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## CHARACTERIZATION OF NEUROIMAGE COUPLING BETWEEN EEG AND FMRI USING WITHIN-SUBJECT JOINT INDEPENDENT COMPONENT ANALYSIS

by

Nicholas John Heugel B.S.

A Dissertation submitted to the Faculty of the Graduate School, Marquette University, in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

Milwaukee, Wisconsin

May 2020

### ABSTRACT

## CHARATERIZATION OF NEUROIMAGE COUPLING BETWEEN EEG AND FMRI USING WITHIN-SUBJECT JOINT INDEPENDENT COMPONENT ANALYSIS

Nicholas John Heugel B.S.

Marquette University, February 2020

The purpose of this dissertation was to apply joint independent component analysis (jICA) to electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) to characterize the neuroimage coupling between the two modalities. EEG and fMRI are complimentary imaging techniques which have been used in conjunction to investigate neural activity. Understanding how these two imaging modalities relate to each other not only enables better multimodal analysis, but also has clinical implications as well. In particular, Alzheimer's, Parkinson's, hypertension, and ischemic stroke are all known to impact the cerebral blood flow, and by extension alter the relationship between EEG and fMRI. By characterizing the relationship between EEG and fMRI within healthy subjects, it allows for comparison with a diseased population, and may offer ways to detect some of these conditions earlier. The correspondence between fMRI and EEG was first examined, and a methodological approach which was capable of informing to what degree the fMRI and EEG sources corresponded to each other was developed. Once it was certain that the EEG activity observed corresponded to the fMRI activity collected a methodological approach was developed to characterize the coupling between fMRI and EEG. Finally, this dissertation addresses the question of whether the use of jICA to perform this analysis increases the sensitivity to subcortical sources to determine to what degree subcortical sources should be taken into consideration for future studies. This dissertation was the first to propose a way to characterize the relationship between fMRI and EEG signals using blind source separation. Additionally, it was the first to show that jICA significantly improves the detection of subcortical activity, particularly in the case when both physiological noise and a cortical source are present. This new knowledge can be used to design studies to investigate subcortical signals, as well as to begin characterizing the relationship between fMRI and EEG across various task conditions.

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### CHAPTER 1: INTRODUCTION AND BACKGROUND

The neuroimaging of brain activity with simultaneous functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) capitalizes on the complementary strengths of the methods, but poses challenges with respect to crossmethod data integration and interpretation (Ahlfors & Hamalainen, 2012; Dale et al., 2000; Kujala et al., 1995; Z. Liu & He, 2008; J. Mangalathu-Arumana, Beardsley, & Liebenthal, 2012). FMRI measures the hemodynamic response related to neural activity at high spatial (millimeter) but low temporal (on the order of seconds) resolution, whereas EEG provides a high temporal (on the order of milliseconds) but low spatial resolution (centimeter) measurement of large-scale neural activity. Due to the differences in spatiotemporal resolution and type of measurement, fMRI and EEG provide complementary information but may reflect the activity of partially divergent neural sources in the brain.

Understanding when and why the fMRI and EEG activity are coupled (i.e. correlated), and when they diverge is important for understanding brain function. When EEG activity is correlated with changes in the hemodynamic response, source localization approaches that leverage the spatial resolution of fMRI, such as fMRI constrained EEG localization, can be used to characterize brain activity over short timescales (R. N. Henson, Flandin, Friston, & Mattout, 2010; T. Nguyen, Potter, Grossman, & Zhang, 2018; Toma et al., 2002). EEG activity that becomes uncoupled from the hemodynamic response can be an indicator of neurologic disease or dysfunction. Diseases including Alzheimer's, Parkinson's, hypertension, and ischemic stroke, have

been shown to have an altered relationship between fMRI and EEG (Frank M Faraci, Baumbach, & Heistad, 1990; Girouard & Iadecola, 2006; Ibarretxe-Bilbao, Junque, Marti, & Tolosa, 2011; Kazama, Wang, Frys, Anrather, & Iadecola, 2003; Mackert et al., 2008; John Polich & Corey-Bloom, 2005; Prvulovic, Bokde, Faltraco, & Hampel, 2011; Sperling, 2011). Thus, the ability to directly measure the relationship between fMRI and EEG can enable detailed non-invasive characterization of the brain network dynamics that support perception, sensorimotor control, and cognition and provide an important avenue for investigating disease pathology.

This dissertation is aimed at developing an analysis approach to characterize the relationship between simultaneously acquired fMRI and EEG data by leveraging joint independent component analysis (jICA) as a data-driven approach to parse task-related brain activity that covary between EEG and fMRI. The analysis approach developed here optimizes the spatial overlap between coupled EEG and fMRI signals to determine how well fMRI and EEG signals account for one other, applies a methodological approach to characterize the relationship between the fMRI and the EEG, and finally, examines the conditions under which jICA of simultaneous EEG/fMRI can enhance the detection of subcortical signals in the brain.

The following sections provide an overview of the origins of EEG and fMRI signals and current understanding about how the two imaging modalities are related. The conditions under which EEG and fMRI signals can become uncoupled are then discussed, followed by a brief review of blind source separation techniques for neuroimaging analysis including jICA.

### 1.1 Electroencephalography and its Origins

While EEG is a recording of the electrical field potentials measured at the scalp, its relationship to neural activity requires an understanding of how neurons produce electrical currents. In neurons, electrical currents result from the transportation of ions across the cellular membrane. This bulk flow of ions outside of the cell, and through the surrounding resistive tissues gives rise to the change in electrical potential measured by EEG at the scalp. Neurons produce electrical currents in two ways, via the action potentials, which transmit information from a neuron via the axon, and post-synaptic currents at the dendrites, which correspond to the input to a neuron (shown in figure 1). While the action potential produces a large signal (~100 mv  $\Delta$ V), it only lasts 1-2 ms (Da Silva, 2010; Olejniczak, 2006). Post-synaptic potentials are generally smaller in amplitude (~20mv  $\Delta$ V) but last for 20-40ms (Da Silva, 2010; Olejniczak, 2006). Due to this longer lingering depolarization, and the neuron being able to receive multiple inputs simultaneously it is much more likely for potentials to overlap in both time and space, the signal observed in EEG is believed to arise primarily from post-synaptic potentials (Da Silva, 2010; Olejniczak, 2006).



Figure 1. Depicted is a cell with dendrites, soma and axon. In orange are indicated the direction of current flow for the action potential (down the axon) and the excitatory and inhibitory postsynaptic potentials (synapsing onto the dendrites and

Although the post synaptic potentials are believed to be the primary contributor to electrical potentials measured at the scalp, the geometry of the neuron they arise from is also believed to play a role. Stellate cells with radially oriented dendrites will tend to generate currents that cancel each other out producing what are referred to as "closed fields" (Figure 2) (Da Silva, 2010; Johns, 2014; Llinás, Joyner, & Nicholson, 1974; Nunez & Srinivasan, 2006). Other cells, Pyramidal and Purkinje cells in particular,



Figure 2. A stellate cell with radially oriented dendrites is shown. In gray an axon synapses onto the soma of the stellate cell producing a current source. At the end of the dendrites excitatory postsynaptic potentials produce current sinks. In yellow is the direction of the generated dipoles. Adapted from (Johns, 2014)

dendrites that run parallel to each other, or extend only in limited directions. These cells produce extracellular currents that sum, rather than cancel, and produce an "open field" (Figure 3) (Da Silva, 2010; Llinás et al., 1974; Nunez & Srinivasan, 2006). In the neocortex, pyramidal cells are highly structured running parallel to each other and perpendicular to the cortical surface. This structure allows for the extracellular currents from multiple pyramidal cells to sum together and produce larger local signals than could be obtained with a less structured anatomy. For this reason, pyramidal cells in the neocortex are believed to be the primary contributor of measurable extracellular currents.

# **Cortical surface**



Figure 3. The general structure of pyramidal cells is shown. The long dendritic trees extend off one side of the cell resulting in net current dipoles (Yellow arrow) that does not cancel within the cell. In the neocortex, the pyramidal cells have a highly structured arrangement with the dendritic trees running parallel to each other, and perpendicular to the cortical surface. The result is that the net current dipoles of each pyramidal cell sum together. Adapted from (Lopez da Silva, 2010).

In pyramidal cells excitatory synapses occur primarily on the apical dendrites, causing a net flow of ions into the dendrite, creating a current sink within the dendrites. Inhibitory synapses occur primarily on the basal dendrites, producing a net egress of ions from within the cell. So, when taken together the source in basal dendrites and the sink in the apical dendrites produce a net current dipole (Figure 3) (Da Silva, 2010; Llinás et al., 1974). In the case of neocortical pyramidal cells, these current dipoles are all oriented in the same direction, so when they are firing synchronously their net current dipoles sum

together, producing a signal measurable by EEG. Single neurons, are not likely to be detectable within the aggregate neural activity occurring inside the brain. To be detectable, two additional conditions are needed. First, neural activity, in this case the inputs to neocortical pyramidal cells, needs to occur synchronously within a localized region ( $\sim 400 \ \mu m$ ) of the brain so that the resulting electrical dipoles overlap temporally and sum together (Kajikawa & Schroeder, 2011). Second, the orientations of the resulting current dipoles need to be aligned so that the electrical current sum spatially as they propagate through the surrounding tissue. When these conditions occur a net current dipole is created, known as a local field potential (LFP), that is detectable by EEG electrodes on the scalp. Due to the regular anatomical structure of pyramidal cells in cortex the dipoles generated tend to be oriented perpendicular to the cortical surface (Figure 3). As a result EEG is believed to be more sensitive to signals from the top of the gyri and bottom of the sulci, where the dipoles point towards the sensors, and less sensitive to activity along the walls of the sulcus, which are oriented parallel to the sensors and more likely to be canceled out by activity on opposite sulcal walls (Figure 4) (Nunez & Srinivasan, 2006). Because electrical currents do not pass unaltered through tissue, the currents become diffused as the tissue density changes between the cerebral spinal fluid and the skull. This diffusion partially offsets the decreased sensitivity to activity along the sulcal walls, since that activity can theoretically diffuse in a way to hit the scalp electrodes but results in a spatially spreading of the signal that reduces the overall spatial resolution of EEG.



Figure 4. A representation of how the net current dipoles (displayed here as arrows in the neocortex) are oriented with respect to the cortical surface, skull, and scalp. Dipoles along the walls of the sulcus are more likely to cancel each other out. The result being that EEG is recordings have greater sensitivity to net current dipoles generated on the top of gyri, or the bottom of the sulci. Adapted from (Nunez and Srinivasan, 2006).

The diffusion of the electrical current through the skull plays a primary role in reducing the spatial resolution of EEG; however, it is not the only contributor. While the forward model explains how the current dipoles sum and project to the electrodes, the mathematics for the inverse model, mapping EEG signals to specific locations in the brain, are not as simple. The solution to the inverse problem is ill-posed; for a finite set of measurements made at the surface of a volume, there are an infinite number of current source combinations and orientations that could produce the surface measurements. By incorporating assumptions about the locations (the cortical surface), the orientations (perpendicular to the cortical surface) and/or the number of current sources, it is possible to produce an estimate of the inverse matrix. This inverse matrix can then be used to help

localize where the signals measured at the electrodes originated on the cortical surface. Since the inverse matric is an ill-posed problem, the localization is not an exact inverse of the forward projection, and as a result there is nonhomogeneous uncertainty in the spatial extent of the EEG activity, contributing to the poor spatial resolution of the modality (Ahlfors & Hamalainen, 2012; Kujala et al., 1995; Ou, Nummenmaa, Golland, Hämäläinen, et al., 2009). For example, a large frontal electrode activation could arise from a source in the frontal cortex that is radially oriented, or from bilateral sources in the auditory cortex that are tangentially oriented (Vaughan, 1974). So depending on the specific topographic map, it is possible for large uncertainties to exist in source locations.

### 1.2 Functional Magnetic Resonance Imaging

As neurons fire action potentials, the local reserves of glucose and oxygen within the cells become depleted. To maintain neural function additional oxygen and glucose must be delivered by the blood supply. This localized increase in blood flow to accommodate increased metabolic demand in response to neural activity is known as the hemodynamic response. While a complete understanding of the mechanisms that link neural activity to the cerebral blood flow is still an active and ongoing inquiry, there are several mediators known to be involved.

As the action potentials and post synaptic potentials fire, and extracellular currents become active the extracellular concentrations of K<sup>+</sup> and H<sup>+</sup> increases. These increased ionic concentrations, then lead to hyperpolarization of the arterials which causes them dilate (F M Faraci & Sobey, 1998; Kuschinsky, Wahl, Bosse, & Thurau, 1972; T. S. Nguyen, Winn, & Janigro, 2000). Another mechanism by which cerebral

blood flow is mediated by neural activity is through extracellular signaling. As glutamate receptors on the arterials become activated, they trigger a chemical cascade that results in the production and release of nitric oxide (NO), a powerful vasodilator (F M Faraci & Breese, 1993; Girouard & Iadecola, 2006; C Iadecola, Li, Ebner, & Xu, 1995; Lindauer, Megow, Matsuda, & Dirnagl, 1999; Nielsen & Lauritzen, 2001). Downstream glial cells synapsed to the capillaries will trigger pericytes to either contract, sealing off the capillary, or relax, to allow blood flow through the capillary, allowing the blood to be shunted to the regions that need it (Costantino Iadecola, 2004). While the increase in extracellular  $K^+$ ,  $H^+$ , and NO all lead to local dilation of the arterials, there still needs to be dilation of the arteries upstream to prevent a drop in blood pressure. This localized increase in blood flow through the arterioles and capillaries is what fMRI ultimately measures.

