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Chapter 1. Introduction

This work serves as a foregoing research of different functional connectivity measures of MEG-based data. The human brain could be modelled as a network with structural and temporal functional connections (Pessoa, 2014). The first one could be referred to as anatomical connectivity, reflecting physical connections, i.e., cellular circuits and long-range fibre (Sporns, 2013). On the contrary, functional connectivity describes the statistical dependencies present between different brain regions based on their activity patterns through the means of statistical analysis. Distinct neural interactions are studied with the help of various non-invasive neuroimaging techniques such as PET (positron emission tomography), fMRI (functional magnetic resonance imaging), MEG (magnetoencephalography), and EEG (electroencephalography) (Aiello et al., 2016; Gaudet et al., 2020) to explore connectivity patterns or physical connections.

The brain dynamics research provides insight into the development and pathology of the human brain (Hohenfeld et al., 2018; López-Vicente et al., 2021), and the founding idea of this approach comes from the concept of the brain as a complex system, "in which mental states emerge from the interaction between multiple physical and functional levels" (Bassett and Gazzaniga, 2011). Connectivity analysis offers a helping hand in identifying patterns of such interactions to reveal brain networks that support cognitive performance. Specifically, functional connectivity analysis is a valuable tool to examine diseases that are believed to exhibit changes in the connectivity patterns, like Alzheimer's disease, dementia, schizophrenia, and multiple sclerosis (van den Heuvel and Hulshoff Pol, 2010), as well as anxiety (Lee et al., 2021) and bipolar disorder (Mamah et al., 2013).

Functional connectivity is the estimate of the information flow within the brain networks which could be dynamically coordinated by changes in the strength and frequency of the oscillatory activity (Bastos and Schoffelen, 2016). Those oscillatory interactions are measured by specific connectivity metrics, or measures, each of which explores an individual component of the signal. A wide variety of metrics have been suggested and explored by many experts in the field (Haufe et al., 2013; X.-J. Wang, 2010; Bastos and Schoffelen, 2016; Pellegrini et al., 2023 and others). These measures could be differentiated by the component they are aimed to analyse. However, higher level division is possible to be made based on the ability of the mea-

sure to capture the direction of the interaction: metrics that capture only the presence of the interdependence between the signals (Bastos and Schoffelen, 2016) and do not assess the direction of the information flow are, thus, called non-directed; and metrics that are designed in such a way to establish the causal relationship between the signals are directed.

The analysis of the information flow within the networks has proved to be quite challenging primarily due to the issue of spatial (or source) leakage caused by the volume conduction properties of neural signals (Haufe et al., 2013; Pellegrini et al., 2023). The EEG and MEG neuroimaging techniques capture the resulting entities of electrical currents generated by neurons: electrical potentials on the scalp (in the case of EEG) and magnetic fields outside the head (in the case of MEG) registered by sensors (Hari et al., 2023). Electrical currents pass through the conductive medium in the head (brain tissue, cerebrospinal fluid, skull, scalp), and this spreading is easily picked up by multiple sensors, resulting in sensors measuring an unknown superposition of brain activities (Shahbazi et al., 2010). As a result, activity from an EEG electrode placed above a portion of the motor cortex does not accurately reflect the activity of motor neuronal populations. It has even been shown that volume conduction artefacts alone could be the reason for high connectivity estimations (Westdrop, 1993), and, thus, they pose a large obstacle to the functional analysis.

According to Pellegrini et al. (2023), one approach to resolve the unknown superposition of the signals in the sensor space is to project them to the source space. This operation refers to solving the inverse problem, estimating source locations from the recorded activity (Baillet and Garnero, 1997; Pascual-Marqui, 1999). Electromagnetic imaging of the brain provides high temporal resolution, however, poorer spatial resolution (Lopes da Silva, 2013) than fMRI or PET can offer. In this way, many solutions to this problem exist, since different source arrangements effectively lead to the same EEG and MEG measurements (Lopes da Silva, 2013). Nevertheless, modern approaches to inverse modelling try to account for the volume conduction artefacts (Haufe et al., 2013). Much attention is paid to finding the optimal analytical pipeline, including both stages of the analysis: reconstructing the source space and utilising the appropriate connectivity metrics. Haufe et al. (2013) and Pellegrini et al. (2023) test popular measures of connectivity and the ability of different source reconstruction techniques to improve the connectivity estimate, with the latter also testing the influence of additional constraints such as the number of interactions between the

signals, signal-to-noise ratio (SNR), the composition of the noise, and the length of the interaction delay (Pellegrini et al., 2023). Both articles use simulated data to test various pipelines to control for the ground-truth interactions. As stated by Haufe et al. (2013), "simulations are the only way to benchmark a method's ability to solve the task". It is important to note that simulated data do not specifically refer to noiseless time series of two sources, since real MEG and EEG data include background brain activity and spatially incoherent brain noise components (Ossadtchi et al., 2018). For that reason, simulated data are biologically relevant taking into account the effects of volume conduction and simulating brain noise. As a result, both papers suggest benchmarks for neural time series connectivity analysis. With guidance from Haufe et al. (2013) and Pellegrini et al. (2023), specific methods included in the analytical pipeline – linearly constrained minimum-variance (LCMV) beamforming and time-reversed Granger causality – have been chosen for the subsequent application in the analysis of MEG data that will follow this paper.

