-tests involve preliminary testing of sequences, equipment and stimuli scripts before any data collection begins. These are obviously limited, often to stimuli script testing only, in the case of iEEG.

Pilot tests

Before collecting data for the experiment, it is necessary to discuss the experiment design with colleagues and have them perform the task to give feedback on its design. Pilot test your experiment behaviorally to make sure you can obtain the predicted behavioral effect before proceeding to collect brain data with actual participants. Due to the nature of iEEG, actual pilot testing and tests of the analysis will be limited, however, tests using scalp EEG to test experiments may suffice in some cases. Unlike with studies performed using other modalities, there is no possibility of using pilot test data in the actual analysis. Essentially, you get a very small window of opportunity to get the study right!
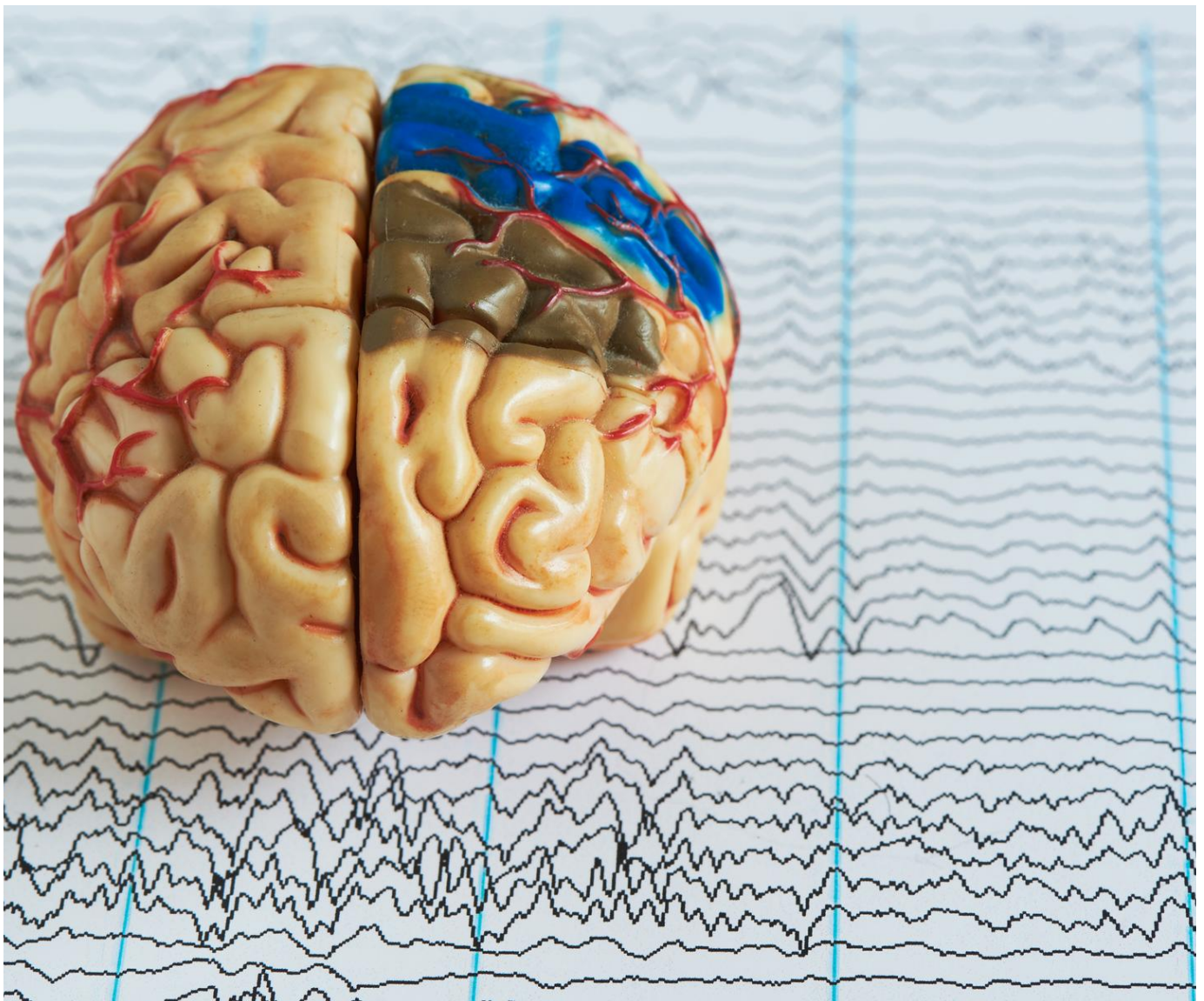
Data Acquisition
Equipment: iEEG electrodes

Several forms of iEEG exist, with the defining feature of each being the type of electrode used and its method of placement. The measurement of electrical activity in the brain using subdural grid or strip electrodes is called electrocorticography (ECoG). Studies using depth electrodes in data collection are referred to as stereotactic EEG (sEEG) (Parvisi & Kastner, 2018). The following table provides an overview of the various electrodes that may be used in iEEG studies.

Type of Electrode	Attributes
Subdural strips or grid electrodes	Typically made of platinum-iridium or steel, these electrodes are implanted under the dura. This type allows for a longer study time, as the electrodes usually remain implanted for a longer period (Mukamel & Fried, 2012). ECoG electrodes are shaped like circular plates and have a diameter of 1.2-3mm (Parvizi & Kastner, 2018).
Depth electrodes	Depth electrodes can record electrical activity from deeper brain structures. These electrodes, which record activity from neurons in proximity to the electrode, are inserted into the brain parenchyma. Microwires may also be used from the tip/sides of the electrodes to cover more area in terms of recording (Mukamel & Fried, 2012). Depth electrodes are cylindrically shaped, with a diameter of .86-1.1 mm and a height of 2.29 or 2.44 mm (Parvizi & Kastner, 2018).
Hybrid depth electrodes (HDE)	Another type of depth electrode used to record action potentials from specific cells or those adjacent to the depth electrode.
Intracortical electrodes	Intracortical electrodes are inserted into the cortex and can record action potentials from specific cells and local field potentials (LFP) from regions of the brain.
Microdialysis probes	Microdialysis probes can measure neurotransmitter levels and are implanted via depth electrodes, or with the subdural strips or grids (Mukamel & Fried, 2012).
Neurotrophic electrodes	A longer-lasting form of intracranial electrode intended for longer-term implantation. These contain a glass tip containing gold wires. These electrodes encourage neurites to attach and grow within its tip. These may be used in creating brain-computer interfaces for the control of devices, for example, for patients with locked in syndrome (Bartels et al., 2008).