The primary way fMRI is used to measure the changes in the cerebral blood flow is through a blood oxygen level dependent (BOLD) contrast, less commonly used contrasts are arterial spin labeling and diffusion MRI. Because oxyhemoglobin is diamagnetic (it produces a magnetic field in the opposite direction of the one it is exposed to) and deoxyhemoglobin is paramagnetic (it produces a weak magnetic field in the same direction of the one it is exposed to) it is possible to measure the local ratio of oxyhemoglobin to deoxyhemoglobin (Belliveau et al., 1990; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Ogawa, Lee, Kay, & Tank, 1990). When cerebral blood flow to a region increases, the ratio of oxyhemoglobin to deoxy hemoglobin changes, which is measured by fMRI. *In vivo* studies of neural vascular coupling have noted that increased cerebral blood flow to a region, and by extension BOLD signal, is delayed with respect to the measured neural activity that generated it (~ 4s) and can last up to 10 seconds (Logothetis et al., 2001; Mazzoni, Whittingstall, Brunel, Logothetis, & Panzeri, 2010). This delayed increase in cerebral blood flow with respect to the originating neural activity is the primary driver of the low temporal resolution of fMRI.

### **1.3** Relationship between EEG and FMRI

EEG and fMRI are characterizing neural activity through two different mechanisms. EEG measures large-scale synchronous neural activity directly through the electrical fields generated by neurons, while fMRI measures neural activity indirectly by way of the increased blood flow in response to increased metabolic demand.

While the relationship between fMRI and EEG is often treated as a linear relationship, the interaction between the measured signals more complex and nuanced. Extensive *in-vivo* research has been conducted to characterize the relationship between local field potentials, the summation of the local current dipoles, and the local cerebral blood flow (Logothetis, 2008a). Multiple studies have shown that the changes in LFPs and cerebral blood blow (termed neurovascular coupling) are strongly correlated (Goense & Logothetis, 2008; Logothetis, 2008a; Logothetis et al., 2001; Mazzoni et al., 2010; Shmuel, Augath, Oeltermann, & Logothetis, 2006), however, it has been shown that by inhibiting nitric oxide production it is possible to elicit neural activity without a corresponding BOLD response(Burke & Bührle, 2006). While this is most relevant in neurological diseases that have been shown to alter the vasculature regulation, such as in hypertension, Alzheimer's disease, or Parkinson's disease, it is also of use when there is damage to the vasculature, as in ischemic stroke (Frank M Faraci et al., 1990; Girouard &

Iadecola, 2006; Ibarretxe-Bilbao et al., 2011; Kazama et al., 2003; Mackert et al., 2008; J. Polich, 2005; Prvulovic et al., 2011; Sperling, 2011). These disease states, as well as the study by Burke, demonstrate that while LFP and BOLD activity may be correlated, they are not tightly coupled, and that there are conditions under which the relationship between them can become nonlinear.

The imaging modalities themselves also offer ways in which the relationship between EEG and fMRI signals (termed neuroimage coupling) could become uncoupled. Because the EEG is primarily sensitive to large-scale synchronous activity, neural activity that is not sufficiently synchronous, or whose current dipoles are not aligned, could produce a weak EEG signal, while eliciting a BOLD response measurable by fMRI. EEG sensitivity is also reduced in response to neural activity localized along the walls of the sulci. FMRI also offers ways for the signals to be uncoupled, fMRI spatial sensitivity is not homogenous, with physiological noise from respiration, heartbeat, and brain activation as well as inhomogeneities in the magnetic field producing spatially dynamic noise (Krüger & Glover, 2001; Triantafyllou et al., 2005). Because the BOLD response takes ~4s to respond to neural activity, a strong transient signal that is present within a period of weaker more sustained activity may not be easily identifiable within the fMRI, while the EEG sensors could more easily distinguish such a transient signals.

EEG and fMRI also have very different spatial sensitivities with respect to each other. The average in-plane resolution of fMRI is approximately 9mm<sup>2</sup> before smoothing (Goense & Logothetis, 2008). This activity is capable of being measured anywhere within the brain, and produces a 3-D volumetric representation of the BOLD response. EEG on the other hand is recording the measurements of activity at the scalp, and while

EEG can be source localized the resolution is only between 3 cm to 6 cm (Babiloni, Cincotti, Carducci, Rossini, & Babiloni, 2001; Burle et al., 2015). This is further complicated by the fact that source localization will localize the activity onto the cortical surface, limiting it to a 2-D sheet, rather than in 3-D. Additionally, since the source localization is an ill-posed problem, the specific assumptions used to perform the source localization can impose spatial shifts to the EEG that vary by spatial location, and temporal activation. This difference leads to challenges in comparing fMRI to EEG, since to compare the two modalities it is often beneficial to bring them into the same space. Most typically, this involves projecting the volumetric fMRI onto the cortical surface as well, which not only gives up the volumetric information, it also requires the user to choose what method to use to determine where fMRI activity falling in voxels covering multiple cortical surfaces should be projected.

Another important aspect to consider when comparing fMRI and EEG sources is their sensitivity to subcortical signals. Due to the ability of fMRI to collect recordings from the entire head volume, it has been able to detect and report subcortical activity. EEG, on the other hand, was long considered to be unable to detect the deeper sources in the brain. This conception has been undergoing revision in the past several years as several studies have reported detecting activity from subcortical regions using EEG and magnetoencephalography (MEG) (Breier, Simos, Zouridakis, & Papanicolaou, 1998; Gross et al., 2001; Ioannides et al., 1995; Jerbi et al., 2007; Tesche, 1996). These have since been backed by simulation studies that have shown that based on our current understanding of the subcortical structures and the strength of their local field potentials, it is possible to detect them with EEG and MEG. However, the sensitivity varies wildly from 40 trials to detect open source signals such as in the hippocampus, to 3500 or more in structures believed to be closed fields such as the thalamus (Attal, Bhattacharjee, Yelnik, Cottereau, Lefevre, et al., 2007; Attal & Schwartz, 2013; T. Dumas, Attal, Dubal, Jouvent, & George, 2011; Thibaud Dumas et al., 2013; Krishnaswamy et al., 2017). These wildly varying sensitivities to subcortical signals represent another way in which fMRI and EEG signals from the same region may be uncoupled.

Finally, coupling and uncoupling between EEG and fMRI can be tied to the task being performed. Studies have reported nonlinear relationships between EEG and fMRI tied to stimulus rate and duration in response to visual (Zhongming Liu et al., 2010; Yesilyurt, Ugurbil, & Uludag, 2008; Yeşilyurt, Whittingstall, Uğurbil, Logothetis, & Uludağ, 2010) and auditory signals (Binder, Rao, Hammeke, Frost, et al., 1994; Rees et al., 1997). In these conditions there seems to be a role in the habituation of the associated regions in the nonlinear relationship. While the regions tasked with the initial processing of the stimuli continue to respond at higher presentation rates regions tied to attention and higher level processing show diminishing evoked responses to the faster rates. The result is an fMRI signal that keeps growing with increased presentation rate, tied to lower level sensory processing, and an EEG signal whose response begins to taper off as higher level areas become habituated.

### 1.4 Joint Independent Component Analysis (jICA)

Since there are multiple ways for EEG and fMRI signals to become uncoupled, developing an approach which can identify when uncoupling occurs, and can characterize the relationship, is crucial for combining imaging modalities to understand brain function. Multiple data-driven approaches have been developed to analyze simultaneous EEG and fMRI signals. FMRI-informed integration approaches bias or limit ERP source reconstruction to regions detected as active with fMRI (Aftanas et al., 1998; Bobes et al., 2018; Dale et al., 2000; Huster, Debener, Eichele, & Herrmann, 2012; Ou, Nummenmaa, Golland, & Hämäläinen, 2009; Xu, Sheng, Qian, Luo, & Gao, 2018). Such approaches are able to address the spatial shift of the EEG sources by restricting them to the location of the fMRI activity. However, this oftentimes comes at the cost of assuming the EEG and fMRI are completely coupled, or guessing the degree to which the signals may be uncoupled. Alternatively, ERP-informed integration approaches will use ERP features defined *a priori* to analyze the fMRI data (Bénar et al., 2007; Debener, 2005; Jann et al., 2009; Liebenthal et al., 2003; Mizuhara, Wang, Kobayashi, & Yamaguchi, 2005; Murta, Leite, Carmichael, Figueiredo, & Lemieux, 2015; Portnova et al., 2018). While these approaches do not impose coupling between the neuroimaging measurements, it only considers EEG signals that were deemed to be of importance, and analyzes the EEG activity at the level of the electrodes. Neurogenerative approaches attempt to model the generation of EEG and fMRI signals to estimate the sources that best explain experimental data, and allow uncoupling between the measurements (Huster et al., 2012; Rosa, Daunizeau, & Friston, 2010; Sotero & Trujillo-Barreto, 2007, 2008). However, neurogenerative modeling approaches are identifying the model that best describes the

data, and not directly informing on the extent of coupling and uncoupling between the modalities. All of these approaches seek to use the patterns present within the data to extract relationships and understanding of the task performed. However, to do so require also requires assumptions to be applied, whose accuracy can strongly impact the outcome of the analysis. Such approaches offer the possibility of extracting relationships that would not be readily detected using standard analysis approaches. Because data-driven approaches can be designed to take all the data into consideration and extract underlying relationships across the modalities, it is ideal for characterizing the relationship between EEG and fMRI.

Recently jICA has been implemented in investigating EEG and fMRI data both across and within subject (Adali, Levin-Schwartz, & Calhoun, 2015; V. Calhoun, Adah, & Liu, 2006; J. Mangalathu-Arumana et al., 2012; Jain Mangalathu-Arumana, Liebenthal, & Beardsley, 2018; Moosmann, Eichele, Nordby, Hugdahl, & Calhoun, 2008).

JICA seeks to take observations from multiple modalities and to estimate the mixing matrix which defines how those underlying joint sources combine into the recorded observations (Figure 5). It takes the inverse of this mixing matrix, and uses it to create multiple components, each containing a joint source. To do this, jICA imposes a strict assumption that the mixing matrix must be identical for all modalities, this forces a linear relationship between the fMRI and EEG within any given joint source component.



Figure 5. Depiction of how the observations  $(X^i)$  used in jICA are assumed to be a combination of an underlying joint source  $(S^i)$ , that has been multiplied through a mixing matrix (A). Adapted from (Levin-Schwartz, 2014).

To estimate the activity within each joint source component *jICA* seeks to identify activity that covaries between modalities when observed across subjects, within-subject jICA modifies this to look for signals that covary across task within a subject, and places that activity within a component. JICA then continues seeking activity that covaries between modality, but adds an additional constraint that seeks to maximize the independence between components. This differs from approaches like principle component analysis (PCA), canonical correlation analysis (CCA), and independent vector analysis (IVA); a generalized form of CCA, in that jICA analysis is seeking to maximize the independence between components, rather than seeking to identify uncorrelated signals. While the terms are often used interchangeably due to the fact independent signals are by definition uncorrelated, the difference is an important one. Independent signals are defined as follows P(X, Y) = P(X) \* P(Y), that is that there joint probability is equal to the product of their individual probabilities. What this means is that the values measured in X have absolutely no impact on the values measured in Y. For a signal to be uncorrelated, its Pearson correlation coefficient must be equal to 0, indicating that there is

not a linear relationship between the two random variables. This importantly does not say there is no relationship between the two signals, only that the relationship between them has to be nonlinear. The result is that approaches like PCA, CCA, and IVA will allow nonlinear relationships to exist between components, while *iICA* is attempting to have no relationship across components. This ability to separate signals that covary across modality but are independent from other signals is of particular interest to this research. When performing specific tasks, networks associated with the task would be expected to covary with the task, whereas unrelated networks would not. What this means for EEG and fMRI is that within-subject jICA is able to extract features from within both modalities that covary with each other and will place them within a component, while separating them from any signals that are independent from them, such as noise or other cortical networks unrelated to the task. It is worth noting that the restriction within-subject jICA imposes that both modalities vary across task conditions identically does have implications on the analysis of the components. Specifically, it produces the effect that when the two modalities have a non-linearity present, it will be split across multiple components (Jain Mangalathu-Arumana et al., 2018). The same study also demonstrated that despite being split across multiple components there was typically a spatial or temporal feature that linked the multiple components together. By checking for such linking features across the components, and recombining any signals that have been identified as being split apart, this feature of jICA analysis can be accounted for and mitigated.

### 1.5 Specific Aims

The goal of this dissertation is to develop an analysis approach to characterize the relationship between EEG and fMRI within-subject and optimize the fusion of EEG and fMRI to study brain function. To achieve this goal, we address three specific aims designed to optimize the spatial correspondence between EEG and fMRI, characterize the task-dependent relationship between EEG and fMRI, and investigate of using jICA applied to EEG and fMRI to characterize deep neural sources in the brain. Each aim is presented in a separate chapter and formatted as a standalone paper.

1.5.1 Specific Aim 1: Develop a method for spatial overlap estimation of electroencephalography and functional magnetic resonance imaging responses.

The use of simultaneous EEG and fMRI to study neural activity has been steadily rising. Multiple approaches have been developed to fuse the two modalities together, from fMRI constrained analysis to jICA constrained approaches. However, these approaches either assume that the EEG and fMRI are both measuring nearly identical activity, or are having to make assumptions as to the degree to which these modalities are recording the same signals. To date there has not been an approach designed to quantitatively assess how well the activity associated with the two modalities correspond to each other. The primary challenge with trying to quantify this is that when EEG is source localized, it aligns poorly with the fMRI source locations. *We hypothesize that the problem in quantifying how well EEG and fMRI correspond to each other is tied to the source localization of the EEG whereby the sources undergo an unknown degree of spatial shifting, and that by accounting for this shift, a better estimate of the correspondence between EEG and fMRI sources should be possible. To test this* 

hypothesis we are going to transform the fMRI data so that it undergoes the same spatial shift the EEG will undergo, thereby transforming them both into a common space. We expect that this transformation, will lead to an improved measure of how well EEG and fMRI activity correspond to each other.