The purpose of this work is to list the most popular connectivity measures and describe the area of their application, providing mathematical motivation for the use of a particular metric. The application area – anxiety research – is given attention in Chapter 3, emphasising the importance of the functional connectivity analysis in the study of anxiety, given its connectivity-altering nature. The research plan is detailed in subsequent chapters, including a description of the experimental data collected by the HSE affiliated group which have been used to study oscillatory activity in learning and decision-making in anxiety (Hein et al., 2023).

Chapter 2. Connectivity research

Cognitive processes are supported by complex temporally and spatially distributed networks (Rolls et al., 1997; Bassett and Gazzaniga, 2011, Bassett et al., 2018, Smallwood et al., 2021). Understanding how these networks are formed and broken apart, how they change, and how they communicate with other networks and within themselves is the goal of the neuroscientific quest. Networks are characterised by functional and structural connectivity, which can be derived using various neuroimaging techniques. The two have been researched in relation to one another highlighting the ideas that 1. functional connectivity is a reflection of structural composition (Greicius et al., 2009) and that 2. functional connectivity might be predicted from structural connections, assuming that strength, persistence, and spatial distribution are constrained by the large-scale anatomical structure of the human brain (Honey et al., 2009).

While structural connections are deemed to be more persistent on a shorter time scale (up to minutes), functional connectivity is highly time-dependent and could change in a matter of fractions of milliseconds (Sporns, 2013). Given the difficulty of characterising dynamic connections formed on the microscopic level (Seguin et al., 2023) and the inability to control for those changes, identifying reliable functional connectivity patterns becomes a challenging issue. Nonetheless, it is an important methodological approach to explore cognitive and perceptual processes such as attention (Parks and Madden, 2013, Madhyastha et al., 2015), decision-making (Cohen et al., 2005, Li et al., 2013), visual perception (Deshpande et al., 2008, Ardila et al., 2015), etc. Neurodegenerative disorders (slowly progressing disorders of the nervous system characterised by necrosis – the death of the nerve cells) such as the Alzheimer's disease, Parkinson's disease, and dementia (Dugger and Dickson, 2017), are also characterised by the structural and functional changes in the brain: for example, Alzheimer's disease is characterised by the damage to one of the local networks of the global neural network – default mode network (DMN) (Hohenfeld et al., 2018), which is activated during the periods of rest, when individuals do not actively focus their attention on the external environment (Buckner et al., 2008).

Connectivity analysis is, thus, aimed at "untangling" recorded sensor time series (in the case of functional connectivity) into more or less coherent patterns of synchronised neuronal activity. Connectivity analysis has only gained popularity in the

recent years, since the hypothesis that synchronisation of the neural oscillations enables dynamical coordination as it reflects the fluctuations of the rhythmic excitability among local neuronal populations, facilitating the flow of neural information within the network (Singer, 1999; Buzsáki and Wang, 2012; Fries, 2015) has been widely accepted in the field of neuroscience (Bastos and Schoffelen, 2016).

2.1 Types of Connectivity

As stated above, connectivity is a comprehensive term combining anatomical connections and statistical dependencies between patterns of activity, which on a larger scale provides the necessary means for near-optimal information processing (Lang et al., 2012). When performing brain connectivity analysis, it is important to differentiate between the two types of connectivity (Sporns, 2013).

2.1.1 Structural connectivity. Structural connectivity describes anatomical links between neural elements: individual neurons, neuronal ensembles, and large brain networks. Neurons are grouped into neural circuits since no individual neuron is isolated (Purves et al., 2018). Structural connectivity is the foundation upon which the structural "connectome" is built. "Connectome" is the term that was independently introduced in 2005 by Olaf Sporns (Sporns et al., 2005) and by Patric Hagmann (Hagmann, 2005). In the field of neuroscience, the word “connectome” can refer to both a complete representation of all neural connections in an organism, i.e., microscale connectome (Van Essen et al., 2013), or the mapping of connections between different regions of an individual’s brain, i.e., macroscale connectome, using various neuroimaging modalities (Gleichgerrcht et al., 2015). Performing the first task regarding the human connectome – mapping 10 trillion connections between around 90 billion neurons (Van Essen et al., 2013; Bassett and Bullmore, 2017) – is a difficult task due to the large amount of information and the lack of a complete picture of the brain (Pessoa, 2014). A currently more practical approach to connectomes is to map the connectivity of the brain regions for each individual using neuroimaging tools.

Structural connectivity data might be extracted using histological methods for tracing neuronal pathways (Meijering, 2010); electron microscopy which allows for ultra-high-resolution (Abbott et al., 2020); and diffusion MRI for revealing white matter fiber tracts (Yeh et al., 2021).

2.1.2 Functional connectivity.

While structural connections are physical in nature, functional connections may only be detected through data analysis. Functional connections are not necessarily structural, since functional connectivity reflects statistical relationships between distinct and distant regions (Lang et al., 2012); thus, it is not a physical entity, but rather a statistical concept.