A combination of different types of electrodes may be used in the same patient in many cases. It is additionally possible to stimulate various regions of the brain with the use of some types of electrodes during awake brain surgery for functional brain mapping (Mukamel & Fried, 2012). Deep brain stimulation (DBS) involves the permanent implantation of electrodes for chronic neurological conditions like Parkinson's disease. As these electrodes are permanently implanted, they may be used in iEEG recording for longer periods of time. Neurotrophic electrodes may be implanted in the long term to form a brain-computer interface which permits the control of external devices for patients with locked-in syndrome or other forms of paralysis.

Channel outputs use a system of reference montage in which the difference in electrode output is compared to either a nearby electrode (bipolar reference) or one reference electrode (Stolk et al., 2018). Knowledge of the placement of the reference electrode, if this scheme is employed, is important, as placement near certain musculature can potentially introduce noise into the data (Lachaux et al., 2003; Nejedly et al. 2018). This is less of a problem with bipolar referencing schemes (Kovach et al., 2011; Jerbi et al., 2009). However, it does pose the risk of not being able to measure fluctuations that result similarly in both electrodes in the bipolar reference and may be subject to "travelling waves", or the bleed over of signal from neighboring electrodes (Lachaux et al., 2003). Therefore, referencing information, including the exact placement of reference electrodes, should also be reported as part of the dataset's metadata because of their implications for the data (Holdgraf et al., 2019). The numbering of the grid and strip electrodes also requires that the research have access to notes acquired under surgery and data acquisition (Stolk et al., 2018).

Researchers at UiO utilize two data acquisition systems for iEEG amplification and data collection: the Micromed system, which is an audio-video iEEG monitoring system for sEEG, and the Neuralynx System.

Usually two computers are used in iEEG recording. One computer presents the stimuli and monitor behavior, while the second records the iEEG. These functions are not ordinarily combined into a single computer, because each requires precise timing, and it is difficult to coordinate multiple real-time streams of events on a single computer. For later analysis, stimulus presentation and responses must be recorded along with the iEEG signal. For this purpose, both the A/D box and the stimulus computer are connected to a trigger box where event codes from the stimulus computer are integrated with the iEEG signal. These event codes are later used to extract time-locked epochs from the iEEG data.
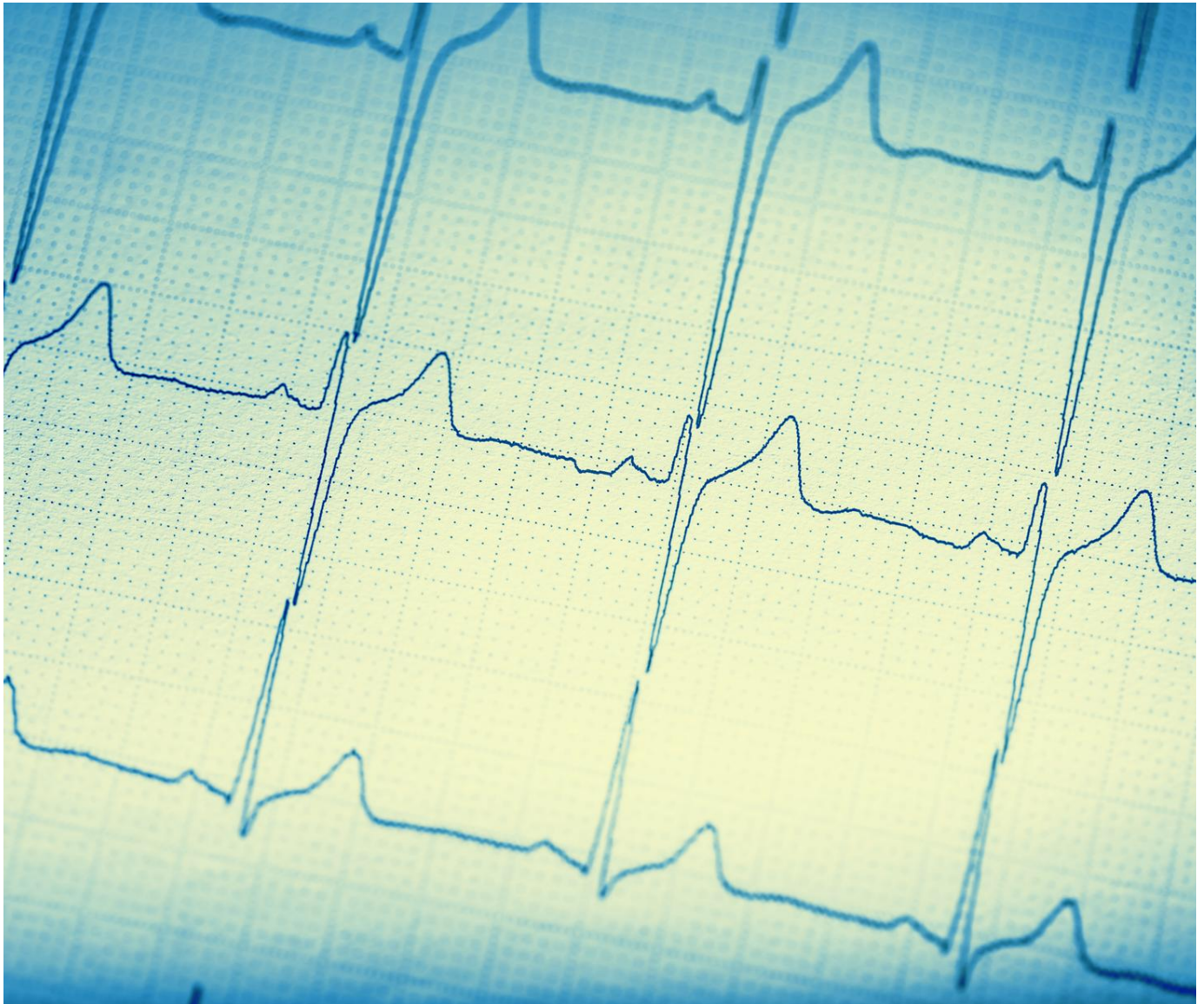
Raw iEEG data types and structure

There are two raw data formats that are output by the acquisition systems most commonly used for iEEG by researchers at UiO. The following section provides a brief overview of their content and purpose.