1.5.2 Characterize neuroimaging coupling between EEG and fMRI in a syllable detection task.

Analysis of simultaneous fMRI and EEG tends to inherently assume a linear relationship between EEG and fMRI based off of observations between LFP and cerebral blood flow, but this has not been closely investigated in the case of the neuroimaging modalities. Previous simulations have demonstrated that by applying jICA and making use of the mixing coefficient it is feasible to extract the relationship between EEG and fMRI, although this has not been shown experimentally yet. *We hypothesize that the weighted mixing coefficient extracted from within-subject jICA can be used to characterize the task-dependent relationship between the EEG and the fMRI in a task with a known nonlinearity.* This will be done by collecting simultaneous EEG and fMRI from subjects performing a task with variable presentation rates and adapting the previously developed approach to produce weighted mixing coefficients will be able to extract, and quantify the nonlinearity present in the experimental task, as predicted by the previous simulations.

1.5.3 Quantify the sensitivity of within-subject jICA for the detection of subcortical signals.

Recent experimental studies have begun to report the detection of subcortical signals with EEG and MEG. Follow up studies and simulations have begun validating

this overturning of the long held belief that only activity from the neocortex was sufficiently structured to be detectable with EEG. These studies considered standard analytical approaches to EEG and MEG data, and did not take into consideration the impact of blind source separation approaches. Because the previous aims are directly investigating the relationship between EEG and fMRI it is paramount to understand how applying within-subject jICA changes the detectability of subcortical activity so that the potential impact of subcortical sources can be properly assessed and accounted for. We hypothesize that the application of within-subject jICA to tasks containing subcortical activity will improve the sensitivity for subcortical source detection compared to when *EEG is used alone.* The experimental data from Aim 2 will be used to define the baseline signal and noise characteristics of the computational model. Subcortical sources in the hippocampus and the amygdala will then be defined using previously developed approaches and placed within the physiological noise. To compare the efficacy of jICA it will be compared against the results obtained using temporal ICA and trial averaging. We expect that within-subject jICA utilizing fMRI and EEG will outperform other approaches when it comes to the detection of subcortical sources.

### CHAPTER 2: METHOD FOR SPATIAL OVERLAP ESTIMATION OF ELECTROENCEPHALOGRAPHY AND FUNCTIONAL MAGNETIC RESONANCE IMAGING RESPONSES

### 2.1. Introduction

The neuroimaging of brain activity with simultaneous functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) capitalizes on the complementary strengths of the methods, but poses challenges with respect to crossmethod data integration and interpretation (Ahlfors & Hamalainen, 2012; Dale et al., 2000; Kujala et al., 1995; Z. Liu & He, 2008; J. Mangalathu-Arumana et al., 2012). FMRI measures the hemodynamic response related to neural activity at high spatial (millimeter) but low temporal (on the order of seconds) resolution, whereas EEG provides a high temporal (on the order of milliseconds) but low spatial resolution (centimeter) measurement of large-scale neural activity. Due to the differences in spatiotemporal resolution and type of measurement, fMRI and EEG provide complementary information but may reflect the activity of partially divergent neural sources in the brain.

Both the blood-oxygen-level-dependent (BOLD) fMRI and scalp event related potential (ERP) responses are thought to be near-linearly correlated with local field potentials (LFPs), but only scalp ERPs are also correlated with fast spiking activity (Logothetis, 2008a; Logothetis et al., 2001; Mathiesen, Caesar, Akgören, & Lauritzen, 1998; Mazzoni et al., 2010; Viswanathan & Freeman, 2007). Second, depending on the location and orientation, synchronous electric sources may summate or attenuate one another, resulting in a potential mismatch with the BOLD response. Third, because the primary generators of ERP activity are presumed to be large pyramidal cells in the neocortex that have a highly regimented structure and orientation relative to the cortical surface, the source activity is typically modeled by electrical dipoles limited to the neocortical layer and with an orientation perpendicular to the cortical surface (Ahlfors & Hamalainen, 2012). Thus, there may be a mismatch between the imaging modalities, for example if subcortical sources are measured only with fMRI.

We propose a data-driven approach to estimate the spatial overlap between maps of brain activity generated from fMRI and ERP measurements that assumes that overlapping, but not identical, sources of neural activity contribute to each measurement. That is, different from fMRI-informed integration approaches that limit or bias the ERP source reconstruction to regions detected as active with fMRI (Aftanas et al., 1998; Bobes et al., 2018; Dale et al., 2000; Huster et al., 2012; Ou, Nummenmaa, Golland, & Hämäläinen, 2009; Xu et al., 2018), or ERP-informed integration approaches that use predefined ERP features to analyze the fMRI data (Bénar et al., 2007; Debener, 2005; Jann et al., 2009; Liebenthal et al., 2003; Mizuhara et al., 2005; Murta et al., 2015; Portnova et al., 2018), the approach presented here does not impose coupling between the neuroimaging measurements. Neurogenerative approaches that model the generation of EEG and fMRI signals to estimate the sources that best explain experimental data allow uncoupling between the measurements (Huster et al., 2012; Rosa et al., 2010; Sotero & Trujillo-Barreto, 2007, 2008). However, neurogenerative modeling does not explicitly inform on the extent of coupling and uncoupling between the modalities.

The proposed fMRI and ERP spatial overlap estimation (fMRI-ERP SOE) method is applied to task-related activity extracted from individual data and consists of the following key steps: 1) distributed source reconstruction of the task-related ERP activity (*ERP source model*), 2) transformation of the volumetric fMRI activity to the ERP spatial scale by forward modelling of the scalp potential field distribution and backward source reconstruction (*fMRI source simulation*), and 3) optimization of fMRI and ERP thresholds to maximize spatial overlap without *a priori* constraints of coupling (*overlap calculation*). The representation of both fMRI and ERP signals in a common 'nonnative' source imaging space enables the fMRI-ERP SOE approach to maximize the ability to spatially correlate fMRI and ERP sources of activity while minimizing assumptions regarding neuroimaging coupling.

In this study, the extent to which simultaneous BOLD fMRI and ERP measurements reflect common versus distinct sources of neural activity was estimated in an auditory oddball paradigm with parametric variation of the deviant size. The results indicate that approximately 73% of the activity measured with ERPs overlapped spatially with that recorded with fMRI, and vice versa. Most, but not all, of the regions in which activity was recorded with only fMRI or only ERPs were adjacent to areas of joint activity, suggesting a relatively tight but imperfect coupling between the neuroimaging measures in this paradigm.

#### 2.2. Methods

EEG and fMRI were acquired simultaneously from 24 subjects as they performed an auditory oddball discrimination task with five levels of tone frequency deviants. Details of the experiment design, image acquisition, pre-processing and jICA were reported previously (J. Mangalathu-Arumana et al., 2012) and are briefly summarized here.

### 2.2.1. Subjects

Twenty fours subjects, ages 18–40, participated in the original study (J. Mangalathu-Arumana et al., 2012). Of these, seven subjects were excluded from the analysis because their anatomical MR-images did not cover the entire skull (as needed to construct a head model). Two additional subjects were excluded from the group analysis during preprocessing because jICA returned components with non-physiological data structures (z-scores >30 and no spatiotemporal variation across electrodes), indicating a failure of jICA to parse the signals into independent components. Data from the remaining fifteen subjects (8 females and 7 males) were used in the current analyses. All subjects provided written informed consent according to the Institutional Review Boards of the Medical College of Wisconsin and Marquette University, and were compensated for their participation in the study.

### 2.2.2. Experimental Design

The experiment consisted of an auditory oddball paradigm with four-tone sequences, each composed of three standard 1000 Hz tones and one deviant tone (in 3<sup>rd</sup> or
4<sup>th</sup> position), presented binaurally. The task consisted of pressing one of two buttons to indicate whether the deviant tone sounded higher or lower in frequency than the standard tones (J. Mangalathu-Arumana et al., 2012). The tones were 100 ms duration with rise/fall times of 5 ms and were presented at 800 ms stimulus onset asynchrony. The deviant tone frequencies (five lower, and five higher, than the standard tone frequency) were selected individually to correspond to 50, 65, 75, 85, and 95% task performance accuracy (as determined in a prescan test). 144 trials were presented per task level, for a total of 720 trials, broken into 12 runs, acquired in 2 sessions on separate days. The onset of each tone sequence was jittered relative to the time of image acquisition, such that the deviant tone was always presented 4 s before the middle of the next image acquisition block, and the image acquisition coincided with the estimated peak of the BOLD response (Hall et al., 1999). Auditory stimuli were delivered using a pneumatic, MRIcompatible headphone system (Avotec, Inc., Stuart, FL), and the sequence of stimulus presentation was controlled with the Presentation software (Neurobehavioral Systems Inc., San Pablo, CA).

#### 2.2.3. Data Acquisition and Pre-Processing

The study was conducted on a GE 3 T Signa Excite scanner (GE Health Care, Milwaukee, WI). High-resolution whole brain anatomical images were acquired first in each session, using a 3D spoiled gradient-echo (SPGR) sequence  $(0.9 \times 0.9 \times 1 \text{ mm})$ voxels). Functional MR images consisted of axially-oriented T2\*-weighted, gradientecho, echo planar images acquired using a clustered volume acquisition and covering the whole brain (TE = 25 ms; flip angle = 77°; TR = 2 s; stimulus blocks = 7 s; 3 × 3 × 3.5 mm voxels), such that a single functional volume was acquired during each trial 4 s after stimulus onset. EEG was recorded continuously during fMRI, at 500 Hz sampling rate, using an MRI-compatible MagLink system consisting of a 64-channel MagLink cap (62 monopolar electrodes, and 2 bipolar leads for ECG and VEOG), SynAmps amplifier, and a Scan 4.4 Workstation (Compumedics Neuroscan, Inc., TX). Sintered Ag/Ag-Cl electrodes were positioned per the extended International 10–20 system, with a hard-wired reference at CPz.

MR image preprocessing was performed in AFNI (Cox, 1996). The raw fMRI 2D image slices at each time point were transformed to 3D and spatially registered to the third functional image in the first run. The functional image series was then registered to the anatomical image (consisting of an average of the anatomical images from sessions 1 and 2, to obtain higher anatomical accuracy) using the *align\_epi\_anat.py* program in AFNI. Multiple regression was performed to estimate the BOLD activity associated with the response to the deviant in each task level, using level 1 (corresponding to 50% performance accuracy) as a baseline, and translation and rotation motion parameters estimated during registration were used as noise covariates.

The raw EEG was preprocessed with the Scan 4.4 Edit module (Compumedics Neuroscan, Inc. TX). Channels with a variance >  $20\mu$ V in the baseline period (-200 to -50 ms) were excluded from further analysis. An average of 7 (range 0–9) channels per subject was excluded. The EEG was filtered using a 0.1–30 Hz zero-phase bandpass FIR filter with a 48 dB/octave roll-off. The ballistocardiogram artifact introduced by the MR environment was corrected (Ellingson et al., 2004). Removal of MR gradient artifacts was unnecessary because the clustered functional image acquisition design for

simultaneous fMRI/EEG (J. Mangalathu-Arumana et al., 2012) prevented the epochs of interest from being contaminated.

ERPs were computed for each task level using an epoch time from -200 ms to 800 ms relative to deviant onset. The epochs were demeaned to compensate for slow drifts occurring during EEG acquisition. Epochs in which the signal exceeded  $\pm 200 \,\mu\text{V}$ were deemed to contain artifacts and were discarded. The remaining epochs were sorted and averaged by task level. The average number of accepted epochs per subject and level was 86%.

As with the fMRI preprocessing, the ERP response to task level 1, the hardest task level, was subtracted from the ERP responses to the other four task levels. The resulting fMRI and ERP responses associated with task levels 2–5 were used as input for jICA.

2.2.4. Joint-ICA

The fMRI and ERP datasets were submitted to within-subject jICA, as described previously (J. Mangalathu-Arumana et al., 2012). The datasets were vectorized and concatenated by level. The input to jICA consisted of four features, each containing the fMRI and ERP responses for one of the four task levels, such that the resulting components represented within-subject fMRI and ERP responses that co-varied across task levels (known as Multi-run jICA).

Components containing task-relevant activity were identified in each imaging modality as those exceeding an amplitude threshold of p < 0.05 relative to the distribution of activity across all components in that modality. The joint (multimodal) component containing the most active samples (either ERP time points or fMRI voxels) was used to define a component activity threshold. The threshold (in samples) for including

components in the subsequent analyses was set to  $\# \frac{samplesinmostactivecomponent}{total#of components}$ , based on a monte carlo simulation of the random distribution of active samples across components when task-related activity is constrained to a single component. This approach set a permissive (low) threshold for the inclusion of task-related activity from other components by underestimating the number of active samples per component when no task-related activity is present. In 12 subjects, only one joint component passed the threshold. In the remaining 3 subjects, there were 2 suprathreshold joint components, which were summed for subsequent analysis to avoid losing activity of interest.

2.2.5. FMRI and ERP Spatial Overlap Estimation (fMRI-ERP SOE) Method

A schematic overview of the fMRI and ERP spatial overlap estimation (fMRI-ERP SOE) method is shown in Figure 6. The approach includes three main components, 1) distributed source reconstruction of the task-related ERP activity (*ERP source model*), 2) transformation of the volumetric fMRI activity to the ERP spatial scale by forward modelling of the scalp potential field distribution and backward source reconstruction (*fMRI source simulation*), and 3) optimization of fMRI and ERP thresholds to maximize spatial overlap without *a priori* constraints of coupling (*overlap calculation*). It is important to note that the proposed analysis pipeline can be applied to data that is not processed using jICA. It can also be applied separately to the individual jICA components, which would be recommended in studies where the task-related activity is consistently parsed to several components (e.g., studies with more experimental levels.



