FUNCTIONAL AND EFFECTIVE CONNECTIVITY STUDY OF THE HUMAN BRAIN TOPOLOGY USING A NOVEL UNIFYING FRAMEWORK

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by

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In the name of Allah, The Most Gracious, The Most Merciful.

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LIST OF SYMBOLS

$\alpha_{X,Y,Z}$	Associator morphism involving 3 objects X,Y,Z in monoidal category
β	Bayesian Mixed Model's coefficient
δ_p	Depth weighting scaling factor used in wMNE
Δ	Copying operation
$\square$	Deleting operation
∇	A composition natural morphism mapping local tensor product to tensor product sent by a monoidal functor
ε	A unit natural morphism mapping local unit object to unit object sent by a monoidal functor
ε	scale parameter
η	1^{st} morphism in connectivity theory describing the operation of features extraction
$\gamma_{X,Y}$	Braiding natural isomorphism
Γ	Network density of a graph G
$\iota(w_{u,v})$	Map from connectivity weight $w_{u,v}$ to its length
κ	Weighted clustering coefficient
λ	Left unitor in monoidal category
Λ	Currying morphism
Λ^{-1}	Uncurrying morphism
μ	Mean or location parameter of a probability distribution

ν	A monoidal natural transformation
ϕ	A coherence isomorphism
φ	Order of depth weighting parameter
π_x	Projection function which project variable x from its input source
ϖ	A morphism in prop
ϱ	Right unitor in monoidal category
ρ	2^{nd} morphism in connectivity theory capturing the operation of statistical dependencies computation
ψ_A	Weighted network small-worldness of a graph A
σ	Scale parameter of a probability distributin
Θ	Angle between 2 vector
θ	Model's parameters
ϑ	Tikhonov regularization parameter
τ	Time delay or interval
τ_{max}	Free parameter denoting the maximum time interval considered in generating self-similar time series
ω	Frequency in Hz
υ_s	Subject s intercept
ξ	Symmetry isomorphism
$\mathbb{C}$	Complex number
$\mathbb{R}$	Real number

ae	Amplitude envelope function
bpf	Band pass filter function
$\circ$	Composition operator between 2 functions
$\sqcup$	Concatenation function forming a vector from a tuple of input vectors
$\bullet$	Copy operator used in string diagram
$x \in \mathbf{x}$	x is an element of **x**
$H(x_i)$	Entropy of signal x_i
$\langle . \rangle$	Expectation operator
$\lfloor . \rfloor$	Floor operator
$\mathcal{F}\{.\}$	Fourier transform
hfd	Higuchi fractal dimension function
$\mathcal{H}\{.\}$	Hilbert transform
$\Im()$	Imaginary projection
lim	Limits
$\int$	Integration operator
ln	Natural Log operator
log	Log operator
$[.]^{-1}$	Matrix inverse operator
$[.]^{\dagger}$	Matrix pseudoinverse operator
$[.]^{T}$	Matrix or vector transpose operator
$[.]^{*}$	Matrix or vector complex conjugate

$\|.\|$	Norm operator
$\Psi_{i,j}$	Normalizing function which normalizes the connectivity strength
$\perp$	Orthogonalization operation
$o(.)$	Observer function
$p(y\|x)$	Probability of y given x
$r(.)$	Regularization function
$s(.)$	State function
$\mathrm{P}_{i,j}$	Shortest path between vertex v_i and vertex v_j
$\sqcap$	Segmentation function which takes a vector and segment it to multiple vector of length l
Σ	Summation operator
$\otimes$	Tensor product
var	Variance function which compute variance from its input vector
$\mathcal{C}_{i,j}(\omega)$	Coherency between time series $\hat{X}_i(\omega)$ and $\hat{X}_j(\omega)$ at frequency ω
$d^f(\omega,w)$	Fractal dimension of a time window w at frequency ω
$\mathcal{L}$	Weighted characteristic path length
$half\mathcal{N}$	Half normal distribution
$log\mathcal{N}$	Log normal distribution
$\mathcal{N}(\mu,\sigma)$	Normal distribution parameterized by location parameter μ (mean) and scale parameter σ(standard deviation)
$\mathfrak{r}_{i,j}$	Connectivity strength between channel i and channel j

$\mathcal{S}_{i,j}(\omega)$	Cross spectral density between the Fourier transformed time series $\hat{X}_i(\omega)$ and $\hat{X}_j(\omega)$ at frequency ω
$\mathcal{T}_i$	Geometric mean of triangle around vertex v_i
$\mathscr{C}, \mathscr{D}$	Symbols denoting a category
$\mathscr{M}$	Connectivity model
$\mathscr{T}$	Connectivity theory
$\mathbf{A}$	Matrix of AR model coefficient which can be regarded as connectivity strength
$\mathbf{B}$	Matrix of connectivity strengths modulated by experimental inputs
$\mathbf{C}$	Matrix specifying which inputs are directly connected to which brain regions
$\mathbf{D}$	Data covariance matrix with dimension $\mathbb{R}^{N\times N}$
$\mathbf{L}$	Lead field matrix for N sensors and M sources with dimension $\mathbb{R}^{N\times 3M}$
$\mathbf{P}$	Matrix of features with dimension $\mathbb{R}^{M\times T}$
$\mathbf{Q}$	Covariance matrix of the multivariate Gaussian distribution
$\mathbf{R}$	Correlation matrix of the multivariate Gaussian distribution
$\mathbf{S}$	Source covariance matrix with dimension $\mathbb{R}^{3M\times 3M}$
$\mathbf{W}$	Matrix of weights $w_{i,j}$ of edges in a graph G
$\mathbf{X}$	Matrix of time series with dimension $\mathbb{R}^{N\times T}$ of N channels and length T
$\mathbf{1}_A$	Identity arrow of an object A
$\mathbf{a}_i$	i-th column vector of matrix $\mathbf{A}$
$\mathbf{d}_s^f(\omega)$	Vector of FD for frequency ω and for brain region s

$\mathbf{j}(t)$	Vector of M sources potential at time t with dimension $\mathbb{R}^{3M\times 1}$
$\mathbf{l}_{1p}$	Column vector of $\mathbf{L}$ that correspond to source at location p along first orientation
$\mathbf{n}(t)$	Vector of sensors noise at time t with dimension $\mathbb{R}^{N\times 1}$
$\mathbf{p}_i$	Vector of features for the i-th channel or brain region
$\mathbf{u}$	vector of experimental inputs
$\mathbf{x}(t)$	Vector of N sensors potential at time t with dimension $\mathbb{R}^{N\times 1}$
$\mathbf{y}$	Vector of N sensors recording with dimension $\mathbb{R}^{N\times 1}$
$\mathbf{z}$	Vector of N neural states
$\dot{\mathbf{z}}$	Vector of N neuronal dynamics
$A,B,C,\dots$	Objects within a category $\mathscr{C}$
$f,g,h,\dots$	Morphism between pair of objects $\mathscr{C}(A,B)$
$a_{i,j}$	The i,j-th element of matrix $\mathbf{A}$
$\breve{a}(t,\omega)$	Amplitude envelope of signals at time t and frequency ω
$c(x,y)$	Similarity metric between x and y
C_j	The j-th experimental condition
d^{τ}	Delay function
$d(x,y)$	Distance metric between x and y
$d_{i,j}$	Shortest path length in a graph G
E	Global efficiency of a graph G
E_V	A set of edges between vertices (v_i,v_j)