Neural time series can be extracted by means of neuroimaging techniques, including MEG, EEG, and fMRI. Statistical analysis relies on a variety of statistical measures, which will be described in more detail below. However, it is important to note here, that those measures could be directed and non-directed, highlighting different aspects of connectivity. While non-directed metrics characterise statistical dependencies regardless of their direction and causal influence, directed measures aim to describe the influence one region exerts upon another (Friston, 2011), reflecting specific relations between the signals. Such directed connections fall under the definition "effective connectivity," which strives to explain observed functional dependencies.

While some explicitly differentiate between the two – functional and effective connectivity (Friston, 2011; Lang et al., 2012; Haufe et al., 2013; Sporns, 2013) – others are not as strict (Bastos and Schoffelen, 2016; Pellegrini et al., 2023). In this paper, this distinction is addressed by differentiating between connectivity types using directed and non-directed measures, which correspond to effective and functional connectivity, respectively.

2.2 Measures of Connectivity

It has been stated that connectivity measures are divided into non-directed and directed. Additionally, within directed and non-directed measures, another differentiation can be made based on the assumption of linearity: model-based measures assume that all interactions are linear, while model-free measures do not require this assumption (Bastos and Schoffelen, 2016). The third basis for differentiation involves the specific component of the signal that is of interest, whether it is phase-to-phase coupling, phase-to-amplitude coupling, or amplitude-to-amplitude coupling. Generally, oscillations can be characterised by three main components – phase, power (or amplitude, which is the square root of power), and frequency (Cohen, 2014) – which could be represented in time or frequency domains. The phase of the signal refers to the timing of the oscillation, the amplitude measures the magnitude of the change

of the oscillation, and the frequency refers to how fast an oscillation is. Phase-based connectivity measures are aimed at assessing phase-to-phase coupling and are widely used (Cohen, 2015; Bastos and Schoffelen, 2016) under the hypothesis that phase changes and synchrony of these changes underlie neuronal communication (Bastos et al., 2015).

While sensors record activity as a function of time, neural time series are conveniently represented and analysed in the frequency domain. Neural oscillations reflect the electrical activity of neuronal populations, and this rhythmic brain activity is composed of multiple frequencies simultaneously. These frequencies can be separated using various signal-decomposition techniques such as Fourier decomposition, wavelet transform, Hilbert transformation with band-pass filtering, etc. (Brookes et al., 2004; Cohen, 2014; Bastos and Schoffelen, 2016, Zhou et al., 2020). Rhythmic oscillations are grouped into different bands by the frequency intervals that underlie different cognitive processes (Ward, 2003; Thut et al., 2012; Cannon et al., 2014). Subsequently, connectivity measures estimated in the frequency domain can be used to assess such neuronal interactions.

The given work will focus on the model-based measures of phase relations. Linear methods are able to capture oscillatory interactions, given the assumption that phase coupling is the primary regulator of such interactions. (Bastos and Schoffelen, 2016; Pellegrini et al., 2023). In this chapter, several measures will be described: coherence, coherency, additional metrics focused on the imaginary part of coherency (the imaginary part of coherency and maximised imaginary coherency), Granger causality with its time-reversed version, and phase-slope index. All these metrics are derived from the cross-spectrum, which is used to define the relationship between two time series in the frequency domain. Cross-spectrum can be defined as the Fourier transform of cross-covariance, which measures how common activity between two processes is distributed across frequencies. Cross-covariance function, in turn, measures one signal's covariance with another at each pair of time points. Equivalently, cross-spectrum can also be computed as follows (Nunez et al., 1997):

$$S_{xy}(f) =< x(f)y^*(f) >$$

where $S_{xy}(f)$: the cross-spectrum defined at frequency f
$x(f)$: the Fourier transform of the multivariate time series $\overline{x}(t)$ where
$t \in \{1, \ldots, T\}$ refers to indices of time samples

$y^*(f)$: the complex conjugate of the Fourier transform of the multivariate time series $\overline{y}(t)$ where $t \in \{1, \ldots, T\}$ refers to indices of time samples
$< >$ operation: expectation value (average).

2.2.1 Non-directed metrics. Non-directed measures do not assess the influence one time series has over another, they are merely an indication of statistical correlation between the two time series. One such measure to quantify phase synchrony is the coherence, which is the equivalent of the cross-correlation function in the time domain. Coherence is a real-valued number, which provides information about the strength of linear correlation between the two time series (Pellegrini et al., 2023) and ranges from 0 to 1, where 0 indicates no linear relationship at a specific frequency, while 1 indicates an ideal linear relationship at a specific frequency.

However, coherence captures both zero-lag interactions and non-zero-lag synchronisation. Due to the volume conduction artefacts introduced by the nature of electrical conduction in the conductive tissue of the head, substantial zero-lag interactions are explained by spatial leakage, and, thus, contaminate the result of the connectivity analysis with volume conduction artefacts are deemed to be genuine interactions (Nolte et al., 2004). As suggested by Nolte et al. (2004), the imaginary part of coherency is a measure that estimates true brain interactions, since by definition it is only sensitive to non-zero-lag synchronisation. The fundamental assumption that lies behind this approach is that volume conduction is instantaneous. By taking the imaginary part of coherency, one discards artificial interactions that are not related to genuine neuronal communication.