Neuralynx uses an acquisition software called Cheetah. Neuralynx system outputs its own proprietary file formats. Its standard setting is to create a separate file for each individual channel. These channel files are written into a 'dataset directory' and the files therein are able to be read concurrently. The Fieldtrip toolbox contains reading functions that work with these file types. See http://www.fieldtriptoolbox.org/getting_started/neuralynx/ for a listing of the exact functions.

Neuralynx file types

File type	Extension	Attributes
LFP file	.ncs	Continuous channel file. Required to set the sample time axis. Called LFP file after the local field potentials it captures.
NSE file	.nse	Stores electrode waveforms.
Stereotrode file	.nts	Individual stereotrode file.
Timestamp file	.nst	Spike timestamps.
Tetrode file	.ntt	Individual tetrode file.
Events file	.nev	Contains event information. Commonly called events.nev.
NRD files	.nrd	Large raw data file with all channels sampled at 32kHz, multiplexed. Also contains a 16kb ASCII header. Also contains trigger, timestamp and event data.
Split DMA files	.sdma	File created by Fieldtrip toolbox that splits the data found in the .nrd file into individual channels. This file format is better suited to analysis and long-term storage of the data due to its reduced size. An original dataset should be saved prior to pre-processing for storage.
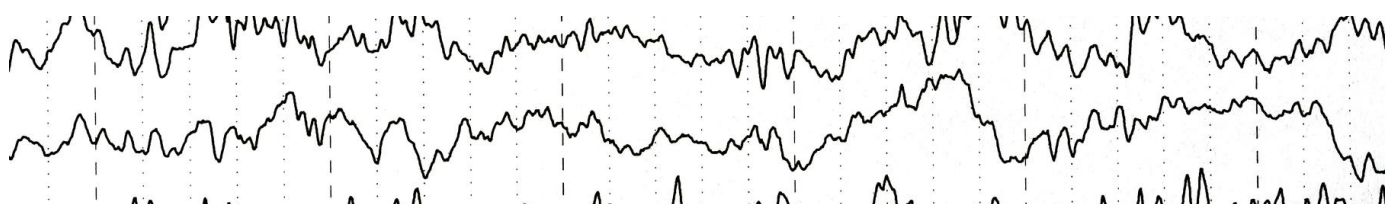
Micromed also has its own acquisition and analysis software, Brain Quick EEG. The system permits two types of raw data formats as outputs.

Micromed file types

| File type	Extension	Attributes
TRC files	.trc	Micromed's own proprietary file format for EEG data.
European Data Format	.edf	Non-proprietary file format created for medical time-series data.
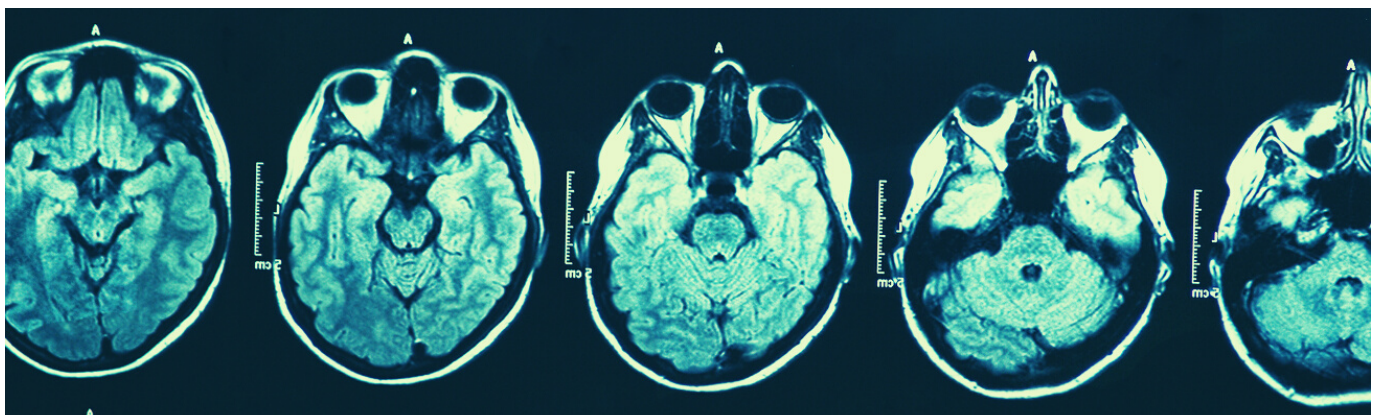
Localization: MRI, CT and Photographic Raw Data

Structural magnetic resonance imaging (MRI) scans are often made of participants to aid localization. Some studies may also combine scalp EEG, iEEG and fMRI. For example, fMRI may be used in advance of electrode placement to identify networks and specific areas of interest (Fox et al., 2018). Thus, it is important to also have some basic understanding about MRI data as well. For a more thorough introduction to (f)MRI data, please see our guide on the topic.

Without knowing the precise placement of the electrodes, claims to the superior spatial resolution of iEEG are difficult to make (Lachaux et al., 2003). For iEEG, structural MRI scans are often made after surgical implant of the electrodes to assist in electrode localization, i.e. the labeling of anatomical placement as it pertains to the individual, strip or mesh of electrodes. A cortical mesh can be constructed by using the normalized structural scan and co-registering EEG data according to the fiducials (Henson et al., 2019). Because of the very individual nature of iEEG