F	Functor
G	A graph characterized by an ordered tuple (V, E_v) of a set of vertices V and a set of edges E_V
k_i	Weighted degree of vertex v_i
K	Mean weighted degree of a graph G
$\ell_{i,j}$	Shortest weighted path length between vertex v_i and vertex v_j
l	Parameter indicating length of time segments segmented by segmentation function $\sqcap$
$L_m(\tau)$	The normalized sum of the absolute difference of adjacent pairs of points for each interval τ
$\bar{L}(\tau)$	The mean of $L_m(\tau)$
M_i	The i-th connectivity measure
$N(\varepsilon)$	The number of measurement unit for the scaling factor ε
PV	Cauchy principle value
S_X	A strong symmetric monoidal functor defining a supply
T	Transitivity of a graph G
V	A set of N vertices $(v_1, \cdots, v_N)$ in a graph G
$w_{i,j}$	weight of an edge between vertices (v_i, v_j)
$x_i(t)$	Potential at time t of sensor i
$\hat{X}_i(\omega)$	Fourier transformed signal of sensor i
X_τ^m	A set of self-similar time series
$y_{i\|s}$	Subject s i-th value of the dependant variable

$z(t, \omega)$ Analytical signals at time t and frequency ω

LIST OF ABBREVIATIONS

AAL3	Automated Anatomical Labelling Atlas 3
AEC	Amplitude Envelope correlation
AIC	Akaike Information Criteria
AR	Autoregressive
BCT	Brain Connectivity Toolbox
BF	Bayes Factor
BIDS	Brain Imaging Data Structure
BOLD	Blood Oxygen Level Dependent
BRMS	Bayesian regression models using Stan
CAEC	Complexity of the amplitude envelope correlation
CI	Credible Interval
COH	Coherence
COR	Correlation
DCM	Dynamic causal modelling
ECG	Electrocardiogram
EEG	Electroencephalography
EOG	Electrooculogram
EPSP	Excitatory Post-Synaptic Potentials
IPSP	Inhibitory Post-Synaptic Potentials

ESS	Effective Sample Size
FD	Fractal Dimension
fMRI	Functional Magnetic Resonance Imaging
FOCUSS	Focal Under-determined System Solution
GABA	Gamma Aminobutyric Acid
GC	Granger Causality
HDI	Highest Density Interval
HFD	Higuchi Fractal Dimension
HMM	Hidden Markov Model
HPI	Head Position Indicator
ICA	Independent Component Analysis
ICBM152	International Consortium for Brain Mapping
ICOH	Imaginary part of Coherency
KL	Kullback-Leibler
LORETA	Low Resolution Brain Electromagnetic Tomography
MAP	Maximum A Posteriori Estimation
MEG	Magnetoencephalography
MI	Mutual Information
MLE	Maximum Likelihood Estimation
MNE	Minimum Norm Estimation
MPRAGE	T1-weighted Magnetization Prepared Rapid Gradient Echo

MVAR	Multivariate Autoregressive
PDC	Partial Directed Coherence
PET	Positron Emission Tomography
PLI	Phase Lag Index
PLV	Phase Locking Value
ROPE	Region of Practical Equivalence
RS	Resting State
SNR	Signal to Noise Ratio
tSSS	Temporal Signal Space Separation
wMNE	Weighted Minimum Norm Estimation
XCOR	Cross-correlation

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KAJIAN FUNGSIAN DAN PENYEBAB JARINGAN TOPOLOGI OTAK MANUSIA MENGGUNAKAN KERANGKA PENYATUAN NOVEL

ABSTRAK

Kajian berkaitan neurosains yang menggunakan analisa perhubungan telah berkembang secara pesat. Antaranya, kajian berkenaan mekanisma saraf penyakit-penyakit otak dan rawatannya. Menariknya, kesan terapeutik pelbagai rangsangan auditori telah dikenal pasti dalam beberapa kajian. Tetapi, mekanisma sarafnya belum difahami. Selari dengan itu, semakin banyak ukuran-ukuran perhubungan telah dibangunkan. Percubaan telah dibuat untuk mengklasifikasikannya mengikut taksonomi yang berbeza. Sehingga kini, tiada rangka kerja yang menyatukan semua ukuran-ukuran perhubungan ini. Matlamat kajian ini adalah untuk membina rangka kerja bagi menyatukan ukuran-ukuran perhubungan. Rangka kerja ini digunakan sebagai acuan untuk membina ukuran perhubungan baru yang kemudiannya dibandingkan dengan ukuran-ukuran perhubungan lain menggunakan dataset sumber terbuka. Di samping itu, kajian ini juga memperkenalkan pendekatan statistik yang boleh menguji ketiadaan dan kehadiran kesan eksperimen yang seterusnya digunakan untuk mengkaji kesan rangsangan-rangsangan pendengaran pada topologi rangkaian otak pemprosesan emosi. Rangka kerja menyatukan ukuran-ukuran perhubungan telah dibina menggunakan Teori Kategori dengan mengenal pasti struktur asas yang sama diantara ukuran-ukuran perhubungan dan menghimpukannya ke dalam satu kategori yang dipanggil teori perhubungan. Ukuran perhubungan baru, iaitu, *complexity of the amplitude envelope correlation* (CAEC) telah dibangunkan. CAEC digunakan untuk menganggarkan perhubungan antara kawasan otak yang terlibat dalam pemprosesan wajah dan dua ukuran rangkaian