Both coherence and the imaginary part of coherency are derived from the coherency, which is a complex-valued measure and provides information not only about the strength of correlation between the two time series but also about the average phase difference between them. As given by Nunez et al. (1997), coherency is defined as the normalised cross-spectrum:

$$C_{xy}(f) = \frac{S_{xy}(f)}{\sqrt{S_{xx}(f)S_{yy}(f)}}$$

where $C_{xy}(f)$: the coherency defined at frequency f
$S_{xy}(f)$: the cross-spectrum defined at frequency f
$S_{xx}(f)$: the power spectral density (PSD) of the Fourier transform of the signal

$\overline{x}(t)$

$S_{yy}(f)$: the PSD of the Fourier transform of the signal $\overline{y}(t)$.

The PSD used in the calculation represents the amount of power (squared amplitude) present in the signal at a specific frequency. Coherence is derived from the coherency by taking the absolute value: $\text{COH}_{xy}(f) = |C_{xy}(f)|$, where $\text{COH}_{xy}(f)$ is the coherence defined at frequency f, $C_{xy}(f)$ is the coherency defined at frequency f, and $|\ |$ operation is the absolute value defining the magnitude of the measure.

The imaginary part of coherency is obtained from the coherency by projecting it onto the imaginary y-axis (Bastos and Schoffelen, 2016) and calculated by, thus, taking the imaginary part of the coherency: $\text{ImCOH}_{xy}(f) = C_{xy}^{\Im}(f)$, where $\text{ImCOH}_{xy}(f)$ is the imaginary part of coherency, $C_{xy}(f)$ is the coherency, and $\Im$ operation refers to taking the imaginary part. The absolute value of $\text{ImCOH}_{xy}(f)$ ranges from 0 to 1, where 0 refers to no consistent phase relationship with a non-zero lag, indicating no connectivity; 1 refers to ideally consistent phase relationship with a non-zero lag, indicating significant connectivity.

The metrics described above are not meant to provide one aggregated functional connectivity score, but instead, they measure connectivity for all pairs of channels (sensors). A single functional connectivity measure can be obtained by averaging all $\text{COH}_{xy}(f)$ or $\text{ImCOH}_{xy}(f)$ functional scores, respectively (Pellegrini et al., 2023).

Between $\text{COH}_{xy}(f)$ and $\text{ImCOH}_{xy}(f)$, the former is non-robust, while the latter is. $\text{ImCOH}_{xy}(f)$ is robust to volume conduction artefacts, meaning that it vanishes for independent sources (i.e., they do not interact in any way) even if they are mixed and detected by multiple sensors. Thus, if the metric is non-zero, it is a signature of true interactions between brain sources (Ewald et al., 2012). Another such measure is MIC (maximised imaginary coherency). It generalises $\text{ImCOH}_{xy}(f)$, which explains its robustness against spatial leakage. Apart from being robust, it also deviates from the previous coherency-based methods by being multivariate, while the former ones are bivariate, i.e., estimating connectivity between a pair of signals. Multivariate measures, on the other hand, capture interactions between groups of signals. The multivariate approach offers methodological improvements to the connectivity analysis such as reducing the biased estimations of the connectivity based on the spatial proximity of sensors (Ewald et al., 2012), easier results interpretability following the dimensionality reduction, and enhanced SNR.

MIC utilises the projection operation. $x(f)$ and $y(f)$ are the Fourier trans-

form of multivariate time series $\overline{x}(t)$ and $\overline{y}(t)$. Each of them forms a linear subspace with a number of dimensions being equal to K and L, respectively. K and L refer to the number of data dimensions that could come from the representation of the three dipole orientations along axes x, y, and z. Neural dipole represents the current generated by a neuronal population with a certain orientation (that could be fixed or free, thus, referring to the three dipole orientations) and location. MIC is based on finding projections (linear transformations from and to a vector space) from two multi-dimensional spaces to two one-dimensional spaces; such projections should provide the maximal value of $\text{ImCOH}_{xy}(f)$ between the projected signals (Pellegrini et al., 2023). As shown by Ewald et al. (2012) and Pellegrini et al. (2023), MIC is calculated as follows:

$$\text{MIC}_{xy}(f) = \max_{a,b} \left(\frac{a^T \overline{S}^{\Im}_{xy}(f) b}{|a||b|}\right)$$

where a and b: projection weight vectors that correspond to subspaces of $x(f)$ and $y(f)$, respectively

$\overline{S}^{\Im}_{xy}(f)$: the whitened imaginary part of the cross-spectrum $S_{xy}(f)$.

The use of the imaginary part of the cross-spectrum ensures that only genuine interactions are captured, and the whitening operation on the imaginary part of the cross-spectrum transforms the power spectrum, making all frequencies have equal power by removing the auto-correlations in the time series (Ewald et al., 2012). Auto-correlation is a correlation of a signal with a time-delayed version of itself. Due to the nature of the signal spread, volume conduction introduces spatial correlations between different sensors. If one source is picked up by multiple sensors, auto-correlation of that source signal will contaminate all affected sensors. Thus, the whitening operation helps achieve a clearer signal of true brain interactions. MIC ranges between 0 and 1, where 0 indicates no functional connectivity, and 1 indicates ideal functional connectivity.