Figure 6. Workflow for fMRI and ERP spatial overlap estimation (fMRI-ERP SOE) method. The functional imaging measurements used as input to jICA, and the anatomical images used to create the head and cortical surface models, are shown in orange. The structural/functional pre-processing steps used to create the anatomical model and extract task-related activity are shown in green. Processing steps for the task-related ERP activity are shown in red and those for the fMRI activity, including projection to the common source space, are shown in blue. The steps for ERP and fMRI threshold optimization, and characterization of source map spatial overlap, are shown in purple.

# 2.2.5.1. ERP Source Model

Distributed source reconstruction was used to localize the cortical areas contributing to the scalp ERPs (see steps in red, Figure 6). For each subject, models of the head and pial surface were created in Freesurfer (https://surfer.nmr.mgh.harvard.edu/) using the *recon-all* script on the subject's averaged MR anatomy. The head model was then imported into Brainstorm (http://neuroimage.usc.edu/brainstorm/), the pial surface was down sampled to 15,000 vertices, and a boundary element model (BEM) of the cortical surface was created. Whitened and depth-weighted linear L2-minimum norm estimates were used to estimate the amplitude of source activity at each vertex oriented perpendicular to the cortical surface. Finally, the absolute value of source activity at each vertex and time point was converted to z-scores computed relative to the baseline period (-200 ms to -50 ms).

#### 2.2.5.2. FMRI Source Simulation

To facilitate comparisons in the spatial domain, the fMRI volumetric activity was simulated as ERP activity by projection to the cortical surface, forward construction of the scalp potential field distribution, and backward source reconstruction (see steps in blue, Figure 6). For each subject, the volumetric fMRI component was projected orthogonally onto the inflated pial surface in Freesurfer using *mri\_surf2vol* and smoothed with a 6 mm full width half maximum Gaussian kernel to fill in small spatial discontinuities resulting from the projection. The map of surface activity was imported into Brainstorm and down sampled to 15,000 vertices. The amplitude of activity at each vertex was multiplied by a 400 ms unit amplitude square-wave to simulate a time course and the resulting spatiotemporal activity was forward projected to the scalp electrodes using the lead field matrix. Gaussian noise was added to each electrode to match the noise covariance of the experimentally-measured EEG. The fMRI activity was then submitted to the same source localization procedures used for the ERP analysis.

### 2.2.5.3. Overlap Calculation

The estimate of overlap between fMRI and ERP source maps may vary as a function of individual differences in activation, and the statistical threshold defining significant activity. In the present work, we opted to identify on an individual basis, the amplitude threshold for the fMRI source map and the temporal and amplitude thresholds for the ERP source map that maximized their spatial overlap on the cortical surface (see steps in purple, Figure 6). This individualized optimization procedure assumes that simultaneous fMRI and ERP measurements largely reflect the local field potential activity of the same neural sources, with partial divergence driven primarily by differences in the spatiotemporal resolution of the measurements.

The thresholds were optimized on a vertex-wise basis. The amplitude thresholds spanned the range [0, 95] % of the maximum amplitude (steps of 0.01), and the ERP temporal thresholds spanned the range [20, 800] ms (20 ms steps). Thresholds were optimized using a class membership function (*O*) based on the vertex-wise correspondence between the ERP and fMRI source maps,

$$O = \frac{Intersection*Union^2*Exclusion^3}{\left(\frac{total_{vertices}}{2}\right)^6}$$
 where the intersection corresponds to the number of

vertices with significant activity in both imaging modalities, the union corresponds to the number of vertices with significant activity in at least one imaging modality, and the exclusion is defined by the difference between the union and the total number of vertices. The denominator scales the membership function to one when the ERP and fMRI maps overlap completely and the union is balanced by the exclusion. Optimization of the membership function within the threshold space was used to maximize the spatial overlap between fMRI and ERP sources while promoting sparsity in the activation map.

The optimized thresholds were applied to create binary ERP and fMRI source maps, with edge correction to account for stochastic variations in the boundaries of active regions. Vertices that were inactive but surrounded by active vertices in one imaging modality, and were active in the other modality, were labeled as active in both modalities.

To determine the statistical significance of the optimized ERP temporal threshold, a Monte Carlo simulation with 1000 iterations was used to determine the likelihood that a phase-randomized signal with the same power spectrum would exceed the temporal threshold. The distribution of consecutive data points in the phase-randomized signal that met or exceeded the ERP amplitude threshold at each vertex was calculated to determine the 0.05 confidence interval. A Šidák correction was applied to adjust for multiple comparisons across vertices (Sidak, 1967). Vertices in which the activity did not exceed the temporal threshold were marked as inactive in the binary maps. In a second Monte Carlo simulation with 1000 iterations, the spatial distribution of active vertices in the fMRI and ERP source maps was randomized to estimate the probability of obtaining the observed spatial overlap between source maps.

#### 2.2.5.4. Overlap Estimation

Regions of overlap (and no overlap) between ERP and fMRI source maps were estimated within, and across, subjects. For the analysis across subjects, the individual cortical surface models were aligned to Freesurfer's *FSaverage* anatomy using spherical transformations, and the same alignment transform was applied to the individual signed Z-score and binary overlap maps. The individual binary maps were summed at each vertex to determine the number of subjects with supra-threshold activity across imaging modalities.

Regions of interest (ROIs) were created that corresponded to the areas of overlap in ERP and fMRI activity across the group. First, an ERP-fMRI overlap mask was created by thresholding the group overlap count map at 9 subjects, and applying a cluster threshold of 3 vertices, resulting in a corrected p < 0.05 (computed using a 1000 iteration Monte Carlo simulation of expected cluster sizes based on a randomized distribution of the vertices with overlapping fMRI/ERP activity in the source projection space). The overlap mask was then grown by one vertex in every direction to smooth the boundaries and account for 99% of the fluctuations in the spatial extent of backward projected ERP sources simulated using the experimentally measured electrode noise covariance.

The final ERP-fMRI overlap mask consisted of six distinct ROIs, in the right and left superior temporal planes, right lateral superior temporal sulcus, right and left inferior parietal lobules, and right ventral central sulcus. Within in each ROI, the number of vertices per time point that exceeded the global (p < 0.05) amplitude threshold were counted in each subject and averaged across subjects to create mean time courses of activation.

The degree of fMRI-ERP overlap obtained with the SOE approach was compared to the degree of fMRI-ERP overlap obtained with strictly jICA, that is, without simulating the fMRI as ERP activity, and with independent thresholding of the components in each modality. When the SOE approach was not used, the ERP amplitude threshold in each subject was set leniently (p < 0.1) using the amplitude distribution across all components to maximize spatial overlap and Monte Carlo simulations were used to set the temporal threshold (= 50 ms) resulting in a corrected map-wise threshold of p < 0.05. The volumetric fMRI in each jICA component was projected onto the cortical surface. The fMRI amplitude threshold was set to p < 0.05 using the amplitude distribution across all components and Monte Carlo simulations were used to set the vertex cluster threshold resulting in a corrected map-wise threshold of p < 0.05. Counts of the number of subjects with activity at each vertex were computed as detailed above, for ERP, fMRI, and ERP - fMRI overlap.

### 2.3. Results

Table 1 summarizes the results of the optimal (i.e., maximizing the overlap) threshold calculation and the ERP and fMRI spatial overlap estimation in each subject. Across the group, the mean amplitude threshold of the ERP maps was a z-score of 2.68 (standard deviation – SD = 2.14). The mean temporal threshold of the ERP maps was 442 ms (SD = 258.2 ms). The mean amplitude threshold of the fMRI maps was 9 (SD = 2.1). The optimized ERP amplitude and temporal thresholds were negatively correlated across subjects (R = -0.85). FMRI amplitude thresholds were not correlated with ERP amplitude or temporal thresholds (R = -0.01 and R = 0.23, respectively).

Subject Number	ERP amplitude threshold (Z-score)	ERP temporal threshold (ms)	fMRI amplitude threshold (Z-score)	Extent of fMRI activity overlapped by ERP activity (%)	Extent of ERP activity overlapped by fMRI activity (%)
4009	0.37	740	5.71	69.1	73.03
4018	4.53	20	3.92	70	73.5
4137	1.44	640	18.58	76.3	74.3
4138	0.25	740	5.24	79.2	66.8
4170	2.39	660	7.29	80	84
4177	0.66	620	12.4	65.9	67.3
4192	1.22	720	9.78	74.5	76.8
4237	1.57	420	6.75	81.4	76.1
4282	1.05	580	9.7	69.8	71.3
4283	3.76	440	21.63	82.2	85.5
4284	6.14	260	7.79	58.15	65
4287	3.12	300	5.35	69.9	78.01
4296	4.39	60	5.71	64.7	62.6
4410	2.06	400	5.34	79.5	78.3
4498	7.3	40	10	66.7	68.3

Table 1. Individual ERP (amplitude and temporal) and fMRI (amplitude) threshold values that maximize the overlap between ERP and fMRI source maps.

Figure 7 shows an example of the class membership function following an exhaustive search of the ERP amplitude and temporal threshold space for a representative subject. The figure illustrates the trade-off between the ERP amplitude and temporal thresholds that resulted in similar levels of overlap between ERP and fMRI source maps.



Figure 7. Example of the ERP threshold optimization map for a representative subject (#4287) at an fMRI amplitude threshold of 5.35. The color map depicts the output from the overlap class membership function as a function of ERP amplitude and temporal threshold for the subject. The extended region of dark red indicates a trade-off between amplitude and temporal thresholds to maximize the spatial overlap between the ERP and fMRI source maps.

The extent of spatial overlap between ERP and fMRI source maps across subjects is shown in Figure 8. For the fMRI source maps, the extent of overlap with the ERP source maps ranged from 58.15% to 82.2%, with a mean overlap of 72.5% (SD = 7.2%). For the ERP source maps, the extent of overlap with the fMRI source maps ranged from 62.6% to 85.5%, with a mean overlap of 73.4% (SD = 6.7%). Across subjects, the extent of ERP activation overlapped by fMRI activation and extent of fMRI activation overlapped by ERP activation were positively correlated (R = 0.73). For the sample population, the slope of the best fit line (=0.68x+23.85) was not significantly different from a unit line (ANCOVA, F (1) = 1.37, p = 0.187).



Figure 8. Spatial overlap between ERP and fMRI source maps computed with the fMRI-ERP SOE method. The percentage of ERP activation overlapping with fMRI activation is plotted against the percentage of fMRI activation overlapping with ERP activation (blue squares). The two measurements were positively correlated (R = 0.73), and their relationship was well described by the line y = 0.68x+23.85 (in black). The unit line is shown in green. The percentage overlap obtained with a randomized spatial distribution of ERP and fMRI activity is represented by the red square dot (red circle denotes +5 standard deviations).

Figure 9 shows the ERP and fMRI source maps, and areas of activity overlap, in a representative subject. For this subject, the suprathreshold fMRI activity overlapped with 84% of the suprathreshold ERP activity, and the suprathreshold ERP activity overlapped with 80% of the fMRI activity.



Figure 9. Example of the spatial overlap estimation between ERP and fMRI source maps in a representative subject (#4237). Activity exceeding the significance

# threshold only in the ERP source map is shown in red, only in the fMRI source map is shown in blue, and in both the ERP and fMRI source maps is shown in green

Figure 10A shows the count of subjects with suprathreshold activity in both imaging modalities at each vertex on the cortical surface mesh. Regions of consistent ERP and fMRI overlap in activity (in 9 or more subjects) were observed in the bilateral insula and inferior parietal lobule, and in the right superior temporal gyrus and ventral central sulcus. Additional regions with less consistent ERP and fMRI overlap (in 6–8 subjects) were observed in the middle temporal, frontal, and superior parietal cortices (primarily in the right hemisphere). Figure 10B shows six ROIs in which there was consistent ERP and fMRI overlap, and the time course of activation within the ROIs measured as the mean (across subjects) number of suprathreshold vertices. In the early (<300 ms) period of the ERP, there was only weak activity in the superior temporal cortex, peaking in the bilateral insula at 140 ms, and in the right superior temporal sulcus and insula at 242 ms. The later (>300 ms) ERP activity, which was stronger and sustained, originated from the perisylvian ROIs.



Figure 10. Group fMRI and ERP spatial overlap estimation (fMRI-ERP SOE) map. (A) Color map representing the number of subjects with overlapping fMRI and ERP activity at each vertex. For visualization, the maps were thresholded at 6 subjects. B) ROIs with consistent (in 9 or more subjects) ERP and fMRI activity overlap and the time course of activity in each ROI. The time course was measured as the mean (across subjects) number of suprathreshold vertices at each time point.

Figure 11 shows regions in which there was significant activity in one imaging modality but not the other, in 6 or more subjects. Small regions of non-overlap between fMRI and ERP activity were observed in the Sylvian fissure, and in the posterior superior temporal and orbitofrontal cortex. The maximal number of subjects with activity in only one modality was 8.



Figure 11. Non-overlap between fMRI and ERP source maps, computed with the fMRI-ERP SOE method. Non-overlap is expressed as the number of subjects with activity in one modality (ERP, top; fMRI, bottom) but not the other. For visualization, the maps were thresholded at 6 subjects. The color bar indicates the number of subjects with non-overlap at that location.

For comparison with a generic method (using only jICA), the spatial overlap between fMRI and ERP joint components that were thresholded independently is shown in Figure 12. A high degree of spatial overlap was observed across subjects within each imaging modality (up to 8 subjects), in temporoparietal regions implicated in the auditory oddball response. However, between ERP and fMRI maps, the regions of maximal overlap were limited to 4 subjects (Figure 12c).



Figure 12. Group spatial overlap in (A) ERP, (B) fMRI, and (C) both ERP and fMRI, estimated using strictly jICA, and independent thresholding of source maps in each neuroimaging modality. Overlap is expressed as the number of subjects with activity at each vertex. For visualization, the maps were thresholded at an overlap of 2 subjects (note the different scale of 2–8 subjects in this Figure).