telah diperolehi: *transitivity* dan *global efficiency*. Ukuran-ukuran rangkaian tersebut dibandingkan dengan ukuran-ukuran rangkaian yang diperoleh menggunakan ukuran-ukuran perhubungan yang lain: *amplitude envelope correlation* (AEC) dan *imaginary part of coherency* (ICOH). Selain itu, satu kajian bersilang telah dijalankan untuk menilai kesan 8 rangsangan auditori terhadap topologi rangkaian pemprosesan emosi otak dalam 30 subjek yang sihat. Tiga ukuran rangkaian: *mean weighted degree*, *transitivity*, dan *global efficiency* telah digunakan. Untuk menguji ketiadaan atau kehadiran kesan eksperimen, distribusi posterior bagi perbezaan antara masa rehat dan setiap stimulus dianggarkan. Kawasan ekuivalen ditakrifkan sebagai perbezaan ukuran rangkaian antara dua masa rehat sebelum dan selepas rangsangan. Dalam rangka kerja ini, sembilan ukuran-ukuran perhubungan telah dikenal pasti sebagai model teori perhubungan. Dalam eksperimen pertama, CAEC menghasilkan topologi rangkaian yang berbeza berbanding AEC dan ICOH untuk rangsangan yang sama. Kesan manipulasi eksperimen pada topologi rangkaian didapati bergantung kepada ukuran-ukuran perhubungan yang digunakan dalam analisa. Dalam eksperimen kedua, ukuran rangkaian merentas semua rangsangan auditori didapati sama dengan ukuran rangkaian masa rehat dalam semua jalur frekuensi. Rangka kerja yang dicadangkan mampu menyatukan ukuran-ukuran perhubungan dan menyediakan acuan untuk membangunkan ukuran perhubungan baru dan akan membantu usaha selanjutnya dalam membina ukuran-ukuran perhubungan baru. Dapatan eksperimen pertama menunjukkan bahawa hasil analisa perhubungan harus ditafsirkan berdasarkan ukuran-ukuran perhubungan yang digunakan. Eksperimen kedua menunjukkan bahawa pendekatan statistik yang diperkenalkan dapat menguji ketiadaan kesan eksperimen. Pendekatan ini amat berharga dalam mengembangkan hala tuju kajian pengimejan otak pada masa akan datang.

FUNCTIONAL AND EFFECTIVE CONNECTIVITY STUDY OF THE HUMAN BRAIN TOPOLOGY USING A NOVEL UNIFYING FRAMEWORK

ABSTRACT

There has been a rapid expansion of neuroscientific research employing brain connectivity analysis. Among these are studies unravelling the neural mechanisms of brain diseases and treatments. Of interest, the therapeutic effects of various auditory stimulus have been demonstrated in several studies. However, neural mechanisms of these therapy remain elusive. In parallel, many new connectivity measures have been developed, adding to the ever-growing connectivity tools. Attempts have been made to classify them according to different taxonomies. To date, however, no general framework has been developed to unify these measures. Thus, this study aimed to build a unifying framework of various connectivity measures. The study also aimed to build a novel connectivity measure using the framework as a template and then compared it with other established measures on an open-source dataset. The study also sought to introduce a statistical approach for testing both the absence and the presence of experimental effects, which was then used to investigate the effects of listening to several auditory stimuli on emotion-processing brain network topology. A unifying framework was devised in the language of category theory by identifying common underlying structures shared among connectivity measures and assembling them into a single category called connectivity theory. A novel connectivity measure called the complexity of the amplitude envelope correlation (CAEC) was developed. Functional connectivity among brain regions involved in face processing was estimated using CAEC, and two network measures were derived: transitivity and global efficiency. Both network measures were compared with the network measures derived using established connectivity measures: amplitude envelope correlation (AEC) and imaginary part of coherency (ICOH). Additionally, a cross-over study investigating the effects of 8 different auditory stimuli on emotion-processing network topology in 30 healthy subjects was conducted. Three network measures were used: mean weighted degree, transitivity and global efficiency. The posterior distribution of differences between the resting state and each stimulus was estimated to test for the absence and presence of effects. Equivalence region was defined as differences in network measures between pre- and post-stimuli resting MEG. Within the proposed framework, connectivity measures were shown to be models of connectivity theory. The first experiment showed that CAEC produced a different network topology compared to AEC and ICOH for the same stimulus. Overall, the effects of experimental manipulations on network topology were shown to be dependent on the connectivity measure used. In the second experiment, the network measures across all auditory stimuli were equivalent to that of the resting state in all frequency bands. The categorical framework unifies connectivity measures and provides a template for developing a novel connectivity measure, thus illuminating further work on constructing new connectivity measures. The first experiment indicated that connectivity analysis results should be interpreted based on the utilised connectivity measure. As shown in the second experiment, the novel statistical approach was able to test for the absence of experimental effects. This approach would be valuable in expanding the direction of future neuroimaging studies.

CHAPTER 1
INTRODUCTION

Human brain is arguably the most complex information processing system ever designed that is known to mankind. The fact that it is still poorly understood despite the rapid expansion of research and the technological advancements over the last few decades, is a testament to its complexity. The level of complexity is not surprising considering that there are about 80 billion of neurons with 10^{14} of neuronal synapses in the human brain (Azevedo et al., 2009). Albeit seemingly near impossible, unravelling this complexity represents one of the most important challenges for neuroscientists.

As neuroscientists, our general goal is to understand how the dynamics of a collection of neurons give rise to cognitive process, which in and of itself is still poorly understood. So far, our progress has been, on one hand, quite promising such as identifying and linking specific brain regions to specific cognitive, perceptual, and motor functions. On the other hand, however, we still have a long way to go when even a simple process like categorizing audio-visual stimuli remains poorly understood.

With the availability of multiple non-invasive neuroimaging modalities and the ever-expanding resultant data, we have been trying to understand brain functions using several paradigms including but not limited to localizing specific brain areas that are associated with certain tasks, identifying brain areas that are active in resting state, measuring event related potentials or fields of particular brain areas in relation to specified task or stimulus and measuring blood flow responses. All of these paradigms boil down to reducing the complexity of brain functions to two dimensions: brain locations and their activities. The main assumption is that brain functions are uniquely identifiable to specific activities of specific brain regions.

Using only these two dimensions, however, was found to be insufficient to characterize all the space of highly complex neurocognitive functions. There is no bijective mapping between cognitive processes and brain regions (Price & Friston, 2005). A single cognitive process can activate multiple brain regions and activation of a particular region correlates with different cognitive processes. A new paradigm was thus required to resolve the issue and move forward. This came, among many other, in the form of viewing brain structures and functions in terms of network organizations. Cognitive functions are, therefore, perceived as the result of orchestrated symphony among networks of neuronal ensembles in cortical and subcortical structures (Von Der Malsburg, 1994).

This insight has brought about a paradigm shift in neuroscience from the restrictive reductionist approach of identifying an isolated unit responsible for a specific cognitive function to a more wholistic approach of exploring and characterizing networks of brain functional units working together on performing cognitive tasks. Functionally cohesive networks which emerged through the recruitment of coordinated in spite of spatially separated brain regions are central to the way in which brain processes and integrates information (Schnitzler & Gross, 2005).