2.2.2 Directed metrics. Directed measures assess the influence one time series has over another, they assess the existence of the interaction and estimate its direction. As stated above, $\text{ImCOH}_{xy}(f)$ is a non-directed measure, however, the positive imaginary part of coherency $\text{ImCOH}_{xy}(f)$ would generally suggest that the signal $x(f)$ precedes $y(f)$, and the negative value would suggest that the signal $x(f)$ lags

$y(f)$ (Haufe et al., 2013). Nonetheless, due to the periodicity of the oscillations, it cannot be surely determined which signal precedes or lags. One approach that utilises this and resolves the issue has been suggested by Nolte et al. (2008): the phase-slope index (PSI) is based on the aggregation of the information contained in the non-zero-phase lags bounded by specific frequency (Haufe et al., 2013). The concept of using the phase slope is based on the idea that interactions take time to occur, and thus, when waves travel at comparable speeds, the phase difference between the source and the destination increases with frequency, leading to an anticipated positive slope in the phase spectrum (Nolte et al., 2008). Nolte et al. (2008) suggest the following equation to estimate PSI:

$$\Psi_{xy} = \Im\big(\sum_{f \in F} C_{xy}(f + \delta f) C^*_{xy}(f)\big)$$

where Ψ_{xy}: PSI estimated for the Fourier transforms $x(f)$ and $y(f)$ of the signals $\overline{x}(t)$ and $\overline{y}(t)$, respectively
$C_{xy}(f)$: the coherency defined at frequency f from F set of defined frequencies over which the slope is summed
$C^*_{xy}(f)$: the complex conjugate of the coherency
δf: the frequency resolution (the smallest frequency difference that can be distinguished).

PSI utilises the temporal argument to estimate the direction: the preceding process is the driver of the lagging process. PSI ranges from negative to positive values, where the sign and the magnitude indicate the direction of the interaction and its strength. The causal direction is estimated to go from $x(f)$ to $y(f)$ if Ψ_{xy} is positive, and from $y(f)$ to $x(f)$ if Ψ_{xy} is negative. $\Psi_{xy} \sim 0$ indicates that little to no consistent directional interactions exist between the signals. PSI is a robust measure, being derived from the imaginary part of coherency; it is insensitive to non-interacting signals even if they are mixed.

The temporal argument behind the estimation of the direction of an interaction underlies the conceptual basis of another measure – Granger causality (GC). It was originally developed in the field of econometry (Granger, 1969), but is now widely applied to many different time-series involving problems, including the ones in the field of neuroscience. Given two univariate time series $\overline{x}(t)$ and $\overline{y}(t)$, signal $\overline{x}(t)$ is said to be Granger-caused by $\overline{y}(t)$ if the past information from $\overline{y}(t)$ enhances the pre-

diction of future values of $\overline{x}(t)$ beyond what can be predicted solely based on the past values of $\overline{x}(t)$ (Pellegrini et al., 2023). GC can be defined in both time and frequency domains. In the time domain, GC is calculated using autoregressive modelling, where the weighted combination of past values of the time series is used to model the future values of the said time series (Bastos and Schoffelen, 2016). As given by Bastos and Schoffelen (2016), GC is defined as "the natural logarithm of a ratio of residual variances from two different models". One is a univariant autoregressive model, where past values of the time series $\overline{x}(t)$ are used to create a weighted combination to predict future values of the said time series. Another is a bivariate autoregressive model, where past values of the time series $\overline{x}(t)$ and past values of another time series $\overline{y}(t)$ are both used to predict future values of the time series $\overline{x}(t)$.

In the frequency domain, a spectrally resolved extension of GC is used, which involves the calculation of the additional spectral transfer matrix, describing how one time series frequency components are linearly transformed to produce the frequency components of another time series. GC is not a robust measure of connectivity (Haufe et al., 2013), and it fails to account for the volume conduction artefacts, thus, mutually "improving" the prediction between two channels. To account for this problem, a robust version of GC is introduced, which is based on testing the temporal order of the time series. Thus, it is named the time-reversed GC (TRGC). It estimates the directed information flow using the original time series and then once again on a time-reversed time series (Pellegrini et al., 2023). The idea behind this approach is that if GC is reduced when the order is reversed, then the observed effect is not a volume conduction artefact, but instead, could be explained by true brain interactions (Haufe et al., 2013).

2.3 Additional Constraints to Connectivity Analysis

The described methods assist in estimating functional connectivity, however, the analysis of this connectivity is limited by various issues and confounding factors. These constraints introduce an uncertainty in the estimation of functional connectivity, posing two main questions: whether the observed neural interactions are genuine, and whether the observed connections are directed or whether they are modulated by an intermediate entity (Bastos and Schoffelen, 2016).

The volume conduction problem is an important issue in the field of non-invasive neuroimaging. Volume conduction is a physiological phenomenon, occur-

ring in real-time during signal propagation. Generally, it refers to the flow of currents in the conductive head tissue which surrounds the active neuronal source (Bastos and Schoffelen, 2016). Sources being picked up by multiple sensors give rise to the spatial leakage problem, i.e., the "leakage" (or spill) of the activity estimates across neighbouring brain regions, where true brain activity from a specific region is mistakenly attributed to the nearby areas. Volume conduction can introduce purely artificial functional connectivity estimates: instead of the true brain interaction between distinct source, two channels and their respective signals would reflect the presence of the same neural source (Bastos and Schoffelen, 2016).