electrode placement, researchers will likely have to plot out the location of electrodes manually with the assistance of a graphic interface. Photographic images taken during surgery, both before and after electrode placement can also greatly assist in this task (Dalal et al., 2008). It is important that the MRI images be taken after surgical implantation if possible, because of the brain-shift phenomena, which results from the surgical procedures, electrodes themselves and post-operative swelling. This can cause electrode displacement. This problem is most likely to occur with grid and strip electrodes and is less common in depth electrodes. T1 MRI scans taken post-implantation are the best method to use in terms of localizing electrodes, as brain-shift is less of a problem. However, in some cases electrodes may be difficult to identify in a T1 scan because they can appear dark and ill-defined due to artifacts caused by the electrodes themselves. In such cases, co-registration to a post-operative CT and pre-operative MRI scan may be preferred (Lachaux et al., 2003; Stolk et al., 2018).
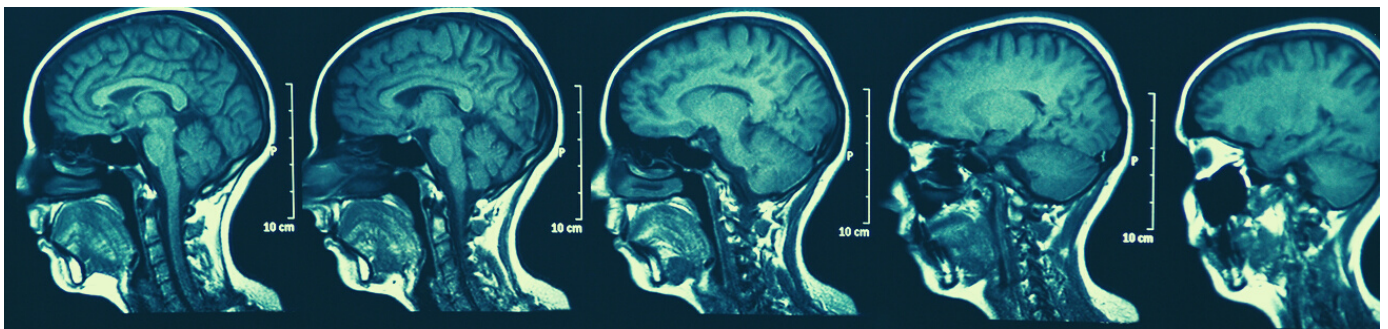
The raw data which is taken directly from the scanner is typically extracted as DICOM files. DICOMS entail a very high volume of data. Thus, one should ensure that the password-protected, encrypted hard drive used for transferring files from the scanner to Lagringshotell is large enough to account for this. DICOMS must be converted to NIfTI files, which is the format used by most modern neuroimaging analysis software. DICOMS may need to be sorted and re-named prior to conversion to NIfTI. Some conversion applications will automatically create a single NIfTI file from the DICOM images (.nii), while others may offer a two file option with an image file (.img) and a header (.hdr). Alternately, JSON files can be created by some programs to supply metadata that may be lost in DICOM conversion.

File	Extension	Type	Content
DICOM raw data	.dcm sometimes no extension	image	Structural or functional MRI data. DICOM files have an embedded header file.
NIfTI	.nii .nii.gz (compressed) .img & .hdr	image	Structural or functional MRI data file used by most analysis software. Can be produced as one file (.nii) or as two files with both the image (.img) and a header (.hdr). Files produced in pre-processing and analysis may also be NIfTI format.
JSON	*.json	metadata	Often created along with a .nii to capture metadata that otherwise may be lost in conversion from DICOM to NIfTI.

Data Extraction and Transfer

DICOM and iEEG data are temporarily stored on a password-protected, encrypted hard drive at the point of collection. It is important to retrieve this data on the day of data collection whenever possible. For example, DICOM images are routinely removed from the scanner console and will no longer be available for transfer unless arrangements are made with the radiographers in advance. The encrypted hard drive will then typically be delivered to the data manager. The data manager will then anonymize the data by removing any remaining sensitive information from header files and defacing the MRI scans. The original images will be kept in TSD and the data will be deposited in the durable folder on Lagringshotell for use. It is important that you make a copy of this data and do not work with data stored in the durable folder directly. You may instead copy the data to your own user folder on Lagringshotell for preprocessing and analysis. The data should never be stored on personal computers, and must remain in Lagringshotell.
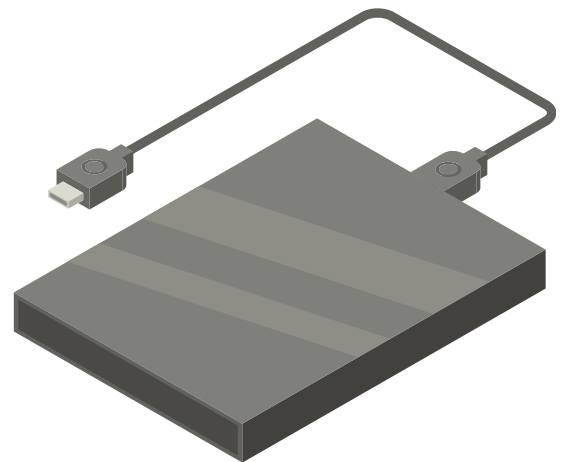
Analysis

VDI – Virtual Desktop Infrastructure. Recently, VDI's have become a popular tool for preprocessing and data analysis. VDI offers users access to a virtual computer with the software and processing power they need. This computer can be used in the same way you use your local computer but can be reached from different devices and operating systems. Which programs that are mounted and can run on the VDI machine is decided together by yourself, your local IT and program managers at the departments. A VDI may offer advantages over using one's office desktop computer for analysis, as the VDI processing capabilities are more powerful. The lab engineer can be contacted for more information about how to connect and use UiO's VDI's.

Software

Many of the available iEEG systems come with analysis software packages with varying levels of detailed descriptions of how the different preprocessing tools are implemented. In addition, several free and commercially available software packages that run on MATLAB/Python/R platforms, offer alternative implementations of data analysis tools. At the psychology department at UiO, MATLAB is the dominant software used for iEEG data preprocessing, analysis, and visualization. MATLAB is a high-level programming environment that is relatively easy to learn and use. The mostwidely used iEEG analysis packages are MATLAB-based, with the most commonly used being Fieldtrip (Oostenveld et al., 2011). MATLAB has a development environment that makes it easy to access large amounts of data. This is advantageous because one can easily inspect data during each stage of processing and analysis. One can also easily inspect and compare results from different subjects. MATLAB is also able to compute plots of your data that are customizable. These can be exported as pixel-based image files (.jpg, .bmp, .png, .tiff), vector files (.eps), or movies, which can be used to make presentations and publication-quality figures. In addition, custom-written software for preprocessing and subsequent analysis is commonly used. In-house software is usually notated by the researcher with descriptions and comments on the script..