Prior to identifying and characterizing brain networks, it is necessary to perform brain connectivity analysis. Brain connectivity analysis is a multivariate time series analysis of interdependence between simultaneously recorded signals from multiple brain regions. Commonly, these time series are acquired using Electroencephalogram (EEG) and Magnetoencephalography (MEG) due to their non-invasive nature and high temporal resolution. These recording methods are often complemented by functional magnetic resonance imaging (fMRI) which has higher spatial resolution but lower temporal resolution. However, in contrast to EEG and MEG which directly measure electrical activities of ensembles of neurons, fMRI is an indirect measurement of the underlying neuronal activity since it captures the haemodynamic of blood oxygen level dependent (BOLD) signals.

There are many connectivity measures that are available as tools to quantify connectivity between brain regions. Within the context of EEG and MEG, these include cross-correlation, amplitude envelope correlation (AEC), coherence (COH), ICOH, partial directed coherence (PDC), phase lag index (PLI), phase locking value (PLV), mutual information (MI), Granger's causality (GC), dynamic causal modelling (DCM) and more. However, there is no consensus among experts in the field regarding which measures should be considered as the best or the gold standard method to capture connectivity (Gross et al., 2021). It is more apt to view them as a collection of tools to detect different flavours of brain connectivity, as such, researchers have many tools in their arsenal to suit their research objectives and methodologies (Pereda, Quiroga, & Bhattacharya, 2005). Different connectivity measures might be able to reveal different mechanisms of brain connectivity therefore providing complementary and deeper insights on brain functions and dysfunctions (Guggisberg et al., 2015).

Adopting connectivity paradigm, various studies have been conducted to understand cognitive functions more deeply including among others, attention (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Fox et al., 2005), memory (Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005) and emotional processing (M. J. Kim et al., 2011). In contrast to previously belief, even simple somatosensory and motor functions have been demonstrated to hinge on the precise coordination of multiple brain areas (Jiang, He, Zang, & Weng, 2004).

Increasingly, the approach has also been incorporated in many studies to further elucidate diseases and pathologies in the brain functions. Brain connectivity research enables researchers to gain deeper understanding and more insights on depression (Connolly et al., 2013), anxiety (M. J. Kim et al., 2011), schizophrenia (Lynall et al., 2010), epilepsies (Van Mierlo et al., 2014) and many more. Connectivity studies have demonstrated that these pathologies are the result of abnormalities of large-scale brain networks rather than dysfunction of a specific brain region. Furthermore, this has also opened ways of exploring new approaches to treatment and ways to evaluate effectiveness of treatments.

Treatment modalities that have been explored and used to treat such diseases include surgical, pharmacological, and non-pharmacological. In depression and anxiety specifically, music and other rhythmic auditory stimuli are among the non-pharmacological approach that have been used either alone or in combination with pharmacological intervention and psychotherapy. Of particualr interest, the therapeutic effects of Qur'anic recitation have been shown in several studies (see 2.11). However, the underlying neural mechanisms for these therapy remain elusive (Koelsch, 2009; Maratos, Crawford, & Procter, 2011).

1.1 Problem statement and rationale of the study

Parallel to the growth in research adopting brain connectivity and network paradigm, there has been an increase in the development of new connectivity measures to address several issues that emerge in connectivity analysis. Thus far, connectivity measures were developed by adopting the theory and concepts from diverse fields, such as, information theory, dynamics and chaos theory, econometrics, and statistics. Being derived from different fields and having different theoretical background, these measures are arguably different in one way or the other. To date, there are various ways of classifying these measures. However, there is no general framework that would serve as the unifying foundation which would tie together all of these measures and possibly future novel measures as well.

The present work builds upon the branch of mathematics called category theory. Category theory is an emerging field in mathematics that was developed to serve as the foundation of mathematics. The language of category theory was developed to formalize different mathematical structures and concepts in term of objects and arrows which are morphism between them. It is a way to organize math efficiently. It has been used as the framework not only to unify diverse concepts in mathematics such as topology, probability, and logic but also in other fields such as physics and computer sciences (Baez & Stay, 2010).

Why category theory? To put it succinctly, it can help us organize ideas about a category of related things and identify emerging and converging patterns that keep on reappearing over and over again in multiple places. It may even suggest interesting ways of looking at them. As a useful organizing tool, it provides a powerful universal insight in many problems. By identifying many similar ideas in different areas of mathematics, it offers a common unifying language.

The main goal here is to show that irrespective of the mathematical technique employed, all forms of connectivity measures boil down to a similar underlying structure which can be efficiently described using the language of category theory. One can say that this underlying structure is the blueprint of most if not all connectivity measures. Using the tools and concepts from category theory, one can build a general framework to formalize and unify connectivity measures. This framework should be broad enough to capture all known methods for measuring connectivity.

Since it captures the core underlying structures or the blueprint of connectivity measures, the framework would not only unify connectivity measures but also could serve as the template from which a new connectivity measure could be built. To demonstrate this, a novel connectivity measure was developed on the basis of signal complexity. A concept initially explored in non-linear dynamics and chaos theory, complexity of a system, which comprises of a number of components, describes how these components organise and interact with each other leading to emergence phenomena that cannot be explained by analysing the components in isolation. It has been applied in neuroscientific research to further our understanding of the brain functions and dysfunctions. Several measures of complexity have been developed and applied in neuroscientific researches on normal brain physiology (Born & Pietrowsky, 1995; Mölle, Marshall, Wolf, Fehm, & Born, 1999; Schupp, Lutzenberger, Birbaumer, Miltner, & Braun, 1994; Sheehan, Sreekumar, Inati, & Zaghloul, 2018) and pathologies (Akar, Kara, Latifoğlu, & Bilgiç, 2016; Bodart et al., 2017; Catarino, Churches, Baron-Cohen, Andrade, & Ring, 2011; Lehnertz & Elger, 1995). It is argued, based on the cumulative evidence, that the complexity of the electrical activities of each functional units (Hebb, 2005) in the brain vary continuously in response to the processing load caused by the alterations in the internal and external environments. The changes that occur in the functional units are in terms of the number of recruited neurons or brain regions and their interaction patterns. Altogether, these lead to changes in the complexity of the recorded signals. On this basis, a composable method of computing a connectivity measure between sensors or brain regions was proposed based on their respective signals' complexity. The premise here is that 2 channels or brain regions are connected if their temporal dynamics share similar complexity.

Neuroscientific research and scientific research in general have been relying heavily on arbitrarily set p-value and null hypothesis testing as the statistical approach for making decision about experimental results which ultimately play significant role in guiding study design. p-values would only allow one to reject a null hypothesis when an arbitrarily set threshold has been surpassed. The approach cannot be used as evidence to support or accept the null. Besides, it is susceptible to multiple comparisons problem which is not uncommon in neuroscientific experiments. Thus, relying on the approach arguably put unnecessary restrictions: (i) to the kind of neuroscientific questions that one can address, (ii) to the way one might be able to design and conduct experiments, and (iii) to the interpretation of experimental results. To address these issues, a study design and statistical approach that is free from the shackle of p-value need to be developed.