The benefits of jICA with fMRI-ERP SOE versus just jICA can be seen from a

comparison of Figures 5a and 12 c. Figure 10a shows the spatial overlap across subjects

between ERP and fMRI source maps calculated with the fMRI-ERP SOE method. Figure

12c shows the spatial overlap across subjects between fMRI and ERP source maps without SOE correction of the spatial bias related to the ERP source localization. The spatial overlap peaks at 13 subjects for the fMRI-ERP SOE method and at only four subjects for just jICA.

### 2.4. Discussion

In this paper, we present a data-driven method to estimate the spatial overlap between maps of brain activation originating from simultaneous fMRI and ERP measurements, termed fMRI-ERP SOE. The fMRI-ERP SOE method is based on the parsimonious assumption that simultaneous fMRI and ERP responses largely reflect local field potentials generated by the same neural sources. However, a distinctive feature of the fMRI-ERP SOE method is that it allows divergence in the sources of activity contributing to the measurements in each modality.

FMRI-ERP SOE of sources of the auditory oddball response revealed regions of consistent (in 9 or more of 15 subjects) activity overlap between imaging modalities in the insula, superior temporal, and inferior parietal cortices, in-line with previously reported sources of this response (Justen & Herbert, 2018; Liebenthal et al., 2003; J. Mangalathu-Arumana et al., 2012; John Polich, 2007; Sijbers et al., 1999). Strong activity in these areas was observed predominantly after 300 ms, in the time window of the P3 ERP response associated with cognitive processing during attentive oddball detection (Picton, 1992; John Polich, 2007). The earlier (<300 ms) and weaker (due to subtraction of the level 1 response) activity coincided with the latencies of the N1 and mismatch negativity (MMN) responses associated with automatic auditory processing

and oddball detection (Campbell, Winkler, & Kujala, 2007; Näätänen, Paavilainen, Rinne, & Alho, 2007; Naatanen & Picton, 1987). The magnitude of the P3 is influenced by the cognitive context and demands of the task, whereas that of the N1 and MMN is influenced primarily by the physical properties of the stimuli. In the present experimental design in which the baseline (level 1) corresponded to chance deviant detection, the variation in deviant responses across the experimental levels (2–5, corresponding roughly to 65–95% deviant detection) reflected primarily a change in attentive perceptual and cognitive processing of the deviants, as indexed by P3, and minimally a change in subliminal auditory processing of sound frequency, as indexed by N1 and MMN.

The fMRI-ERP SOE method displayed important benefits relative to strictly jICA of fMRI and ERP. JICA with fMRI-ERP SOE revealed a greater extent of reliable activation in the right superior temporal cortex, considered to contribute to the generation of the auditory oddball response, than just jICA of the same data. Consistent activity was detected in the right superior temporal sulcus in both modalities when estimated with fMRI-ERP SOE (Figure 10A), but not when estimated strictly with jICA. Activity in the right superior temporal sulcus was observed in the jICA-fMRI map (Figure 12B) but not the jICA-ERP map (Figure 12A), resulting in no overlap in this area with jICA. The weak EEG sensitivity to sources of activity in the superior temporal cortex may be due to incomplete (and inconsistent across subjects) coverage of this area by EEG electrodes especially in the ventral portion. Indeed, a study comparing fMRI and ERP activation maps in visual and auditory paradigms reported fMRI-ERP uncoupling specifically in auditory superior temporal areas, and attributed it to sparse EEG coverage (Minati et al., 2008).

The advantages of using fMRI-ERP SOE to characterize the spatial relationships between fMRI and ERP sources center on the 1) projection of both datasets into a common (non-native) source space that accounted for the effects of spatial bias during source localization; and 2) the optimization of the fMRI and ERP thresholds to maximize the overlap between the sources measured with each method. In this sense, the considerably lower overlap of using jICA alone (i.e., when assumptions of neuroimage coupling are minimized), could be related to the spatial error associated with ERP source localization, as well as the arbitrary nature of neuroimaging data thresholding.

The fMRI-ERP SOE also revealed brain regions in which activity was less consistent across subjects, notably in the right inferior frontal cortex (Figure 10A). The right inferior frontal cortex is considered to be part of a ventral attention network involved in stimulus-driven orientation and deviance detection (Justen & Herbert, 2018; Knight, 1984; Pardo, Fox, & Raichle, 1991; M. Posner, 1990; Michael Posner, 1992; Soltani & Knight, 2000). The variability in activation of right frontal areas could reflect attentional fluctuations and individual differences in cognitive control during task performance. However, differences in measurement quality could also contribute to inconsistent signal amplitudes in frontal cortex. Specifically, frontal activity measured with EEG could in some instances be generated by tangentially oriented sources in bilateral temporal cortex as opposed to radially oriented frontal sources (Ahlfors & Hamalainen, 2012). In line with the possibility of 'ghost' frontal sources in the present ERP data, the most consistent activation across subjects in the jICA-ERP map was in the right inferior frontal cortex (8 subjects, Figure 12A), but this area was inconsistently activated in the jICA-fMRI map (2 subjects, Figure 12B).

Across the group, approximately 73% of the activity at each brain location was measured with both neuroimaging modalities, and the remainder 27% was measured in one modality but not the other (Table 1, Figure 8). The activity measured in only one of the modalities largely fell adjacent to areas of ERP-fMRI spatial overlap (see Figure 9, in a representative subject) and was in the same vicinity in both modalities (e.g., sylvian fissure), suggesting that it reflected primarily differences in the extent of overlapping activation rather than complete uncoupling between the modalities. However, there were also regions of single modality activity that were not adjacent to areas of overlap; for example, activity measured only with EEG in the right inferior frontal cortex and bilateral parietotemporal cortex in the representative subject. The non-overlap group map (Figure 11), however, showed that areas of non-overlap were largely inconsistent across subjects. Taken together, the present results suggest the existence of comparatively small areas of modality uncoupling, in variable brain locations. The results demonstrate the potential utility of the fMRI-ERP SOE method to investigate the factors contributing to uncoupling between the fMRI and EEG measurements. The strong positive correlation, with a near unit-slope, between the extent of fMRI and ERP spatial overlap (Figure 8) is also indicative of limited uncoupling between the measurements in each modality. In this analysis, uncoupling between the modalities, i.e., activity measured with one neuroimaging modality but not the other, would be observed as a positive correlation with a steeper slope (reflecting more extensive ERP activity), or a shallower slope (reflecting more extensive fMRI activity).

The optimal amplitude and temporal thresholds for maximizing the spatial overlap between imaging modalities spanned a wide range, with ERP z-scores between 0.25 and 7.3, ERP temporal thresholds between 20 and 740 ms, and fMRI z-scores between 3.9 and 21.6. The amplitude and temporal ERP thresholds were found to be negatively correlated, suggesting a trade-off between them. The amplitude thresholds were generally higher for fMRI than ERP, likely because of the additional temporal threshold applied strictly to ERP signals. The threshold values identified as optimal for maximizing overlap were in some subjects well outside the range typically used for neuroimaging data analysis, yet their application resulted in statistically significant and biologically plausible activation maps. Thus, the proposed threshold optimization and fMRI-ERP SOE analysis may have value for exploring data more comprehensively than possible with more typical analysis approaches.

The fMRI-ERP SOE approach shares some similarities with neurogenerative modeling approaches. Both use statistical methods to investigate the relationship between fMRI and EEG without imposing a constraint of coupling between the signals. However, neurogenerative approaches attempt to reduce the errors associated with EEG source reconstruction by informing the forward generative model with physiological parameters. Our approach on the other hand, attempts to reduce the spatial discrepancies between EEG and fMRI by forward modeling the fMRI as an EEG scalp distribution and applying the same source reconstruction procedure to both modalities (i.e., biasing the fMRI to the EEG spatial scale). While the accuracy of neurogenerative approaches depends on the accuracy of the EEG forward model, our approach accepts that EEG source reconstruction is imprecise and applies the same bias to the fMRI. Thus, the methods can perhaps best be seen as complementary. For example, the fMRI-ERP SOE can be used to identify areas of coupling and uncoupling, and this information can be used to constrain and improve the precision of a neurogenerative source model.

The fMRI-ERP SOE is a data-driven method to quantitatively estimate the spatial relationship between sources of brain activity measured with fMRI and EEG. The present study demonstrated that the addition of this method provides greater spatiotemporal detail of the cortical dynamics than solely jICA, a common method for multimodal integration (Arumana, 2012; Ma, Phlypo, Calhoun, & Adali, 2013; J. Mangalathu-Arumana et al., 2012; Moosmann et al., 2008). Furthermore, the fMRI-ERP SOE method provides a means to estimate the degree of *non-overlap* between the sources measured with each neuroimaging modality, and this aspect could be useful to study uncoupling. As such, we propose that the addition of fMRI-ERP SOE provides a more comprehensive method for the integration of data from the two neuroimaging modalities. The fMRI-ERP SOE method could be used to study the conditions under which uncoupling can occur. For example, at high stimulation rates in healthy individuals (Goense & Logothetis, 2008; Jerbi et al., 2007; Muthukumaraswamy & Singh, 2008; Nagarajan et al., 1999) and in individuals with compromised neurovascular coupling (F M Faraci, Baumbach, & Heistad, 1990; Kazama et al., 2003; Mackert et al., 2008).

One limitation of the approach is the long computation time. The exhaustive search of the amplitude and temporal threshold space performed to maximize spatial overlap is computationally demanding, requiring several hours of processing per subject. In experimenting with optimization approaches, we consistently found that the fMRI-ERP overlap metric plateaued for different ERP amplitude and temporal threshold combinations (see Figure 7 for an example in one subject). Due to this, gradient based approaches that would have sped-up the optimization process were inadequate because they would not consistently converge to the global maximum. To ensure detection of the threshold combination that maximized the spatial overlap between fMRI and ERP measures, it was necessary to employ an exhaustive search of the threshold space in the present study.

In the future, the fMRI-ERP SOE method could be refined and expanded in several ways. First the exhaustive search to optimize thresholds could be made more efficient by refining the class membership function to emphasize sensitivity to a global solution in the amplitude/temporal threshold space. This would in turn facilitate more efficient searches for the optimal thresholds using, for example, gradient-based approaches. The fMRI-ERP SOE approach could be applied to continuous EEG/fMRI data by convolving the fMRI time series with the simulated evoked time course. Finally, the fMRI-ERP SOE could also be examined when subcortical sources are also modeled.

In summary, the new fMRI-ERP SOE analysis pipeline for estimating the overlap of sources of activity measured simultaneously with fMRI and ERP revealed the dynamics of perisylvian regions associated with auditory oddball detection at a spatiotemporal detail not available with measurements from just one of the imaging modalities, or strictly jICA of measurements from both modalities (J. Mangalathu-Arumana et al., 2012). The fMRI-ERP SOE suggested that areas of non-overlap in sources of activity between the modalities were relatively small and inconsistent across subjects, at least in this paradigm. Future research should examine the factors contributing to uncoupling between fMRI and ERP measurements, whether physiological (e.g., due to individual differences in neuroanatomy or function), and/or methodological

(e.g., due to modality differences in imaging sensitivity in specific brain regions).

#### CHAPTER 3:

# CHARACTERIZATION OF THE NEUROIMAGING COUPLING BETWEEN EEG AND FMRI IN A SYLLABLE DETECTION TASK

### **3.1 Introduction**

Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) are complimentary noninvasive neuroimaging measures in that EEG is a direct measure of large-scale neural activity with high temporal (milliseconds) and low spatial resolution, and fMRI is a high spatial (millimeters) and low temporal (seconds) resolution measure of the hemodynamic response associated with neural activity. Whether measuring brain activity with both EEG and fMRI offers a more complete view of brain function depends on an understanding of the factors that affect the coupling and uncoupling between neuroimaging modalities. That is, meaningful integration of EEG and fMRI requires knowledge of the conditions under which they do and do not reflect the activity of the same sources, in healthy and pathological brains.

Neurovascular coupling, and uncoupling, has been demonstrated at the level of single neurons and neuronal assemblies in the brain. Single cell studies in animals have observed correlation of the hemodynamic response to post-synaptic local field potentials, and a weaker correlation to pre-synaptic spiking activity within neurons (Devor et al., 2003; Goense & Logothetis, 2008; Logothetis, 2008b; Logothetis et al., 2001; Niessing et al., 2005; Shmuel et al., 2006). Intracranial EEG studies in patients with epilepsy have found neural activity in the gamma band (> 32 Hz) most strongly correlate to the hemodynamic response in brain regions associated with vision, semantic processing, auditory processing, and attention, while the beta band (15-32 Hz) shows a weaker

correlation, and the delta (<4 Hz) and theta (4-8 Hz) bands show a negative correlation to the hemodynamic response. (Koch, Werner, Steinbrink, Fries, & Obrig, 2009; Mazzoni et al., 2010; Muthukumaraswamy & Singh, 2008, 2009; Niessing et al., 2005).

At the macro scale of EEG and fMRI, neuroimage uncoupling may be a product of the differences in spatial and temporal sensitivity between the modalities. fMRI has good and even sensitivity throughout the brain, whereas EEG has higher sensitivity to cortical activity represented by electrical dipoles oriented perpendicular to the gyri and sulci, and weaker sensitivity to electrical dipoles oriented perpendicular to the sulcal walls (Nunez & Srinivasan, 2006), and located in deep subcortical structures (Grech et al., 2008). On the other hand, the slow rise of the BOLD response (approximately 4s in many cortical areas (Buckner et al., 1996)) renders it insensitive to transient neural activity that is well captured by EEG.