Robust functional connectivity measures and source reconstruction techniques are proposed (Nolte et al., 2004; Haufe et al., 2013; Pellegrini et al., 2023) to overcome this issue. The robustness of the functional connectivity measures relies on the following assumption: volume conduction is instantaneous, meaning that if a source is picked up by two sensors simultaneously, the phase of the signals is the same (or the multiple of π). The usage of the imaginary part of coherency-based measures such as $\text{ImCOH}_{xy}(f)$, MIC, and PSI, is justified by this exact property. These measures ignore zero-phase lag interactions, which are assumed to be generated by volume conduction. However, not all zero-lag interactions are necessarily non-physiological (Viriyopase et al., 2012; Gollo et al., 2014; Ossadtchi et al., 2018). While such measures are blind to instantaneous zero-phase volume conduction artefacts, they also miss out some portion of the true brain interactions with zero-phase or close to zero synchrony. One technique to overcome this issue was proposed by Ossadtchi et al. (2018). Nevertheless, robust functional connectivity measures provide satisfactory results capturing a large portion of the simulated functional and effective connections in the papers by Haufe et al. (2013) and Pellegrini et al. (2023).

Source reconstruction techniques project the sensor signals to the source space, allowing to estimate functional connectivity between pairs of the estimated sources instead of sensors. While it is a widely used technique frequently utilised in EEG/MEG imaging (Schoffelen and Gross, 2009; Haufe et al., 2013; Pellegrini et al., 2023), inverse operators are also contaminated by spatial leakage. Reconstructed signals still contain contributions from other neighbouring sources (Schoffelen and Gross, 2009). Additionally, this approach may lead to the propagation of time series estimation errors to the subsequent functional connectivity estimation. Nonetheless, existing research simulations analysing various analytical functional connectivity pipelines

such as the ones by Haufe et al. (2013) and Pellegrini et al. (2023) demonstrate quite promising results.

Another problem that must be taken into consideration is the SNR problem. SNR is a measure used to quantify the level of a desired signal compared to the level of the background noise. The SNR problem follows partly as a result of the volume conduction problem since it emerges from the fact that the electrodes measure a mixture of signal-of-interest and noise (Bastos and Schoffelen, 2016). The noise component is composed of spatially incoherent brain noise and additive white noise (or sensor noise), that has non-brain origin (Ossadtchi et al., 2018). Mathematically, SNR is expressed as the ratio of the power of the signal to the power of the noise. A higher SNR value indicates that the signal is stronger relative to the noise, and a lower SNR value signifies that the amount of noise exceeds the amount of the signal. Noisy signals (i.e., those with lower SNR) obstruct the estimation of functional connectivity. Some consequences of the SNR problem include the spurious differences in functional connectivity between conditions, where the SNRs differ across conditions, and spurious differences in functional connectivity between signals which were observed under different SNRs (Bastos and Schoffelen, 2016). In the experimental setting, noise should be minimised as much as possible through the placement of the sensors that maximises the SNR (Bastos and Schoffelen, 2016). In the case when this approach is impossible, one could use the stratification technique (Bosman et al., 2012) to make the distributional properties of the signal power as similar to each other as possible (Bastos and Schoffelen, 2016).

Apart from the problems listed above, other constraints impose additional difficulty on the functional connectivity estimation (Bastos and Schoffelen, 2016). Those include:

1) the common reference problem, which refers to how the usage of the same reference electrode for both channels can be the cause of the estimation of the spurious functional connectivity;

2) the common input problem, which pertains to the challenge of distinguishing between direct interactions and those that are indirect (*mediated*);

3) the sample size bias problem, which refers to the uneven sample sizes for two or more conditions when the functional connectivity is estimated between them;

Furthermore, the parameters of the analysed data such as the ground-truth interactions, the noise composition, the length of the interaction delay, and the number of active sources per region, affect the performance of the analysing pipelines and, consequently, the functional connectivity estimation (Pellegrini et al., 2023).

Chapter 3. Neural Changes Underlying Anxiety

As previously stated, functional connectivity analysis is used to evaluate diseases and conditions alternating connectivity patterns. One such condition is anxiety, a mental state characterised by prolonged apprehension and worry about events that are undetermined and might potentially have negative outcomes (Xu et al., 2019; Hein et al., 2023). While anxiety is deemed to have evolutionary value, allowing people to prepare for the detection and management of upcoming threats (Bateson et al., 2011), it is frequently accompanied by unpleasant and unwanted emotions and experiences that, on the contrary, prevent individuals from normal daily functioning. These changes are supported by the imbalance of the interaction between brain networks and altered functional connectivity patterns. Apart from the reduced activity of the DMN, the communication between the affective network (AN) and the executive control network (ECN) is impaired, which contributes to various anxiety disorders such as the generalised anxiety disorder, social anxiety disorder, panic disorder (Xu et al., 2019). Functional connectivity analysis helps identify the neural substrate for anxiety-related changes and improve the understanding of the formation of such conditions.