As the practical part of this work, the theories and the methodologies that were developed in this work, i.e., the novel connectivity measure and the novel statistical approach, were employed in the experimental works to address the neuroscientific questions of interest. These would include queries regarding the differences in the resulting brain network when using the novel connectivity measure compared to other established measures. The 2-way interactions effects between connectivity measures being employed and the probed experimental manipulations or conditions were also explored. Specifically, what are the effects of using different connectivity measure on the brain network topologies for each experimental condition. Also, for every connectivity measure, how brain network topology would change under different experimental conditions. For these queries, a widely known open-source MEG dataset on face processing were used (Wakeman & Henson, 2015). The dataset has also been used by others to demonstrate the applicability of a novel connectivity measure.

Another neuroscientific query investigated in this work was on the neural-correlates of Quranic and music therapy. While most research on music therapy used western music and explored its effects on neurological and psychiatric illnesses, other forms of rhythmic auditory stimuli have not been extensively investigated in terms of their potential therapeutic effects on these diseases. In this study, 8 different auditory stimuli were examined together the underlying functional brain network as the neuro-correlates using MEG recordings. To our knowledge, no such study had been done before in those with neuropsychiatric pathologies or even in healthy individuals.

1.2 Research questions

Thus, the research questions addressed within this work are as follows:

1. How can one unify all of the diverse connectivity measures within a single framework using the technologies available in category theory and what are the minimum components that should be present in the framework?

2. How can a new connectivity measure be developed that capture the notion of complexity using the unifying framework as a blueprint?

3. Are there differences between the newly developed connectivity measure compared to other established measures such as AEC and ICOH in terms of the resultant brain network topology as measured by weighted transitivity T and global efficiency E?

4. For each experimental condition, what are the effects of using different connectivity measures on the brain network topologies as measured by weighted transitivity T and global efficiency E and for each connectivity measure, how these two topological measures would change under different experimental conditions?

5. What is the statistical approach that enables us to test both the absence or the presence of experimental effects?

6. Is there any effect of passive listening to naturalistic auditory stimuli on the topology of brain networks involved in emotional processing as measured by weighted degree K, weighted transitivity T and global efficiency E?

1.3 Research hypotheses

The following are the corresponding research hypotheses. These research hypotheses pertain only to the experimental works carried out in this study:

1. There are no differences in the resultant brain network topology as measured by weighted transitivity T and global efficiency E between the novel connectivity measure and other established connectivity measures such as AEC and ICOH.

2. Within each experimental condition, there are no differences in terms of brain network topological measures weighted transitivity T and global efficiency E when using different connectivity measures.

3. Within each connectivity measure, there are no differences in terms of brain network topological measures weighted transitivity T and global efficiency E for each experimental condition.

4. There are no changes in the topological measures mean weighted degree K, weighted transitivity T and global efficiency E of the brain network involved in emotion processing under all 8 different auditory stimuli for all frequency bands: delta, theta, alpha, beta, and gamma.

1.4 Research objectives

1.4.1 General objectives

The key aims in this thesis comprised of 2 main parts. The first part was to extend the theoretical and methodological aspects of brain connectivity research, in particular, to devise a unifying framework of connectivity measures, to develop a novel connectivity measure and to develop a statistical approach for testing of both the absence and presence of experimental effects in neuroimaging study. The second part was to apply these newly introduced theories to connectivity analysis to gain new insight and deeper understanding on 2 cognitive functions that are important in human interactions namely face and emotion processing. Specifically, the study objectives are as follows:

1.4.2 Specific objectives

1. To develop a novel framework that unifies all connectivity measures using machineries developed within the field of mathematics called category theory.

2. To use the newly developed framework as the blueprint in order to derive a novel connectivity measure.

3. To demonstrate the applicability of the novel connectivity measure and compare the resultant brain network topologies with 2 other established connectivity measures, namely ICOH and AEC, as part of connectivity analysis of an open source

dataset on face processing.

4. To examine, for each experimental condition, the effect of using different connectivity measures and for each connectivity measures, the effect of experimental conditions on the resultant brain network topological measures: weighted transitivity T and global efficiency E.

5. To formulate a statistical approach in neuroimaging that allows for testing both the absence or presence of true experimental effects.

6. To apply the newly introduced statistical approach in combination with connectivity analysis and network analysis in order to examine the effect of listening to naturalistic auditory stimuli on emotion processing brain network in terms of its topological measures: mean weighted degree K, weighted transitivity T, and global efficiency E for all frequency bands.

1.5 Summary

Figure 1.1 summarized the conceptual framework of whole study. The figure depicted the different concepts, theories and experimental works that were brought together in this work and how they are connected to each other. The arrows represent the flow of ideas or the dependence of one concept on the others, as indicated by the arrowheads and the tails of the arrows respectively. Essentially, a unifying framework of connectivity measure were devised in the language of category theory. In this framework, connectivity theory distils and assembles the core components shared by all connectivity measure. A connectivity measure then becomes a model of connectivity theory. The framework also serves as the template for building a novel connectivity measure which was compared with established connectivity measure using an open-source MEG dataset. The novel connectivity measure was developed on the basis of capturing the similarity of the complexity between two brain signals. A statistical approach were also established that allows for testing both absence and presence of experimental effect by defining equivalence regions and using Bayesian posterior distribution estimation of the parameters involved. This was then used to test the potential effects of auditory stimuli on emotional processing network of the brain.

Overall, the scope of this study comprises of 2 parts. The first one is to extend the theoretical and methodological aspects of brain connectivity research by constructing a unifying framework for connectivity measures, developing a novel connectivity measure and developing a statistical approach which capable of accepting and rejecting both null and alternate hypothesis. These theoretical advancements would respectively aids in further development of novel connectivity measures, unravels new insights in terms of brain connectivity research and expands the direction and domain of neuroimaging research. The second part is to apply brain connectivity and network analysis together with these theoretical development to examine brain connectivity patterns in the emotion processing network using MEG in a sample of healthy adult population in response to diverse auditory stimuli. These findings may have implications for our understanding of brain function in particular the emotion processing and could inform the development of interventions for emotional dysregulation.