Preprocessing and Analysis Considerations

The primary derivatives of the traditional, non-invasive scalp EEG are evoked potentials and event-related potentials. Evoked potentials (EP) are an electrical potential in following a stimulus recorded/seen in spontaneous EEG and is NOT time-locked to the event. In the case of EP, one averages the electrical activity within a specific period in which a stimulus was presented. Time-locked/event-related potentials (ERP) are measured brain responses that are a direct result of stimulus presentation and are time-locked to the event.

The iEEG records primarily local field potentials (LFP) and spike-density measures in neural activity (Lachaux et al., 2003). The cortical field potential (CFP), a recording of the activity of a local population of neurons (or the "spikes"); LFP, i.e. the direct measurement of a single or much smaller group of neurons (Fox et al., 2018); and the iERP (Lachaux et al., 2012) are the primary derivatives of iEEG. The LFP is the electrical potential that the iEEG electrodes record either subdurally or within the cortical tissue or other brain structures and is the phenomenon from which EP and ERPs are derived (Lachaux et al., 2012). Microelectrodes also have the potential to record action potentials. The spikes recorded represent the output of neurons, while the LFP represent the post-synaptic potentials, or the input of a neural population (Lauchaux et al., 2003). iERPs are calculated by event-related averaging of the LFP (Lachaux et al., 2012), while post-stimulus time histograms (PSTH) which are the iERP equivalent derived from spikes recorded by microelectrodes (Lachaux et al., 2003). iEEG can be used to study high frequency neural activity (HFA) and gamma-band responses (GBR) (Lauchaux et al., 2012). For a comprehensive description of these phenomena and how they relate to each other see Lachaux et al. 2003 and 2012.
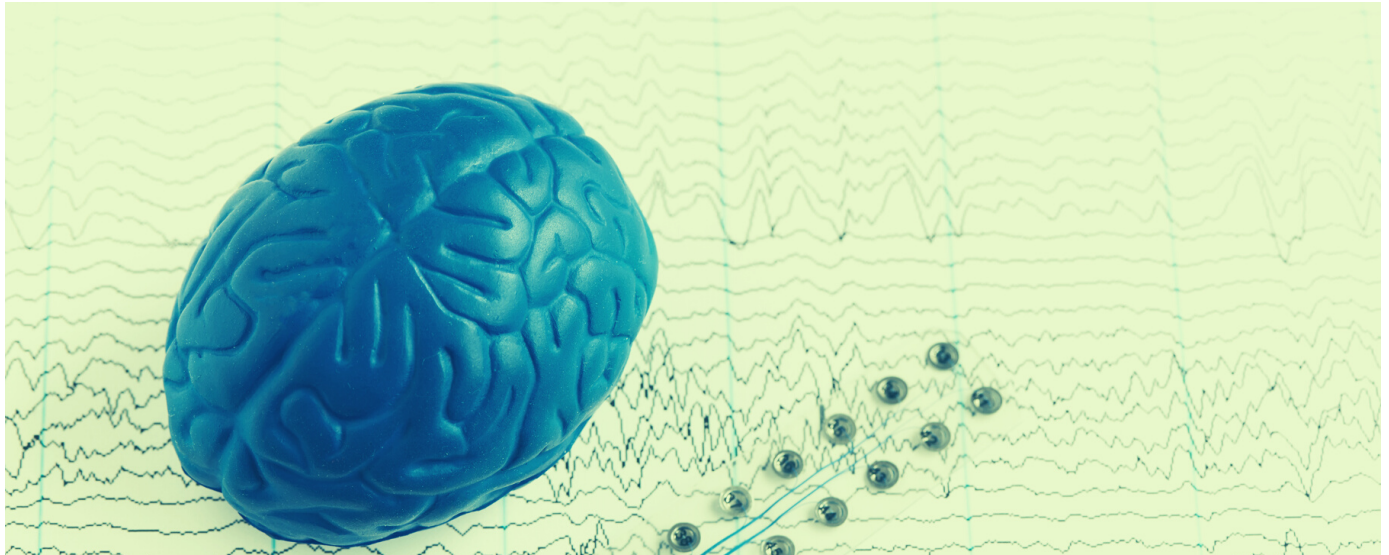
Preprocessing Steps

The high sampling rate of iEEG data means that files are much larger than with most electrophysiological data acquisition systems. That means that for processing iEEG files, you typically will need a computer with more than the standard amount of RAM. After reading the data in MATLAB memory, a common procedure is to downsample it to reduce the sampling rate (using the ft_resampledata function in FieldTrip). [EJ1] This will make all subsequent analyses run much faster and will facilitate doing the analysis with less RAM.

There are generally three workflows involved in processing iEEG data: handling of the MRI data and localization of electrodes/anatomical features, preprocessing of the iEEG data, and analysis itself. Unfortunately, no one program exists that is able to perform all of these steps, and thus the development of multiple workflows is often necessary (Stolk et al., 2018). The following section will provide a very basic description of the steps involved which lead up to analysis. The focus will be placed on the MATLAB-based, open-source Fieldtrip toolbox, which is not only the most widely documented program for iEEG preprocessing. For a more comprehensive description of an iEEG preprocessing and analysis protocol using Fieldtrip, see Stolk et al. (2018) and http://www.fieldtriptoolbox.org/tutorial/human_ecog/ which inform this section of the guide. Both sources also include links to a dataset that can be used as a tutorial to attempt analysis prior to working with data from your own study, as well as step by step directions and useful snippets of code.

The anatomical workflow

The anatomical data must be preprocessed, including conversion of DICOM files to the NIfTI format, defacing or skull stripping and compensating for the brain shift phenomena, spatial normalization and anatomical labeling. The anatomical data must also be coregistered, which can be performed using the most popular neuroimaging software, for example, SPM. Stolk et al. recommend the use of Freesurfer for co-registration and warping to a template, however, because the nature of how it performs these tasks, and the smoothing it performs, which can help accommodate for brain-shift and facilitate comparison across subjects (2018). For a basic guide to some of these tasks, including a brief description of the differences between SPM and Freesurfer, please see our guide Working With fMRI Data.