Joint independent component analysis (jICA) is a blind source separation approach applicable to multimodal neuroimaging data (V. Calhoun et al., 2006; Moosmann et al., 2008). In its instantiation within-subject, jICA of fMRI and EEG extracts independent components containing activity that covaries across modalities as a function of experimental conditions (J. Mangalathu-Arumana et al., 2012; Jain Mangalathu-Arumana et al., 2018). The aim of the present study was to investigate the pattern of coupling between EEG and fMRI as a function of stimulus presentation rate, including the range in which the BOLD response is non-linearly related with presentation rate (J.R. Binder et al., 1994; Rees et al., 1997; Büchel et al., 1998; Rees et al., 1997; Robson et al., 1998)). Speech syllables were selected as stimuli because they naturally occur at relatively high rates (2-4 Hz) in which the BOLD response may change non-linearly. JICA was then used to identify task-relevant brain networks differentiated by the relationship between EEG and fMRI responses across task levels.

#### **3.2 Methods**

#### 3.2.1 Participants

Thirteen neurologically healthy, right-handed, native-English speaking volunteers (9 male, 4 female), ages 20-33 years, participated in the study. All participants provided informed consent in compliance with the Medical College of Wisconsin and Marquette University institutional review board policies and were compensated for their participation in the study.

#### 3.2.2 Experimental Design

EEG and fMRI were recorded simultaneously in a single imaging session during which participants performed a syllable detection task. The task consisted of pressing a button upon detecting an infrequent (5% of presentations) target syllable (/ta/) within sequences of up to 8 syllables presented at rates of 0.25 Hz, 0.5 Hz, 0.75 Hz, 1 Hz, 1.5 Hz, 2 Hz, 2.5 Hz, and 3 Hz. The spoken syllables were derived from natural utterances of /bi/, /ba/, /gi/, /ga/, /da/, and /do/, produced by a male speaker and sampled at 44.1 kHz. The syllables were edited in Praat (www.praat.org), to have a 150ms duration and a 5ms rise-decay envelope. The stimuli were delivered through a silent scan pneumatic headset (Avotec Inc, Stuart, FL) at approximately 65 dB, adjusted individually to accommodate individual preferences in hearing and headphone placement. The stimulus

presentation was controlled with E-Prime 3.0 (Psychology Software Tools, Pittsburgh, PA). Forty trials were presented at each syllable rate, and in a baseline condition during which no stimulus was presented (360 trials total). Each syllable (except the target syllable) was presented 305 times, in random order, across all presentation rates. The EEG and fMRI from trials containing the target syllable (two per syllable presentation rate) were not analyzed. All participants performed the task with accuracy at or above 80%.

### 3.2.3 Data Acquisition

FMRI was collected with a GE 3 T Signa Excite scanner (General Electric Health Care, Milwaukee, WI). Two sets of high resolution whole brain anatomical images were collected using a 3D spoiled gradient-echo (SPGR) sequence  $(0.9\text{mm} \times 0.9\text{mm} \times 1\text{mm})$ voxels), one at the beginning and one at the end of the session. Functional MR images consisted of T<sub>2</sub><sup>\*</sup>-weighted, gradient-echo, echo planar images acquired with a clustered volume sequence modified to obtain two whole brain volumes back to back  $(TE = 20 \text{ ms}; \text{ flip angle} = 90^\circ; TR = 1.8 \text{ s}; \text{ slices} = 29).$  For each 9 s trial, two whole brain volumes were acquired in 3.6 s, and the stimulus sequence was presented in the subsequent 5.4 s during which no images were acquired. This paradigm minimized perceptual masking of the speech syllables by the acoustic noise of the scanner, and avoided contamination of the EEG by artifacts related to MR gradient-switching during syllable presentation. The syllable sequences were positioned such that the last syllable started 4 seconds before the acquisition of the second fMRI volume, to coincide with the estimated peak of the BOLD response (Vagharchakian et al., 2012). EEG was recorded simultaneously and continuously at full bandwidth, and was digitally sampled at 500Hz,

using an MRI-compatible MagLink system consisting of a 64-channel MagLink cap (62 monopolar electrodes, and 2 bipolar leads for ECG and VEOG), SynAmps amplifier, and a Scan 4.4 Workstation (Compumedics Neuroscan, Inc., TX). Sintered Ag/Ag-Cl electrodes were positioned according to the extended International 10–20 system, with a hard-wired reference at CPz. Electrocardiogram activity and vertical eye movements were recorded with bipolar channels. All electrode impedances were kept below 10kΩ.

3.2.4 Pre-Processing

FMRI was preprocessed in AFNI (Cox, 1996). The two anatomical volumes were spatially co-registered and averaged to improve the signal-to-noise ratio of the anatomical structures. The functional image series was spatially co-registered to minimize motion artifacts, and then registered to the averaged anatomical image. Voxel-wise multiple linear regression was used to analyze the individual time series, with a reference function representing the target syllable, and the eight syllable presentation rates. Six motion parameters were included as covariates of no interest. General linear tests were conducted between the activation maps at each syllable presentation rate and the silent condition. For visualization (Figure 14), the individual anatomical and functional statistical maps were projected into standard stereotaxic space (Talairach & Tournoux, 1988) by linear resampling. The statistical maps were smoothed using a Gaussian kernel with 6mm FWHM, and averaged across subjects for each syllable presentation rate.

EEG signals were preprocessed in BrainVision Analyzer v2.1 (Brainproducts GmbH, Gilching, Germany), including scanner artifact correction (Allen, Josephs, & Turner, 2000), bandpass filtering from 0.1Hz to 15 Hz using an 8<sup>th</sup> order zero-phase shift

Butterworth filter, and ballistocardiogram artifact correction. ICA was applied to remove eye blinks, head movement, and residual ballistocardiogram artifacts. The continuous EEG was parsed to trials corresponding to the period from -5000ms to -800 ms relative to the onset of the first functional image acquisition. Trials were rejected if they contained voltage values exceeding  $\pm 200\mu$ V and gradients larger than  $\pm 80\mu$ V/ms. Event-related potential (ERP) responses were computed by averaging trials according to syllable presentation rate (and separately averaging silent trials). The level-wise ERPs were linear detrended, and baseline corrected by removing the mean voltage value from the period -200ms to -50ms before stimulus onset. The ERPs were re-referenced to the mastoid electrodes for visualization and grand-average (across subjects) ERPs were created for each syllable presentation rate and for the silence condition. The grand-average ERP from the silent trials was subtracted from the grand average ERP for each of the eight presentation rates to remove activity unrelated to syllable processing.

### 3.2.5 jICA

The individual fMRI and ERP responses were submitted to within-subject jICA, as described previously (J. Mangalathu-Arumana et al., 2012). Both datasets were vectorized and concatenated by syllable presentation rate. The input to jICA consisted of eight features, each containing the fMRI and ERP responses for one of the eight syllable sequences, such that the resulting components represented the joint fMRI and ERP responses that co-varied across presentation rates.

Components related to syllable perception were identified in each neuroimaging modality as those containing activity within the top 5% of the distribution of activity across all components (p<0.05). Two joint ERP and fMRI components with significant

activity related to syllable perception were identified. The primary component (Figure 133A) contained extensive ERP and fMRI suprathreshold activity, and the secondary component (Figure 133B) contained predominantly ERP supra-threshold activity.

The fMRI components were thresholded voxel wise at p < 0.05, and a voxel cluster threshold was applied resulting in a corrected volume-wise threshold of p < 0.05. The ERP components were submitted to source localization in Brainstorm (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011) using a weighted minimum-norm estimation (wMNE), and thresholded at a corrected map-wise p < 0.05. Regions of interest (ROIs) were created that corresponded to the thresholded activity maps (see Table 4).

For each component and modality, the average activity within ROIs was calculated and multiplied by the mixing coefficients to obtain the weighted mixing coefficient, reflecting the degree to which each syllable presentation rate contributed to the activity (Figure 13).



Figure 13. Steps for computing the weighted (level-wise) mixing coefficients. The joint ERP and fMRI components resulting from jICA (S1, S2) were multiplied by the jICA mixing matrix to reconstruct the level-wise mixing coefficients (C1, C2). The average level-wise activity for each modality and component is calculated within the ROIs, determined by the top 5% of activity after amplitude and cluster thresholds, to obtain the weighted mixing coefficients.

3.2.6 Multiple linear regression analysis

To compare the effectiveness of our approach, multiple linear regression analysis applied to the fMRI data was used to identify regions of cortical activity that varied across task difficulty. To create the multiple linear regression, a general linear model analysis was run for each subject across levels to identify the regions associated with the task. Afterwards, a t-test was applied across subjects to define the statistical significance of the activity at each voxel. Finally, the group-level activation map generated by the multiple regression analysis was obtained by applying an amplitude threshold (p<0.05) and a cluster threshold (corrected p<0.05).

### 3.2.7 Detection of task-related brain networks

To determine if jICA provided improved the ability to detect task-related brain networks, the sensitivity and specificity for detecting regions of significant activity in the fMRI results was compared with those from the multiple regression analysis. For each jICA component containing significant activity, the receiver operating characteristic was measured by varying the amplitude threshold used to define significant activity (p= 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.01, 0.05, 0.001). For each amplitude threshold the sensitivity ( $\frac{True Positive}{True Positive+False Negative}$ ) and specificity ( $\frac{True Negative}{True Negative+False Positive}$ ) associated with significant activity corresponding spatially to the areas identified with the multiple linear regression mask was calculated. True positives corresponded to voxels with a jICA component that exceeded the amplitude threshold and fell within the activity mask from the multiple regression analysis. False positives corresponded to voxels that exceeded the amplitude threshold and fell outside of the activity mask. True negatives were defined by voxels within the jICA components that fell below the amplitude threshold and were outside of the activity mask, and false negatives corresponded to voxels that fell below the amplitude threshold but were located within the activity mask.

For each jICA component, the sensitivity for detecting significant fMRI activity was plotted against 1-specificity to generate the receiver operating characteristic, and the corresponding area under the curve was calculated to characterize the detectability of the brain network with each jICA component using multiple linear regression analysis.

### **3.3 Results**

#### 3.3.1 Level-Wise fMRI Group Maps:

Figure 14 depicts the fMRI group maps at each of the 8 syllable presentation rates. The bulk of the activation was seen on Heschel's gyrus and the lateral aspect of the superior temporal cortex, as well as the inferior parietal cortex, bilaterally, consistent with the location of primary and secondary auditory cortices, and surrounding association areas (Pickles, 2012). The strong bilateral activation over the superior temporal gyrus and sulcus is consistent with the previously documented auditory cortex response to speech syllables (Binder, Rao, Hammeke, Yetkin, et al., 1994; Celsis et al., 1999; Dhankhar et al., 1997; Joanisse & Gati, 2003; Liebenthal, Binder, Spitzer, Possing, & Medler, 2005). Based on the multiple regression fMRI maps, Figure 15, these areas showed increased activation with increased presentation rate. The anatomical regions, cluster size, foci of activity, and amplitudes are recorded in Table 2.



Figure 14. FMRI group maps to trains of syllables presented at rates varying from 0.25 (level 1) to 3 (level 8) Hz. The maps were thresholded at a corrected volume-wise p < 0.05.



Figure 15. A multiple regression map across levels for the group. The maps were thresholded at a corrected volume-wise threshold p<0.05.

Table 2. The anatomical location, cluster size, peak amplitude and coordinates (inTalairach space) of the suprathreshold activation clusters in the group-wise multipleregression fMRI map.

Anatomical location	Cluster size (voxels)	Peak amplitude (arbitrary units)	X (mm)	Y (mm)	Z (mm)
Left superior	2653	2.37	-46	-23	10
temporal gyrus					
Right superior	1675	1.52	52	-20	10
Temporal Gyrus					
Left precuneus	1080	1.47	-4	-63	38
Left cuneus	486	1.46	-23	-80	6
Right middle	447	1.2	48	-63	6
temporal gyrus					
Right precuneus	357	1.2	16	-55	42
Right	310	1.17	42	-28	51
postcentral					
gyrus					
Left precentral	127	1.17	-40	-35	34
gyrus					

### 3.3.2 Level-Wise Grand-Average ERPs:

Figure 16 shows the grand-average ERPs to syllables presented at different rates. To facilitate visualizing the change in the ERP response with rate, the level-wise responses were averaged by pairs as follows: low presentation rate (levels 1+2), mediumlow presentation rate (levels 3+4), medium-high presentation rate (levels 5+6), and high presentation rate (levels 7+8). ERPs were observed to the first syllable in a sequence (Figure 16A) at all syllable presentation rates, and consisted of negative and positive deflections peaking at 214 ms and 304 ms after syllable onset (in electrode Cz). The negative and positive deflections presented with central and frontal topography, respectively, consistent with the obligatory auditory N1-P2 complex (Alcaini, Giard,
Thevenet, & Pernier, 1994; Koerner & Zhang, 2015; Oades, Zerbin, & Dittmann-Balcar, 1995) and the orienting N1 response (Alcaini et al., 1994; Budd, Barry, Gordon, Rennie, & Michie, 1998; Giard et al., 1994). The subsequent positive deflection peaking at 388 ms after syllable onset (in electrode Cz), with parietal topography, was consistent with the novelty P3a (Combs & Polich, 2006; Demiralp, Ademoglu, Comerchero, & Polich, 2001; Oades et al., 1995; John Polich, 2007; John Polich et al., 1997), and was seen only at the lower syllable presentation rates (Figure 16A). The ERPs evoked by the last syllable in a sequence were all attenuated at higher syllable presentation rates (Figure 16B). A 3-way repeated measures ANOVA with syllable presentation rate (low, mediumlow, medium-high, high), syllable position in the syllable sequence (first, last), and ERP component as the repeated measure (N1, P2, P3a), revealed a significant main effect of ERP component (F(2, 16) = 31.63, p<0.001). Significant two-way interactions occurred between syllable presentation rate and ERP component (F(2, 16) = 10.25, p=0.001), and between syllable position in the sequence and ERP component (F(2, 16) = 9.44, p=0.002), and a three-way interaction of ERP component, syllable position, and syllable presentation rate (F(2, 16) = 10.96, p=0.001). The amplitudes of N1, P2, and P3a evoked by the last syllable were reduced at the higher (3 Hz) versus lower (0.25Hz) presentation rates (Table 3.). The ERPs evoked by the last versus first syllable were also reduced at the highest presentation rate.