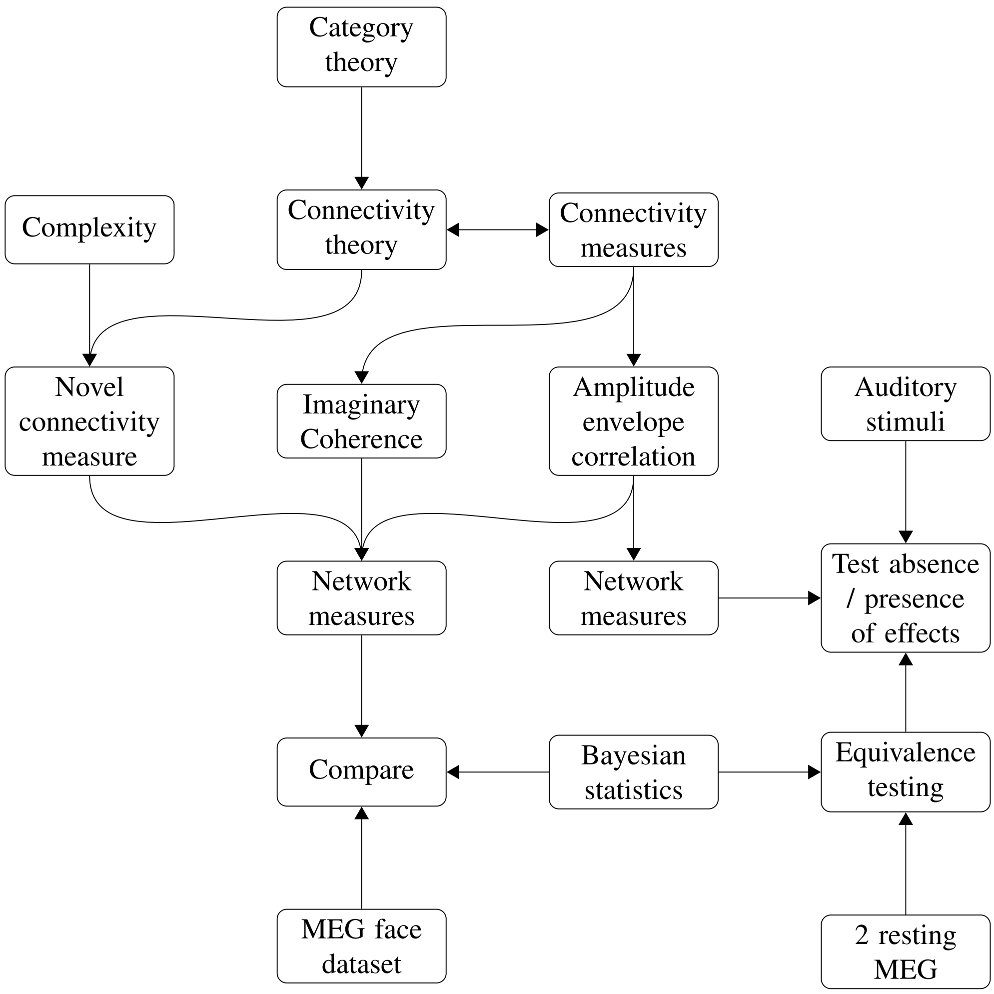

Figure 1.1: The conceptual framework summarizing the whole study.

CHAPTER 2
LITERATURE REVIEW

This chapter deals with the basics and essential principles that are foundational to the understanding of brain connectivity and network analysis using neuroimaging data and set the stage for the theoretical and experimental works by reviewing literature on music therapy and how it induces emotion, Quranic therapy, and by laying the foundation of category theory. In Section 2.1 and Section 2.2, a few aspects of the human brain neurophysiology are covered since it is important to and being exploited by non-invasive neuroimaging techniques such as EEG and MEG for capturing brain activity along with the strengths and limitations of each recording methods. In Section 2.3, the fundamentals and issues on estimating and reconstructing source activity from EEG and MEG data sets are discussed. Of relevance to this work, connectivity measures and additionally several network measures are also reviewed in terms of their mathematical definitions and their research applications in Section 2.4 and section 2.7 respectively. In Section 2.9, the literature on resting state studies are reviewed. In Section 2.10, literature on musical therapy are also reviewed alongside the neurocorrelates of music induced emotion. Therapeutic effects of listening to Qur'anic recitation and variations of Qur'anic recitation are reviewed in Section 2.11. Lastly, in Section 2.5, several concepts and constructs in the field of category theory are introduced as they are heavily relied upon in developing a unified framework for connectivity measures.

2.1 Neurophysiology

The human brain is an extremely complex system containing many types of cells. Of pertinence to the understanding of EEG and MEG signals are neurons. Neurons are excitable cells that collectively play a major role in processing and transmitting information by the means of electrical and chemical signals. A typical neuron has a cell body which contains the nucleus, dendrites which are extensions involved in receiving stimuli from other neurons, and axon which sends information to other neurons. Neurons create fluctuating electrical currents when stimulated. There are two main types of neuronal activation: the action potential and post-synaptic potential.

An action potential is a short lived (lasts ~ 1 *ms*) rapid changes in membrane potential consisting of depolarization and repolarization. It travels down the axon and triggers the release of neurotransmitters which bind to receptors of the post-synaptic neurons. The binding activates post-synaptic potentials which could be either: excitatory post-synaptic potential (EPSP) or inhibitory post-synaptic potential (IPSP). EPSP arises when the neurotransmitter is of excitatory type such as glutamate while IPSP arises when the neurotransmitter is of inhibitory in nature such as gamma aminobutyric acid (GABA).

These post-synaptic potentials are believed to be the main source of the signals captured by EEG and MEG. Action potentials are less likely to play a role since they are short lived and biphasic. Consequently, the positive and negative deflection will cancel out each other since they are less likely to synchronize. In contrast, post-synaptic potentials are long-lived and monophasic. These properties make them more likely to synchronize leading to temporal summation of the total potentials. Together with the spatial summation made possible by the geometrical configuration of the pyramidal cells which are parallel to each other and perpendicular to the cortical surface, it becomes possible for the electrical activities to be detected outside of the skull by EEG and MEG. Therefore, distributed networks of synchronous cortical patches activations are the generators of EEG and MEG signals (Nunez, Srinivasan, et al., 2006).

2.2 Neuroimaging

Functional neuroimaging is one of the many approaches used by neuroscientist to investigate brain functions. This approach deals with the non-invasive brain imaging tools including MEG, EEG, and fMRI. These tools are indispensable in gaining better picture of haemodynamic, electrophysiological, metabolic process of alive and functioning brain. The types of information that they provide are approximate location of brain areas that involve in particular task, time series of activity of those areas, the effect of task or stimulus in modulating the strength of activation. Of note, the tools provide different temporal and spatial resolution that needs to be considered while designing and conducting neuroscientific experiments.

EEG and MEG either alone or in combination have been used to study the dynamics of brain activity due to their high temporal resolution. Compared to fMRI however, they have low spatial resolution and suffer the mixing and field spreading of the local field potentials. fMRI on the other hand, have the best spatial resolution of up to $1mm^3$ per voxel, but provides relatively low temporal resolution of about $1s$.