Electrode location must be established in concert with the anatomical scans and surgical photography, often manually, using a program like BioImage Suite or Fieldtrip with a graphical interface (Stolk et al., 2018; Fieldtrip, 2020). The electrodes must also be sorted and labeled, which can be done manually or with the use of software (Stolk et al., 2018). For the electrode placement step, you first will need to access the header information from the raw data recording file in order to create the electrode labels, which will be inputs in the electrode placement step. You will assign the locations to the different labels drawn from the header. To read the header you will use the command hdr = ft_read_header(<path to file>). The anatomical data may also be warped to an atlas, a universal template brain, for comparison across subjects where possible (Stolk et al., 2018). Alternately, you may opt to use two new semi-automated MATLAB localization and visualization toolboxes for iEEG: iElvis (Groppe et al., 2017) or iElectrodes (Blenkmann et al., 2017), which was developed at UiO.

Next, work must be done to the iEEG data itself to improve the signal to noise ratio.
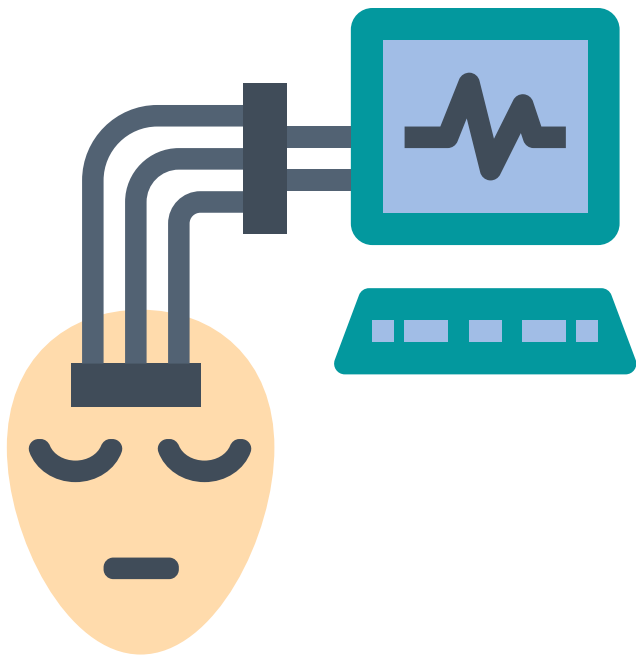
The signal to noise workflow

Because of the sheer size of the Neuralynx .nrd data files, when working with this system, steps must be taken to split the files into the .sdma format, which, as stated previously, splits the .nrd file into separate channels. This can be performed in Fieldtrip. All of the channel files for one session are deposited in one directory by Fieldtrip, which is able to read all files in the same session folder simultaneously.

LFPs are usually studied at a sampling rate of 512 Hz or higher. With the use of microelectrodes, the sampling rate can be as high as 30 kHz (Lachaux et al., 2003). After splitting the .nrd file, the data must be downsampled, for example, from 1,000-10,000 to 250-1,000 samples per second. Downsampling may change the temporal resolution. Downsampling solves the problem of huge data sizes that could otherwise make analysis slow and difficult. After downsampling of the data is performed, Fieldtrip allows for the data to be written into multiple non-proprietary formats, if so desired.

The data must then be segmented into epochs that correspond to the onsets of events of interest in the experiment. This is done using the event codes from the data file (Acheson, 2019). Epochs can also include an entire trial, made up of multiple events, if the data analysis strategy calls for it. It is important to understand that different file and acquisition systems can have very different time stamp definitions (Fieldtrip, 2020). These epochs will be eventually put on the same scale by averaging the signal from a short time prior to the onset, or the 'baseline period' and subtracting the average from every time-point in the epoch (Acheson, 2019).

The next step in preparing iEEG data for analysis is to apply a low pass and high pass filter to achieve a more smooth, defined signal. You can use the command help ft_preprocessing for assistance in applying filters to the data.[EJ1]

In the past it has been argued that iEEG is also not prone to artifacts from movement in the same way as regular EEG, however, several research teams have discovered that although the artifacts are not as severe with iEEG, they are still often present in the data (Nejedly et al., 2018). Movement artifacts may result from the fact that the patient is hooked up to wires outside the body (Parvizi & Kastner, 2018). iEEG is also not entirely immune to artifacts from muscle and eye movement (Jerbi et al., 2009; Kovach et al., 2011) or power-line interference (Nejedly et al., 2020). Movement of the electrode within the brain itself is also a consideration (Nejedly et al., 2018).
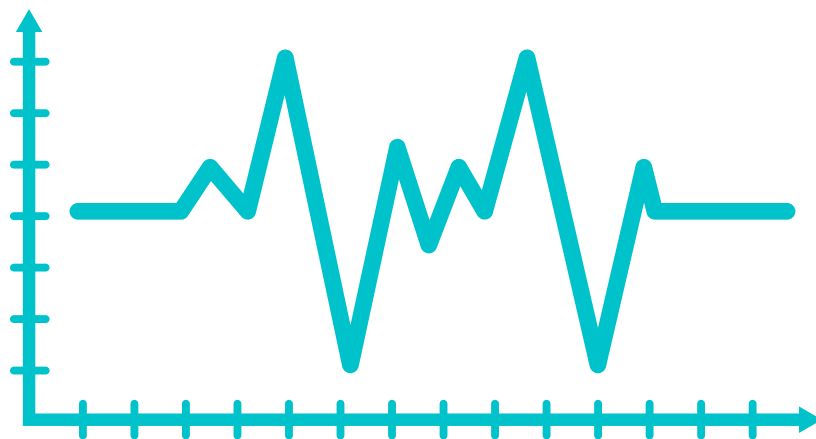
Since you are also working with a patient group which will most likely experience seizure activity during experimentation, it is also important for a clinician to annotate where seizures have occurred so that those signals can be omitted. For a description of the kinds of artifacts one might encounter with iEEG, as well as a visualization of these artifacts, see Nejedly et al., 2020. For suggestions for dealing with these eye movement artifacts see Kovach et al., 2011. Methods of locating noise and pathological activity include manual visual evaluation, independent component analysis, and more recently, convolutional neural networks (Nejedly et al., 2018).

Re-montaging (re-referencing to a different montage scheme can help remove noise occurring across channels. You may re-montage the cortical grids to a common average reference, for example. A bipolar montage may also be applied to depth electrodes. Before this is done, it is important to ensure that bad channels have been removed (Stolk et al., 2018).