ECN (or lateral frontoparietal network) is a large-scale brain network, consisting of functionally connected areas: primarily, the regions of the prefrontal cortex (PFC) such as dorsolateral PFC and dorsomedial PFC (Seeley et al., 2007), as well as regions of the parietal cortex (lateral posterior parietal cortex and inferior parietal lobule) (Xu et al., 2019). Additional regions include the posterior inferior temporal lobe and dorsomedial thalamus (Uddin et al., 2019) (Figure 1). The ECN is involved in the regulation of higher cognitive functions such as decision-making, planning, task-switching, and working memory (Menon, 2011; Uddin et al., 2019).

In the study by Geiger et al. (2016), the ECN has been demonstrated to be affected by anxiety, exhibiting altered connectivity patterns: decrease in the resting-state functional connectivity in the left ECN as well as between PFC and amygdala and the hypoactivation of the medial part of the orbitofrontal cortex (part of PFC) leads to the impaired top-down regulation of fear and anxiety. However, this finding is not universal, and some connectivity studies report an opposing result of increased connectivity between the amygdala and PFC (Blair et al., 2008; Liao et al., 2010).

The amygdala is the nuclear complex in the cerebral hemispheres which is

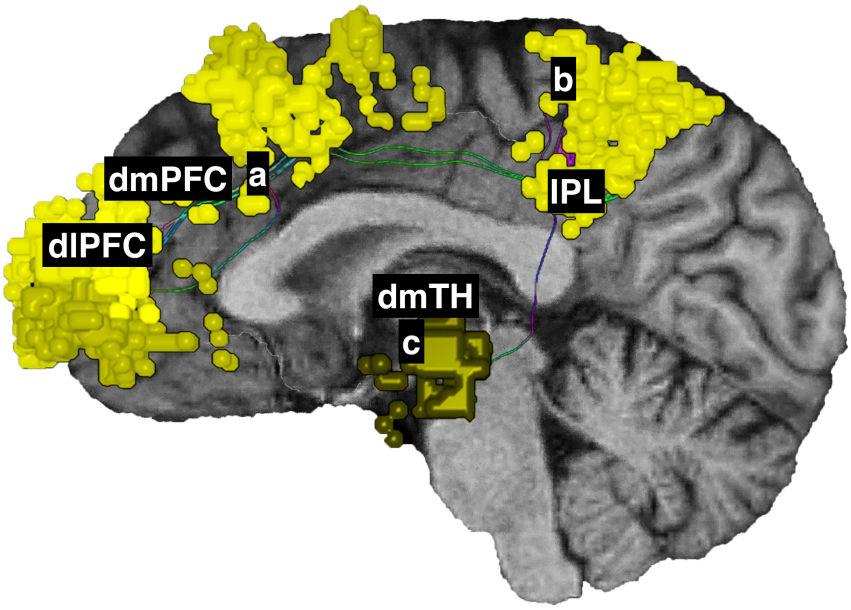

Figure 1: Executive control network consisting of a. prefrontal cortex (PFC) areas, b. parietal cortex areas, c. temporal cortex areas. dlPFC = dorsolateral PFC, dmPFC = dorsomedial PFC, IPL = inferior parietal lobule, dmTH = dorsomedial thalamus. Adapted from Omniscient Neurotechnology (Crawford, 2022, July 1).

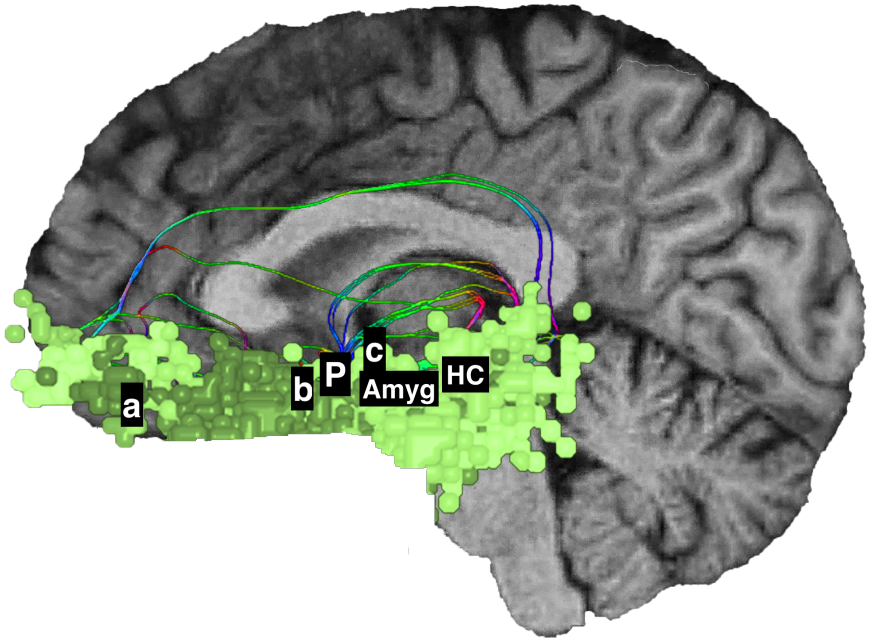

Figure 2: Affective network consisting of a. orbitofrontal cortex (OFC) areas, b. temporal cortex, c. insular cortex. Amyg = amygdala, P = pallidum, HC = hippocampus. Adapted from Omniscient Neurotechnology (Crawford, 2022, July 20).