T-Test for the last syllable between low presentation					
rate (0.25 Hz) and high presentation rate (3 Hz)					
ERP	t	df	Sig. (2-		
component			tailed)		
			р		
N1	3.01	12	0.01		
P2	2.63	12	0.022		
P3	2.58	12	0.026		
T-Test for the 3 Hz presentation rate between the first					
and last syllable					
ERP	t	df	Sig. (2-		
component			tailed)		
			p		
N1	2.68	12	0.02		
P2	2.87	12	0.014		
P3	2.46	12	0.03		

 Table 3. Post-hoc tests for the three-way ANOVA between syllable position, ERP component, and syllable presentation rate.



Figure 16. Grand average ERPs to syllables presented at different rates. A) ERPs at electrode Cz, evoked by the first syllable in the sequence of syllables presented at low, medium-low, medium-high, and high rates. The topographic maps are shown for the low syllable presentation rate at the approximate peaks of N1, P2 and P3a. B) ERPs at electrode Cz, evoked by the last syllable in a sequence of syllables presented at low, medium-low, medium-high, and high rates.

# 3.3.3 JICA of fMRI/ERP:

Figure 17 and Table 4 show the fMRI and ERP responses associated with the primary (panel A) and secondary (panel B) components resulting from jICA. The primary fMRI subcomponent consisted of two large clusters of strong activation in bilateral superior temporal gyrus. The secondary fMRI subcomponent consisted of six relatively smaller clusters of weaker activation, distributed in bilateral perisylvian areas, including the inferior parietal and post central gyri.

The ERP subcomponents are shown as butterfly plots of all electrodes, along with the global power (green trace), over the 4 s during which stimuli were presented. The primary ERP subcomponent contained activity sustained throughout the 4 s window, as evidenced from suprathreshold intervals spanning the entire time window (354ms-372ms, 500ms-538ms, 724ms-796ms, 908ms-1002ms, 1344ms-1362ms, 1916ms-1950ms, 2704ms-2762ms, and 3190ms-3254ms). In contrast, the secondary component, contained periods of activity at specific time windows, with the largest response from 3822ms-4102ms (the only time point all levels had a time-locked stimulus), and a second smaller response from 510ms-540ms. The remainder of the time course showed lower levels of activity compared to the primary component.



Figure 17. fMRI and ERP responses associated with the primary (panel A) and secondary (panel B) components of jICA. The fMRI maps were thresholded at a corrected volume-wise p < 0.05. The ERP breakout plots show three 1250 ms windows corresponding to the periods when, across the 8 syllable presentation rates, the highest number of first syllables (5) was presented (0 ms - 1250 ms), the highest overall number of syllables (6) was presented (1500 ms- 2750 ms), and the highest number of final (perfectly synchronized) syllables (8) was presented (3000 ms - 4250 ms). In the breakout plots, the red lines indicate the times when a syllable was presented. The numbers above the line indicate, on the left, the number of syllables across presentation rates that were presented at that time point, and on the right, the number of syllables across presentation rates that were presented at that time point with an interval greater than 1s from the previous syllable. The asterisks indicate periods when, across levels, several syllables were presented in close temporal proximity (6 syllables within 250 ms).

Primary fMRI subcomponent						
Anatomical location	Cluster size (voxels)	Peak amplitude (arbitrary units)	X (mm )	Y (mm)	Z (mm)	
Left superior temoral gyrus	3793	2.9	-50	-25	10	
Right superior temoral gyrus	3298	2.3 59		-20	8	
Secondary fMRI subcomponent						
Anatomical location	Cluster size (voxels)	Peak amplitude (arbitrary units)	X (mm )	Y (mm)	Z (mm)	
Left precentral gyrus	846	0.63	-31	-20	29	
Left supramarginal gyrus	824	0.51	-35	-33	29	
Right middle frontal gyrus	30	0.5	42	44	16	
Right middle temporal gyrus	223	0.43	52	-12	-3	
Brainstem	212	0.48	-3	-18	-20	
Left precuneus	193	0.64	-27	-61	32	
Right superior temporal gyrus	126	0.43	59	-35	6	

Table 4. The anatomical location, cluster size, peak amplitude and coordinates (in Talairach space) of the suprathreshold activation clusters in the primary and secondary fMRI subcomponents.

Figure 18 depicts the weighted mixing coefficients, representing the dependence of the fMRI and ERP responses on syllable presentation rate, for the primary (A) and secondary (B) joint components. The coefficients for the primary fMRI and ERP subcomponents generally increased with the syllable presentation rate, with a steeper slope in the lower range (below 1 Hz), and shallower slope in the higher range (above 1 Hz). In contrast, the coefficients for the secondary fMRI and ERP subcomponents showed a more complex pattern, with the largest value observed at the lowest syllable presentation rate and generally lower values observed at higher presentation rates. The strength of the weighted mixing coefficients was roughly equal between the primary and secondary ERP subcomponents, but the secondary fMRI subcomponent was an order of magnitude smaller than the primary fMRI subcomponent.



Figure 18. Weighted mixing coefficients for the primary and secondary jICA components, obtained by multiplying the mixing matrix by the average activity within fMRI and ERP ROIs for each component.

3.3.4 Comparison of jICA to multiple regression analysis:

Comparisons between the activity observed in the primary and secondary components with that from the multiple regression analysis revealed several notable differences. Spatial comparison of the regions of significant activity showed a 68% overlap between the multiple regression analysis and the primary component. Regions that did not overlap tended to be located directly adjacent to areas of overlap, which could be due to differences in the thresholds. For the secondary component, however, only 37% of the activity overlapped with the multiple regression analysis. Regions where overlap occurred were limited to the right inferior frontal gyrus, bilaterally in the middle frontal gyrus, in the left and right superior temporal gyrus, and around the right supramarginal gyrus. The remaining regions of activity in the secondary component were not present in the multiple regression analysis when thresholding to a corrected volume-wise p < 0.05.

The results of the sensitivity and specificity analysis as described in 3.2.7 are shown in the region of convergence plot in Figure 19. The area under the curve for the primary component was 0.5, and for the secondary component was 0.38.



Figure 19. Receiver operator characteristic obtained from comparisons of the spatial overlap between significant activity in the multiple regression analysis and

the primary and secondary components respectively (amplitude threshold p<0.05 cluster corrected to p<0.05).

### **3.4 Discussion**

In this paper, we present a data-driven method for the integration of fMRI and EEG recordings of brain function. The method is based on within-subject jICA to identify independent fMRI and EEG signals that covary across experimental levels. The method is demonstrated on simultaneous fMRI and ERP responses to speech syllables presented at varying rates, extending to the range in which the BOLD response is nonlinearly related to the stimulation. The findings suggest that both coupled and uncoupled fMRI and ERP responses can be retrieved and used to characterize brain function with high spatial and temporal resolution.

3.4.1 FMRI Multiple Regression and Grand-Average ERP Analyses:

The fMRI multiple regression analysis showed that the amplitude and extent of the BOLD response increased with syllable presentation rates from 0.5 to 3 Hz, on the left cuneus, left precentral gyrus, right postcentral gyrus, right middle temporal gyrus and bilaterally in the superior temporal gyrus and precuneus. This is consistent with prior reports showing increased activity in these areas with the increase in presentation rate of speech syllables from 0.5 Hz to 4 Hz, and words from 0 words per minute up to 130

words per minute (Dhankhar et al., 1997; Mechelli, Friston, & Price, 2000; Price et al., 1992; Rinne et al., 2005). The grand average ERPs revealed a sequence of negativepositive deflections at latencies and topographies consistent with the auditory N1-P2 complex, and the novelty P3a complex (Fishman, n.d.; Lightfoot, 2016; Morstyn, Duffy, & Mccarley, 1983; John Polich et al., 1997; John Polich & Heine, 1996; Shahin AE Larry E Roberts AE Lee M Miller AE Kelly L McDonald AE Claude Alain, n.d.; Shenton et al., 1989; Vihla & Eulitz, 2003). The decrease in N1-P2 amplitude at high syllable presentation rates is consistent with previous studies observing a  $\log_{1/2}$  relationship between presentation rate and N1-P2 amplitudes, with the largest increases between 0.5Hz and 2Hz (Brattico, Tervaniemi, Näätänen, & Peretz, 2006; Budd et al., 1998; Butler, 1973; H. Davis, Mast, Yoshie, & Zerlin, 1966; P. A. Davis, 1939; Naatanen & Picton, 1987; Nelson & Lassman, 1968; Rigoulot & Armony, 2016; Schweinberger et al., 2008; Webster, 1971; Woods & Courchesne, 1986; Woods, Courchesne, Hillyard, & Galambos, 1980; Zäske, Schweinberger, Kaufmann, & Kawahara, 2009; Zerlin & Davis, 1967). The P3a, characterized by a frontal central positivity, is associated with the detection of novel stimuli and the amplitude of this component is inversely dependent on the rate of presentation of stimuli (Barry, Steiner, & De Blasio, 2016; Combs & Polich, 2006; Demiralp et al., 2001; John Polich, 2007; John Polich & Comerchero, 2003), including speech syllables in the range 545ms-2709ms (Yu, Shafer, & Sussman, 2017). The sources of the N1-P2 and P3a responses to spoken syllables have been localized to the superior temporal and inferior parietal cortex, bilaterally (Ford, Woods, & Crewther, 2018; Mechelli et al., 2000; Papanicolaou et al., 1990; Price, Thierry, & Griffiths, 2005; Rogers, Papanicolaou, Baumann, Saydjari, & Eisenberg, 1990). The fMRI multiple

regression and grand-average ERP responses to syllable presentation rate are consistent with the same sources of activity in the brain; however, sources cannot be separated, and the temporal course of different sources cannot be inferred, from this analysis.

### 3.4.2 Within-Subject JICA:

The primary fMRI subcomponent consisted of the activity in the bilateral Heschel's gyrus and lateral superior temporal cortex, also seen in the fMRI regression analysis. The primary ERP subcomponent consisted of activity that was sustained throughout most of the period of stimulus presentation. The weighted mixing coefficients indicated that the amplitude of the ERP and fMRI responses associated with the primary component increased with the rate of stimulus presentation, at faster pace in the range below 1Hz, and more slowly above 1Hz. This is consistent with the log<sub>1/2</sub> model of the response of the N1-P2 to varying presentation rates, where the range from 0.5 Hz to 2 Hz shows the most rapid change in amplitudes. The spatiotemporal pattern of activity in the primary component is consistent with the obligatory auditory response to sound stimuli in primary and secondary auditory cortex (Fishman, n.d.; Koerner & Zhang, 2015; Sussman, Steinschneider, Gumenyuk, Grushko, & Lawson, 2008).

The secondary fMRI subcomponent consisted of distributed activity in perisylvian regions, with the largest clusters seen in the left supramarginal and precentral gyri. These areas are considered to be part of a dorsal auditory stream, which in the left hemisphere has been associated with phonological processing (Chang et al., 2011; Liebenthal, Sabri, Beardsley, Mangalathu-Arumana, & Desai, 2013; Meister, Wilson, Deblieck, Wu, & Iacoboni, 2007; Osnes, Hugdahl, & Specht, 2011; Wilson & Iacoboni, 2006), and more

generally speech perception. The precuneus is commonly activated in language tasks (R. N. A. Henson, Price, Rugg, Turner, & Friston, 2002; Orfanidou, Marslen-Wilson, & Davis, 2006; Raettig & Kotz, 2008; Rissman, Eliassen, & Blumstein, 2003). This area is thought to be part of an associative cortical network involved in high level processes, including the integration of auditory signals with other sensory information (Cavanna & Trimble, 2006; Tulving et al., 1994). The weighted mixing coefficients for the secondary component suggest that the greatest response was observed in response to a syllable presented after a silent period of at least 2 seconds. Areas of the middle frontal gyrus have been shown to be activated in relation to the orienting response; that is, these areas were more strongly activated to unexpected stimuli. The amplitude of activation in the right middle frontal gyrus and right temporal parietal junction has been found to be correlated with the P3a (Doricchi, Macci, Silvetti, & Macaluso, 2010; Halgren et al., 1995; Horovitz, Skudlarski, & Gore, 2002; Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015; McCarthy, Luby, Gore, & Goldman-Rakic, 1997; Shulman et al., 2009). With the exception of the brainstem, all the regions activated in the secondary component are known to contribute to the N1 orienting response (Naatanen & Picton, 1987; Zhang et al., 2011). Additionally, the right middle frontal gyrus and right temporal parietal junction have been shown to be correlated to P3a activation (Doricchi et al., 2010; Halgren et al., 1995; Horovitz et al., 2002; Japee et al., 2015; McCarthy et al., 1997; Shulman et al., 2009). Activation in these areas does not vary strongly with stimulus presentation rate, rather these areas respond to the first stimulus in a sequence and then adapt quickly (Barry et al., 2016; Budd et al., 1998; Zhang et al., 2011).