Next you want to merge the data into one data structure to make subsequent processing and analysis easier. After this, one may opt to apply a time-frequency analysis and perform interactive plotting of the data as it relates to the electrodes to allow for further analysis exploration.
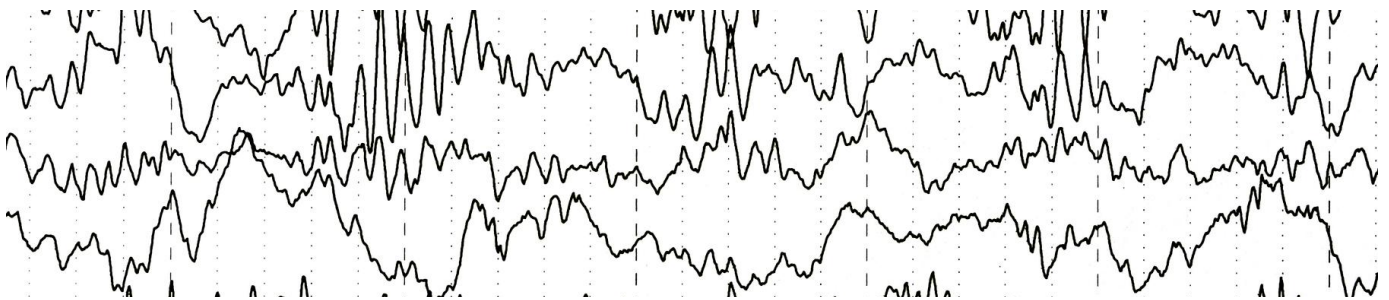
For more precise tutorials on preprocessing and analysis of iEEG data using the MATLAB Fieldtrip Toolbox, see Stolk et al., 2018, as well as the following links:

Analysis of human ECoG and sEEG recordings:
http://www.fieldtriptoolbox.org/tutorial/human_ecog/
Analysis of high-gamma band signals in human ECoG:
http://www.fieldtriptoolbox.org/example/ecog_ny/
Preprocessing and analysis of spike and local field potential data:
http://www.fieldtriptoolbox.org/tutorial/spikefield/

The exact details of analysis will vary by study, and will be based upon the research question at hand, but typically the next steps in analysis entail averaging signals in the events of interest within subjects, followed by averaging these averages across subjects, if possible, given the constraints of iEEG.

The two workflows of preprocessing (steps and order will vary)

Removal of sensitive information from the raw data files	Conversion of raw data neurophysiological data
Conversion of raw data image files to NIfTI	Separate out the trials/events amd merge LFP and spike data.
Establish electrode placement	Filter for high-frequency noise/electrical interference
Cortical surface extraction/skull stripping	Check data to ensure the sampling rate, recording channel and trials are correct
Fusion of CT & MRI images	Add electrode information
Brain shift compensation (as needed)	Identify and remove channels with artifacts, epileptic activity or other issues
Spatial normalization/Volume-based registration/Surface-based registration	Remontage cortical grids to reference and apply bipolar montage to depth electrodes
Anatomical labeling	Combine data from all electrode types (if relevant)

Time frequency analysis/spectral decomposition

Statistical analysis (will vary by study)

Create representation of electrode placements and cortical activity for ECoG and sEEG data

Behavioral Data

Additional behavioral data can be acquired from the stimulus presentation software. This data can be used in conjunction with the iEEG data during analysis. Their use tends to vary according to the study's needs. For example, you may require information about a participant's responses or response times in order to understand the patterns of activation in your iEEG data. Presentation, Psychtoolbox for MATLAB and E-Prime tend to be the most popular programs for experiments in labs, however open source programs like PsychoPy are coming more and more into use. Paradigm, PEBL, and Inquisit are additional programs for creating neuroscience experiments that you may encounter. For more information on the behavioral data you may encounter, please see our guide *Working with fMRI Data.*

Data sharing

When sharing (or intending to share) data, scientists should keep certain things in mind to make the lives of their colleagues easier, as well as to protect privacy of the participants.

Metadata

For the purposes of maintaining as much metadata as possible, it is important to not only keep track of each step carried out in the preprocessing and analysis processes, but also to maintain detailed information about its collection, such as the exact type of electrodes used, their diameter and depth, as well as the data acquisition system that was used (for example, Neuralynx or Micromed, mentioned above). Detailed information about what programs and methods were used to place electrodes, discarded channels and reference electrode placement are also crucial for others to understand and evaluate your data.

The brain imaging data structure (BIDS) (Pernet et al., 2018) is a format to share neuroimaging data using agreed upon standards created by the neuroimaging community. BIDS offers a systematic way to organize data into folders using dedicated names, in association with text files, either as tabulated separated value file (.tsv) or JavaScript Object Notation file (.json) to store metadata.

BIDS was originally created for the fMRI modality, however, it has recently been adapted to several other modalities, and more are in the works. One recently added specification is iEEG (Holdgraf et al., 2019). BIDS for iEEG demands that an electrode coordinate system is provided as well as the images that allow one to visualize the electrode placement (typically defaced MRI or CT scans). These should be provided as NIfTI files with the BIDs naming scheme. Localization data is stored in the _electrodes.tsv and _coordsystem.json files. Event timing data is presented in a _events.tsv file. BIDS for iEEG allows for several neurophysiological data formats to be used. This is because it was difficult to reach a consensus about a gold standard among researchers. Therefore, BIDS allows for two compliant formats: the European Data Format (.edf) and the Brain Vision Core Data format (.vhdr, .vmrk, .eeg). For more information on the Brain Vision format, see our guide Working with EEG Data. Unofficially supported formats include Neurodata Without Borders (.nwb), EEGLab (.set), and Multiscale Electrophysiology Format (MEF3).

BIDS additionally has a javascript validator that can help researchers pinpoint issues when their dataset does not conform to the standard.

We encourage the iEEG community to share their data by using this data structure as it facilitates communications, increases reproducibility and makes easier to develop data analysis pipelines. It also facilitates compliance with the FAIR principles of findability, accessibility, interoperability, and reusability. Incentives to using the structure increase continuously, and include the creation of toolboxes that automate working with BIDs compliant data. See our handbook Structuring Data with BIDS for more information.See our handbook *Structuring Data with BIDS* for more information.