mainly responsible for the processing of emotions. It is a part of the affective network (AN) (or limbic network) which also includes the orbitofrontal cortex (OFC), regions of the temporal cortex, deeply folded insular cortex, pallidum, and hippocampus (Kim et al., 2015) (Figure 2). Various anxiety functional connectivity studies highlight the hyperactivity of the amygdala (Bishop, 2007), decreased extrinsic connectivity between the AN and the ECN networks (Bishop, 2007; Prater et al., 2013; M. Wang et al., 2021), and also focus on the intrinsic connectivity of the AN, ECN, and DMN (M. Wang et al., 2021, and Toazza et al., 2016; Sylvester et al., 2012) in anxiety states.

Research proposal

Difficulty in dealing with uncertainty is one of the key features of anxiety. It has been shown by several studies that anxiety impairs decision-making under higher rates of volatility, i.e., faster changes in the environment (Browning et al., 2015; Pulcu and Browning, 2019; Hein et al., 2021). One approach to investigating the specific mechanism behind this is the computational modelling, allowing one to assess different forms of uncertainty and how they could explain the differences in behaviour (Hein et al., 2023). In the study by Hein et al. (2023), one such model (Bayesian predictive coding) was used to test whether the neural sources overlapping with the regions responsible for the changes in decision-making and reward-based learning in anxiety contribute to the alternations in the oscillatory activity. As a result, it was shown that anxiety leads to the overestimation of volatility, which subsequently results in faster belief updating about the possible outcome of a decision (Hein et al., 2023).

In an MEG experiment, conducted by Hein et al. (2023), two groups of participants pre-screened with higher and lower rates of anxiety perform a probabilistic reward-based learning task. The participants were asked to predict the winning stimulus (win = 5 pence) out of the blue and orange fractals that were randomly presented either to the left or the right of the screen (1300ms ± 125 ms). Immediately after the selection of the stimulus, the participants saw the fractal of their choice highlighted (1000 ms ± 200 ms), and then they were made known which fractal was, in fact, the winning one by declaring if they won or lost (1900 ms ± 100 ms). The fixation cross followed the sequence (1750 ms ± 250 ms) (Figure 3). The task consisted of overall

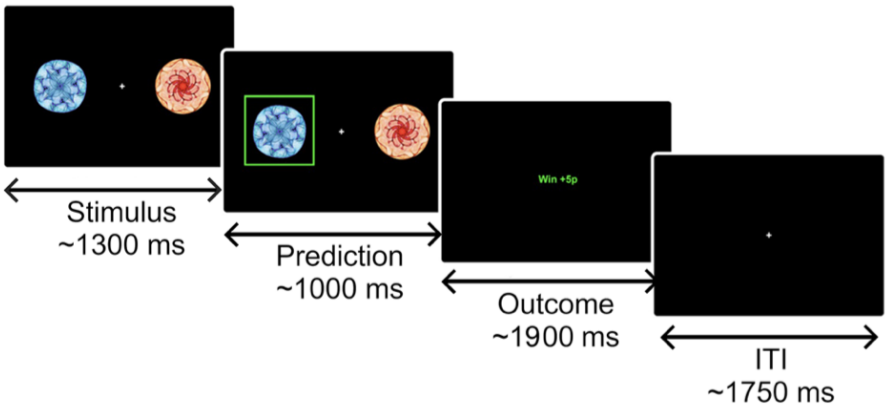

Figure 3: The structure of the behavioural task. Adapted from Hein et al., 2023.

320 trials, divided into two blocks. The stimulus outcome probabilities were subject

to the pseudorandom change that took place four times in each block separately for each participant. Five possible outcome probabilities were 0.9 and 0.1; 0.1 and 0.9; 0.7 and 0.3; 0.3 and 0.7; 0.5 and 0.5 (Hein et al., 2023).

Hein et al. (2023) used the modelling approach to investigate the neural sources that exhibit oscillatory alterations in anxiety. The research that will follow this exploratory work will explore the existing MEG data, collected in the experiment described above. The research aims to investigate the functional connectivity changes in anxiety that could explain the changes in behaviour. The analysis will be restrained to the brain regions that overlap with the circuitry of anxiety and decision-making under uncertainty, which include:

1) areas of the cingulate cortex, which is responsible for a number of reward and uncertainty-related behaviours (Monosov, 2017);

2) areas of the OFC, which is a part of the AN;

3) superior frontal gyrus, which contributes to the higher cognitive functions (Boisgueheneuc et al., 2006).

As described in the previous chapter, the analysis will follow the guidelines of Haufe et al. (2013) and Pellegrini et al. (2023): specifically, the LCMV beamforming technique will be utilised to reconstruct the source space, where the functional connectivity will be estimated using the TRGC. Expected results include the decreased functional connectivity between the areas of the ECN and the AN, prefrontal cortices and the amygdala, respectively (as stated in the number of papers mentioned above), as well as the increased intrinsic connectivity within the AN.

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