Information processing in the brain and cognition occurs in the milisecond time scale (Koenig et al., 2002; Papo, 2013) which is similar to the temporal resolution that can be attained by EEG and MEG. Compared to fMRI, EEG and MEG does not depend on surrogate marker of neuronal activity such as glucose or oxygen consumption, but directly measure electrical activity in real time.

2.2.1 EEG

EEG was invented and developed by Hans Berger in 1924 (İnce, Adanır, & Sevmez, 2021). EEG works by measuring the differences in electrical potential recorded between pair of electrodes that are placed on the scalp. It can directly measure the electrical activity of a population of neurons in real time and thus has been used to monitor spontaneous and evoked brain activity. EEG records on the surface of the scalp, both the tangentially and radially oriented cortical dipole activity. With multi-channels elecrodes placed evenly on the scalp, one can estimate the spatiotemporal location of neuronal activity. Due to its low cost and non-invasive nature, EEG has been widely used in clinical and research settings to observe and monitor brain electrical activity.

This non-invasive procedure of recording brain activity from the surface of the scalp hinge on electrical conductivity of different layers of head compartments which unavoidably leads to volume conductions problem. Volume conduction problem is not inconsequential as it can cause spurious connectivity estimation between sensors when in actuality there is no synchronization. This is due to electrical activity in single brain region is being simultaneously recorded by multiple EEG sensors.

Facing with the problem, many researchers sought to estimate the electrical activity at the level of sources or brain regions. This necessitates solving the inverse problems which will be discussed in the next few sections. This, however, only solve the volume conduction issues to a certain degree as signal leakage is still present within the computed signals. Moreover, since the electrical current passes through different layers of tissues having different conductivity, the forward model or the head model must be realistic enough to account for these differences. This, in turns, results in higher computational complexity and load within the overall analysis.

2.2.2 MEG

MEG is another non-invasive neuroimaging technique that is widely used to record brain activity based upon measuring the magnetic flux induced by synchronized neural firing. MEG uses an array of sensors that are extremely sensitive to the changes in the magnetic fields. These high-density sensors (100 to 300 in numbers) are arranged within the helmet-shaped MEG dewar surrounding subject's head. MEG is closely related to EEG since both electrical field and magnetic field are parts of a single entity called electromagnetic field. Thus, both MEG and EEG measure the same underlying neuronal activity. While EEG measures both tangential and radial components of a current dipole, MEG is only sensitive to the tangential components. Thus, EEG is able to capture activity in both sulci and gyri while MEG captures activity mainly originated from the sulci.

Since neural activity generates extremely weak magnetic fields, MEG measurement faces both opposing challenges in terms of requiring extremely high sensors' sensitivity while simultaneously needs to suppress external interferences that are of several orders of magnitude stronger than the brain signals. The weakness of the brain magnetic field necessitates the use of extremely sensitive magnetic sensors, that is, superconducting Quantum interference device (SQUID) sensors. To reduce the effects of background magnetic noise, the recording session are conducted in a magnetically shielded room. Nevertheless, external noises can still creep into the recording thus requiring pre-processing steps before any analysis and inferences on the recordings could be done.

There are a few types of MEG sensors including: magnetometers, axial gradiometers, and planar gradiometers. A magnetometer consists of a single pick-up coil and no compensatory coil. This configuration allows it to measure magnetic field component that is along the direction perpendicular to the surface of the pick-up coil. The problem is it is sensitive to both brain signals and external sources. In contrast, a gradiometer consists of pick-up coil as well as compensatory coil. This configuration allows it to measure the spatial gradient of the magnetic field component. This makes it sensitive to the near-by brain signals but blind to far-away sources. The two coils of gradiometer can be arranged in axial and planar configurations. An axial gradiometer is most sensitive to sources around the rim of the sensor while a planar gradiometer is most sensitive to sources that are exactly beneath them.

There are several advantages of using MEG in researching neural processes, especially when demonstrating how activity of one cortical field can affect and interact with the activity of other parts in the brain. First, similar to EEG, MEG can record neural activity at the temporal resolution of milliseconds. Second, recording from MEG sensors enables researchers to investigate oscillatory neural activity in higher frequency ranges (alpha, beta, gamma) compared to those achievable in both fMRI/PET. In addition, the sampling rate in MEG (commonly greater than 1 kHz) is not constrained by electrode impedance which is an issue in EEG recording. Hence, it enables researchers to study the ultra-high frequency (>100 Hz) brain activity. Third, compared to EEG, volume conduction artifacts are significantly reduced in MEG since head structures for example skull and CSF do not affect the transmission of the magnetic fields (Leahy, Mosher, Spencer, Huang, & Lewine, 1998).

2.3 Source reconstruction

As mentioned before, due to volume conduction in EEG and field spread in MEG, brain activity at any single location is being picked up by multiple sensors simultaneously. This poses a serious challenge for the connectivity analysis (Bastos & Schoffelen, 2016; Nolte et al., 2004). One of the possible solutions is to reconstruct the signals at the level of the source using established methods prior to connectivity estimation (Gross et al., 2013). Source reconstruction also has other benefits. It makes result independent of any particular sensor configuration, the result can be interpreted in terms of brain regions involved and it enables comparison with other neuroimaging modalities such as fMRI, PET and more (Gross et al., 2013; Schoffelen & Gross, 2009). Many sophisticated techniques have been developed to reconstruct and estimate the distribution of electrical activity within the human brain from EEG and MEG recordings. These include: beamformer, minimum norm estimation (MNE) (Hamalainen, 1984), low resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui, Michel, & Lehmann, 1994), focal under-determined system solution (FOCUSS)(Gorodnitsky, George, & Rao, 1995) and many more.

In addition to being widely used in research investigating higher brain function, source imaging has also become essential tools in clinical application such as localizing the epileptogenic zone prior to surgery (Van Mierlo, Vorderwülbecke, Staljanssens, Seeck, & Vulliémoz, 2020). This has been driven not only by the availability of increasingly higher computational power which enables the analysis to be completed quickly, but also has been fuelled by the increase in research developing better and more robust source imaging techniques.

As an alternative, if a researcher wants to infer connectivity at the sensors level circumventing the need for more complex source based analysis, they can apply connectivity measures that are insensitive to volume conductions such as ICOH, PLI, envelope of the imaginary coherence (EIC) (Bornot, Wong-Lin, Ahmad, & Prasad, 2018). However, the interpretation of the results is limited as there is no conclusive information about the location and distribution of the source activity. This is due to the fact that maximal activity at any particular sensor is not indicative of the maximal activity of the brain area underneath it. Besides, a single topographical distribution of electrical potentials or magnetic fields at the sensors level could be generated by more than one underlying neuronal activity configuration (Fender, 1987).