Research data archives

There are both national, international, and domain-specific archives that meet international standards for archiving research data and making it accessible. UiO's researchers can choose the archiving solutions that are most appropriate to their discipline and that meet the conditions of applicable legal frameworks. Depositing data resources within a trusted digital archive can ensure that they are curated and handled according to best practices in digital preservation.

Some archival resources are:

- Re3data.ord (a global list of archives)
- Zenodo (EU's archive)
- NSD (national archives)
- NIRD/Sigma 2 (national archives)
- DataverseNO (national archives)

For more information, see our guide *DataManagement: DMPs & Best Practices.*

Anonymization

iEEG data on its own (as well as the related behavioral data) do not constitute sensitive data, however, the headers associated with the iEEG raw data files contain sensitive data that is recorded for clinical purposes, including the participant's name. Due to the large number of files produced by iEEG acquisition systems, the removal of this sensitive data must be automated. You may contact the data manager for help with this task, or it may be performed for you in advance before the data is placed in Lagringshotell.

It is important to anonymize data from the start of data collection by providing participants with participant numbers and keeping any identifying information like name, address, phone number, birthday or national identification number separate from the EEG data. Name, contact information and the subject's ID are not stored together. Documents where ID and name are linked are stored on encrypted storage mediums. Those devices should be stored in locked cabinets separate from the data. These steps are of even greater importance when one is working with patient populations.

MRI or fMRI data used in conjunction with EEG data is inherently sensitive and requires safe handling of data. Data is removed from the scanner on password-protected, encrypted hard drives. At the point of transfer of data from the scanner to external encrypted hard drive, one must always remember to check the box for anonymization of the data at the scanner console and designate a participant number or alias instead. This is because DICOMs have headers that contain identifying patient data. If anonymization is not performed at the source, the DICOM headers must be anonymized by hand, which can be time-consuming. Storage of neuroimaging data is permitted only in TSD or Lagringshotellet at UiO. Some patient groups may only be stored in TSD. Prior to data archival and sharing, neuroimaging data must be defaced.

Creating a Data Management Plan for EEG Research

Now that you are familiar with some of the data-related topics and concerns that should be considered when conducting an iEEG study, you may feel better equipped to complete a data management plan document. The following offers questions specific to iEEG data to guide the creation of such a document. For a more in-depth exploration of how to create a data management plan, please see the HTD guide *Data Management. DMPs & Best Practices.*

- **Who is the study's P.I.? What other team members will be involved in data collection and analysis? What medical personnel will be involved in the research and at what hospital will the research be performed?**

- **What software will you use for stimuli/experiment presentation and behavioral data collection?**

- **What software do you foresee using for analysis?**

  Knowing what software will be used ahead of data collection will help you to make an appropriate data management plan from the start.

- **How will your data be handled in the curation phase, once the study is over? What data repository will you use? What requirements do they have for data management? Can you maintain this standard throughout the study? What will data curation cost?**

  Many data repositories have requirements for file structure and naming conventions, as well as the file types that are preferred. If you are aware of these requirements beforehand, you can save time once the time for curation arrives by using those guidelines over the course of the study. You will need to know and plan for the costs that will be incurred for data sharing and curation when applying for funding.

- **What types of electrodes will be used? What programs will be used in their localization and what neuroimaging methods will be employed in this process?**
- **What iEEG system will be used in data collection? What file types does it generate?**
- **Who will be responsible for identifying epileptic activity in the data and which channels will be discarded? How will this process be carried out?**
- **What file types do your behavioral data programs generate?**
- **Will you share your data? Under what license will you share your data? What limitations will be placed upon access to your data?**
  For a comprehensive description of the different licenses that can be applied to data sharing and usage see https://www.ucl.ac.uk/library/research-support/research-data-management/licenses-data-sharing-creative-commons
- **How will you pilot your project? What will be done with the data from the pilot study?**
- **How many participants will your study have? How will you ensure the welfare of the patient group?**
  Special considerations must be taken when handling data related to studies involving patient groups to ensure their welfare and anonymity.
- **How many runs or sessions will the study have per participant?.**
- **Will you collect sensitive classes of data?**
  Sensitive classes of data include identification numbers, birthdates, neuroimaging, information related to health conditions, information about race/ethnicity, political affiliation, sexual orientation or in some cases gender identity/biological sex (for example when working with transgender or intersex populations).
- **What ethics committees will you need to apply to? What are their data management requirements?**
  Most studies conducted under PSI will be required to submit applications to REK, NSD or both. Their data management requirements are detailed on the committees' websites.

- **Who is funding the study? What are the funder's requirements for data management plans?**

  Most funding entities require at least a basic data management and data sharing plan to accompany funding applications.

- **What information will be provided to participants in advance of participation and in what form? What are your plans for collecting informed consent? How will you store the consent forms once they are collected?**

- **How will you store the data key linking participants to their data?**

- **If you will collect sensitive data, how will it be stored and analyzed? What protections will be put in place to ensure anonymity is maintained?**

  At UiO, sensitive data can be stored and analyzed in TSD or on Lagringshotellet, depending on the degree of sensitivity of the data.

- **How will you store non-sensitive data? In what environment do you plan to analyze it?**

- **Who will have access to the data? Who is responsible for transferring data to storage once it is collected?**

- **What file naming conventions will be used for the various file types that make up your dataset?**

- **Will you use in-house written code? What programming language will you use? Will this code be made available to the scientific community? If so, where will it be made available?**

- **Will you maintain a lab notebook? How will the lab notebook be used and who will have access?**

  Digital lab notebooks are now quite common, but can raise questions of data security.

- **Will you convert proprietary file types to more standardized file types prior to sharing your data?**

- **How will the findings be disseminated?**

- **How will you record metadata related to the study for future sharing?**

  Metadata is data about your data that can help researchers who later want to access your data to understand how the study was conducted. It may also help members of your current team understand the data they are working with.

- **Who will be responsible for the data in the long term once the study is completed?**

  This is important to consider for all studies, but especially important for longitudinal studies. Personnel and staff may leave your institution or be difficult to contact in the future. A primary contact person who is responsible for the data should be designated. Should they leave the institution or retire and a new responsible party is designated, then the repository should be updated with their information.

Recommended Resources

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Elian E. Jentoft & Rene S. Skukies

Human Time Data 2019