2.3.1 Forward modelling and inverse problem

Source localization or source estimation involves both forward modelling and inverse problem. Forward modelling is the process by which scalp potentials is predicted from the source current in the brain using a volume conductor model of the head. Forward modelling is a straightforward practice which require fewer computations provided the complete description of the model and all the model parameters are available. Since the frequency of interest is below 1000 Hz, quasi-static approximation of Maxwell's equations is used (Baillet, Mosher, & Leahy, 2001; Sarvas, 1987). To be precise, let N and M denote the number of sensor and the number of brain voxels respectively. The voxels can be derived by dividing the source space uniformly such that each voxel has a point source. The equation which connects scalp potential $\mathbf{x}(t)$ and source current $\mathbf{j}(t)$ at time t is defined as follows:

$$\mathbf{x}(t) = \mathbf{L}\mathbf{j}(t) + \mathbf{n}(t) \tag{2.1}$$

where $\mathbf{x}(t) \in \mathbb{R}^{N\times 1}$ is a vector of recorded potential taken from N sensors, $\mathbf{L} \in \mathbb{R}^{N\times 3M}$ is the lead field matrix (also known as gain matrix) for N sensors and M source current dipoles, $\mathbf{j}(t) \in \mathbb{R}^{3M\times 1}$ is the source current dipoles and $\mathbf{n}(t) \in \mathbb{R}^{N\times 1}$ is the noise. $\mathbf{L}$ has all geometric and conductive information of the head volume conductor tissues such as skin, skull, cerebrospinal fluid and etc. This can be modelled as a single homogeneous compartment (Frank, 1952), four concentric spheres (Hosek, Sances, Jodat, & Larson, 1978), and subject specific anatomy MRI using boundary element method (BEM) method (Akalin-Acar & Gençer, 2004) or finite element method (Wolters et al., 2006).

On the contrary, the inverse problem works in the opposite direction of forward modelling, i.e., it estimates the location and magnitude of the source currents from the measured scalp potentials. In general, inverse problem or source estimation can be stated as the solution to a minimization problem of the following form:

$$\hat{\mathbf{j}}(t) = \underset{\mathbf{j}(t)}{\operatorname{argmin}} \left(\|\mathbf{x}(t) - \mathbf{L}\mathbf{j}(t)\| + r(\mathbf{j}(t)) \right) \tag{2.2}$$

where the first term is the norm of the error term between observed signals $\mathbf{x}(t)$ and the estimated signals $\mathbf{L}\mathbf{j}(t)$ and $r(.)$ denotes regularization function. Regularization is important to optimize and stabilize the solution by finding the balance between minimizing the residual and minimizing the contribution of noise.

In practice, only a finite amount of data is available to estimate models and their parameters which usually involves higher degree of freedom. Thus, inverse problem is not unique which means there are many models together with their respective parameters (can be up to infinity) that are able to explain the data equally well. It is also not stable as the solution is highly sensitive to small changes in the data. These make inverse problem an ill-posed problem. In general, there are two approaches for solving the problem: the approach of discrete source reconstruction also known as dipole fitting and the approach of distributed source reconstruction. Dipole fitting method is mainly used to localize only one or a few focal sources in the brain at each time point (Michel & He, 2019). This method is appropriate when the neuronal activity is localized at a small regions of the brain (Komssi, Huttunen, Aronen, & Ilmoniemi, 2004). Such as in the case of localizing epileptic spikes and localizing sensorimotor cortex (Lantz, Holub, Ryding, & Rosen, 1996; Willemse, Hillebrand, Ronner, Vandertop, & Stam, 2016). When expecting the involvement of more than one region of the brain as in the case of connectivity analysis, distributed source modelling is recommended since it is better at simultaneously representing multiple sources (Tadel et al., 2019).

2.3.2 Minimum norm estimation (MNE)

There exists a variety of methods for distributed source space reconstruction, of which, MNE and beamformers are among the commonly used methods. These methods are reviewed extensively elsewhere (Asadzadeh, Rezaii, Beheshti, Delpak, & Meshgini, 2020; Grech et al., 2008; Michel et al., 2004). Among these source reconstruction methods, MNE is a popular technique to estimate brain electrical activity if the detailed information about the generator profile was not available. MNE was introduced and developed by Hämäläinen and Ilmoniemi (1994) to address the limitation and issues of previous method (equivalence current dipole model) with minimal assumptions. The method's only assumption is that the source currents are spatially restricted to a certain area.

In distributed source space reconstruction, dipoles are distributed over the whole brain to simultaneously model the activity over all locations. The number of active sources is defined by the density of the grid. Based on the forward model equation, the estimated source current $\hat{\mathbf{j}}(t)$ can be calculated as follows:

$$\hat{\mathbf{j}}(t) = \mathbf{L}^{\dagger}\mathbf{x}(t) \tag{2.3}$$

where $\mathbf{L}^{\dagger}$ is the linear inverse operator which is obtained by solving the minimization problem. To solve the problem, MNE applies l^2-norm for the error term and $r(\mathbf{j}(t)) = \vartheta^2\mathbf{j}(t)^T\mathbf{S}^{-1}\mathbf{j}(t)$ for the regularization term. ϑ denotes the Tikhonov regularization parameter. Entering these into equation 2.2 yields the following equation:

$$\hat{\mathbf{j}}(t) = \underset{\mathbf{j}(t)}{\operatorname{argmin}} \left((\mathbf{x}(t) - \mathbf{L}\mathbf{j}(t))^T (\mathbf{x}(t) - \mathbf{L}\mathbf{j}(t)) + \vartheta^2\mathbf{j}(t)^T\mathbf{S}^{-1}\mathbf{j}(t) \right) \tag{2.4}$$

which when solved would result in:

$$\mathbf{L}^{\dagger} = \mathbf{S}\mathbf{L}^T(\mathbf{L}\mathbf{S}\mathbf{L}^T + \vartheta^2\mathbf{D})^{-1} \tag{2.5}$$

where $\mathbf{S} \in \mathbb{R}^{3M\times 3M}$ is the source covariance matrix, $\mathbf{L}^T$ is the matrix transpose of $\mathbf{L}$, and $\mathbf{D} \in \mathbb{R}^{N\times N}$ is data noise covariance matrix.

However, MNE is bias towards superficial sources since the sensitivity of the sensors decreases as the distance from the source increases. The weighted MNE (wMNE) method has been introduced to mitigate this problem by minimizing the weighted norm of the solution. This is achieved by modifying the source covariance matrix $\mathbf{S}$ to augment deeper source location. Specifically, the element of $\mathbf{S}$ that corresponds to the p-th source location are scaled by the following factor δ_p:

$$\delta_p = \left(\mathbf{l}_{1p}^T\mathbf{l}_{1p} + \mathbf{l}_{2p}^T\mathbf{l}_{2p} + \mathbf{l}_{3p}^T\mathbf{l}_{3p}\right)^{-\varphi} \tag{2.6}$$