The secondary ERP subcomponent consisted of suprathreshold activation primarily 3823ms to 4102ms. In this time window at 3750 ms, a syllable was presented in each of the eight stimulus levels, and in the four lowest levels the syllable was presented after a long (>1sec) interval. For the lowest presentation rate, this time corresponded to the only syllable presented in the sequence. The pronounced N1 response to stimuli presented at large intervals is consistent with the involuntary initial orienting response to a first stimulus (Budd et al., 1998; Escera, Alho, Winkler, & Näätänen, 1998; Giard et al., 1994; Naatanen & Picton, 1987; Sussman, Winkler, & Schröger, 2003; Wetzel, Berti, Widmann, & Schröger, 2004)

The weighted mixing coefficients revealed that the ERP activity in the primary and secondary components was of comparable magnitude, while the fMRI activity in the secondary component was an order of magnitude smaller than the fMRI activity in the primary component. This uncoupling between the fMRI and ERP signals in the secondary component could reflect differences in the sensitivity of the imaging modalities to the activation dynamics, location, and/or electrical orientation of the sources. A likely cause of the neuroimage uncoupling seen is the fMRI being less sensitive to transient signals compared to EEG. Thus, the within-subject jICA implemented here permitted the separation of sources in the brain that have different spatiotemporal characteristics. The spatiotemporal pattern of activation of each source provided the basis for estimating its function. JICA revealed the spatiotemporal dynamics of the secondary source despite the uncoupling between the imaging modalities. The approach to studying neuroimaging coupling developed here can be applied to characterize variations in the relationship between fMRI and ERP across experimental conditions and brain regions in healthy individuals. The method could also be applied to studying diseases that may affect neurovascular integrity; for example Alzheimer's disease and hypertension in which changes in the cellular structure of the vasculature that impair the automatic regulation of blood flow (Frank M. Faraci & Heistad, 1998; Girouard & Iadecola, 2006; Costantino Iadecola, 2004; Kazama et al., 2003; Mackert et al., 2008; John Polich & Corey-Bloom, 2005; Prvulovic et al., 2011; Sperling, 2011).

3.4.2 Comparison between jICA and multiple regression analysis:

When the jICA-fMRI results were compared spatially against the multiple regression analysis, several regions of significant activity were observed with jICA that were not present in the multiple regression analysis. While the strong fMRI activity in the primary component was well captured by the multiple regression analysis, the weaker activity associated with the secondary component was largely undetected using a volume corrected p<0.05. Subsequent ROC analysis showed that the multiple linear regression analysis was more sensitive to activity returned in the primary component than the secondary component. This is consistent with the fact the fMRI activity in the secondary component is an order of magnitude smaller than that associated with the primary component. When the primary and secondary activity is combined in a single statistical analysis such as multiple linear regression, the activity observed in the secondary component largely falls below the thresholds typically applied for statistical significance. By leveraging EEG's ability to capture faster, more transient, signals *jICA* was able to identify fMRI activity associated with the orienting response that was not easily detectable in the multiple regression analysis.

There are several limitations to the proposed method. First, because the mixing coefficients in jICA are shared between imaging modalities, nonlinearities between modalities are represented across multiple components (Jain Mangalathu-Arumana et al., 2018). Nevertheless, we have previously shown that components reflecting split activity from the same source can be recombined based on residual shared features (Jain Mangalathu-Arumana et al., 2018). Other blind source separation approaches such as IVA, create a separate mixing matrix for each modality, but does so at the cost of decreased sensitivity for lower SNRs (Adali et al., 2015). Another limitation is that the interpretation of the temporal content within a component may not be trivial due to the methodological approach overlapping the temporal information across all levels. This can be mitigated in part by choosing experimental designs that intentionally separate the timing of task relevant features.

In summary, the approach developed here for quantifying the relationship between activities measured with fMRI and EEG revealed distinct brain networks with coupled and uncoupled EEG/fMRI activity. The component with coupled EEG/fMRI activity reflected activity in primary and secondary sensory cortices, which increased with syllable presentation rate. The uncoupled component (reflecting EEG but not fMRI activity) was consistent with activity in higher order association cortices which was not dependent on syllable presentation rate. The approach was able to characterize the neuroimage coupling between networks by leveraging the mixing matrix produced by jICA. By leveraging EEG's ability to capture faster, more transient, signals jICA was able to parse fMRI activity that was not easily detectable with multiple linear regression analysis. This method could be applied to characterizing the neuroimage coupling of neural networks in healthy subjects as well as diseases that degrade neurovascular integrity.

# CHAPTER 4: ASSESSMENT OF THE IMPACT OF JICA ON THE DETECTION OF SUBCORTICAL SIGNALS

# 4.1 Introduction

The value of combining functional magnetic resonance imaging (fMRI) with electroencephalography (EEG) for studying the dynamics of cortical activity is relatively well established. However, this simultaneous fMRI/EEG has rarely been applied to studying subcortical activity because the sensitivity of EEG to sources located deep in the brain is not well-defined. Here, we use computational simulations of subcortical and cortical activity to examine the potential utility of applying blind source separation on fMRI and EEG, for increasing the detection and recovery of subcortical activity.

The detection of neural activity with EEG depends on a number of factors, including the type of neural sources and their spatial organization in the brain. The hippocampus is an archicortical structure with sub regions comprised of pyramidal cells that are highly organized in space, similar to the neocortex albeit with fewer layers (LeDoux, 2007; Nunez and Srinivasan, 2006; Olucha-Bordonau et al., 2015; Whalen and Phelps, 2009). The current dipoles generated within such highly organized structures sum constructively to amplify synchronous activity, resulting in open field current sources. In contrast, the amygdala is comprised of neurons with radial dendritic geometries (e.g., stellate cells), and pyramidal cells with an irregular spatial organization (Attal et al., 2007a; Attal and Schwartz, 2013; Berretta et al., 2007; Olucha-Bordonau et al., 2015). The current dipoles generated within this type of disorganized structure can sum constructively or destructively, depending on the spatial orientations of the active

neurons. When there is no dominant orientation among active neurons, the current dipoles will tend to cancel out resulting in a closed field current source.

The detection of current sources in the hippocampus and amygdala with magnetoencephalography (MEG) has been reported for a number of perceptual and cognitive tasks (Balderston et al., 2013; Breier et al., 1998; Cornwell et al., 2008; Garolera et al., 2007; Gross et al., 2001; Ioannides et al., 1995; Jerbi et al., 2007; Luo et al., 2007; Maratos et al., 2009; Tesche, 1996). Computational simulations accounting for the neuroanatomical structure of the hippocampus and amygdala support the idea that activity from these sources can be detected with MEG, as well as EEG (Attal et al., 2007a; Attal and Schwartz, 2013; Dumas et al., 2013, 2011; Krishnaswamy et al., 2017). These simulations suggest that open field current sources in the hippocampus can be detected with relatively few trials (21-45), whereas smaller and weaker signals from closed field sources require more trials, 100-200 in the amygdala up to 10,000+ in the reticular perithalamic nucleus and external pallidum, to be detected (Attal et al., 2007a). A recent study using simultaneous scalp and intracranial electrodes demonstrated that epileptiform discharges from the amygdala, hippocampus, and thalamus were all detectable with scalp EEG recordings (Pizzo et al., 2019).

One approach to informing EEG analysis with fMRI is to constrain the locations of sources to brain regions indicated as active with fMRI, based on an assumption of constant spatial coupling between EEG and fMRI signals across subjects and/or experimental conditions (Aftanas et al., 1998; Bobes et al., 2018; Dale et al., 2000; Huster et al., 2012; Ou et al., 2009; Xu et al., 2018). On the other hand, data-driven analyses such as joint independent component analysis (jICA) relax the constraint of constant fMRI-EEG coupling. JICA is based on an assumption of correlation between EEG and fMRI sources across subjects and/or conditions without requiring coupling between the imaging modalities (Arumana, 2012; Heugel et al., 2019; Lee et al., 2008; Levin-Schwartz et al., 2014; Ma et al., 2013; Mangalathu-Arumana et al., 2018; Moosmann et al., 2008; Rosa et al., 2010).

This paper reports on a simulation study designed to examine the performance of within-subject jICA of fMRI/EEG (jICA-fMRI/EEG) relative to ICA of EEG uninformed by fMRI (ICA-EEG), and relative to simple trial averaging of EEG (TA-EEG) for the detection of subcortical signals under experimentally realistic conditions. Three sets of simulations estimate the detection of current sources in the hippocampus and the amygdala, representing respectively open and closed field sources, and in the presence or absence of a synchronous cortical current source with similar topography as the subcortical source.

## 4.2 Methods

## 4.2.1. Structure of simulations

Three sets of simulations were designed to examine the performance of jICAfMRI/EEG for the detection of sources in the hippocampus and amygdala, as detailed in Table 5. The first set of simulations compared the detection of sources with different net orientations within the hippocampus using jICA-fMRI/EEG, ICA-EEG, and TA-EEG. The second set of simulations compared the detection of sources with varying open field strengths within the amygdala using jICA-fMRI/EEG, ICA-EEG, and TA-EEG. The final set of simulations examined the effect of a simultaneous cortical source on the detection of sources in the hippocampus and amygdala, as a function of the pattern of stimulus response with respect to the subcortical source.

Two hundred trials per subject were used in each set of simulations across the three analysis approaches. This number of trials was selected because it was found adequate for detecting amygdala activity in prior simulations (Attal and Schwartz, 2013), and considered practical for simultaneous EEG/fMRI experiments.

Table 5. Parameters used for the three sets of simulations. Included in () are the specific values or conditions used.

	Simulation 1	Simulation 2		Simulation 3	
Sources	Hippocampu	Amygdala	Amygdala	Hippocampus+	Amygdala+
	S			cortex	cortex
ROIs	8	1	1	1	1
Orientation	n/a	17	1	n/a	1
S					
Field			6 (0.3%,		
strengths	n/a	1 (1%)	1%, 3%,	n/a	1 (1%)
(percent of			5%,7%,		
open field)			9%)		
Analyses	jICA-	jICA-	jICA-	jICA-	jICA-
	EEG/fMRI,	EEG/fMRI,	EEG/fMRI	EEG/fMRI,	EEG/fMRI,
	ICA-EEG,	ICA-EEG,	, ICA-	TA-EEG	TA-EEG
	TA-EEG	TA-EEG	EEG, TA-		
			EEG		
Detection				AUC,	AUC,
measure	AUC	AUC	AUC	Correlation	Correlation
				Coefficient,	Coefficient,
				FFT ratio	FFT ratio
Patterns of					
activity					2 (same,
(between	n/a	n/a	n/a	2 (same,	different)
cortex and				different)	
subcortex)					
Trials	200	200	200	200	200
Simulated	7	7	7	7	7

subjects					
Conditions					
(ROIs X					
Orientation					
s X Field					
strength X	56	42	119	14	14
Pattern X of					
activity X					
Simulated					
subjects)					
Simulations					
per set of	1000	1000	1000	1000	1000
conditions					
Total					
number of	56,000	42,000	119,000	14,000	14,000
simulations					

## 4.2.2 Anatomical model

A head model containing the cortex and subcortex was constructed using the Colin 27 brain (Holmes et al., 1998) using the standard anatomical feature segmentation in Freesurfer version 6.0 (Dale et al., 1999). The segmented features were imported into Brainstorm version: 3.190502 (Tadel et al., 2011) and a boundary element head model which included the scalp, outer skull, inner skull, hippocampus, amygdala and the entire cortex for each hemisphere, was constructed. The entire cortex and left hippocampus were represented by 15,000 and 750 vertices, respectively, placed on their surface. The left amygdala was represented by 10 vertices placed in isotropic voxels covering the 1 cm<sup>3</sup> volume of the amygdala. Electrode locations on the head model were specified using a 64-channel template of the extended international 10-20 system. The forward and inverse projection matrices were generated for all vertices on the cortex, hippocampus, and amygdala.

### 4.2.3 Experimentally derived noise

EEG noise was simulated from EEG obtained in a simultaneous fMRI/EEG experiment in seven subjects performing a syllable detection task (Heugel et al., in preparation). For each set of simulations in one subject, 1600 ms segments of experimental EEG from random trials (including silent trials) were used to simulate the EEG noise. At each electrode, the EEG segments were Fourier-transformed into the frequency domain, the phases were randomized across frequencies, and frequency representation was transformed back into the time domain to remove any temporal structure. The result was noise that had the same spectral power as the experimental EEG, but no temporal structure related to experimental conditions.

Similarly, fMRI noise was simulated from experimental fMRI activation in the hippocampus and amygdala, collected simultaneously with EEG in the same seven subjects (Heugel et al., in preparation). The mean and standard deviation of the fMRI response to silent trials was calculated for each voxel and used to define a normal distribution. The normal distribution at each voxel was randomly sampled to create noise that was matched statistically to the experimental data but without spatial structure.

For the first two simulations JICA-EEG/fMRI and ICA-EEG, 200 trials were split evenly between five experimental levels varying in signal strength (20%, 60%, 100%, 140%, and 180% of the variance of the noise). For TA-EEG, 200 trials were drawn from the middle level corresponding to the average signal strength across levels.

### 4.2.4 EEG signal generation

The approach outlined in (Attal et al., 2007b) was used to define the amplitude of the current sources in the amygdala and hippocampus. For each subcortical region, the current density weighting ( $\gamma_i$ ) was defined relative to the strength of a cortical source such that  $\gamma_i = \frac{\sigma_c}{e_c * d_i}$ , where *i* represents the subcortical structure being modeled,  $\sigma_c$  is the surface current density of the cortex,  $e_c$  is the cortical thickness of the cortex, and  $d_i$  is the estimated cellular density of the subcortical structure. The current density weighting was subsequently used to scale the subcortical signal.

The subcortical signal was simulated as a 300 ms, 12 Hz sinewave placed at 726 ms from the onset of a 1600 ms window. The variance of the signal was scaled to simulate changes in activity across five experimental levels in simulation sets 1-2, and ten levels in simulation set 3. An additional cortical source was defined such that it overlapped with the subcortical signal in the period of 726-875 ms, and there were only subcortical and cortical signals, respectively, in the initial period of 876-1025 ms and the final period of 576-725 ms (simulation set 3, Figure 23A). The levels provide independent observations for within-subject jICA (referred to here as jICA-EEG/fMRI). The variance of the signal at the middle level was scaled to equal that of the noise so that signal variance of the two lower experimental levels were greater than the noise (Figure 20). Based on the type of subcortical current source being simulated (hippocampus or amygdala), the signal was additionally scaled by the current density weighting representing the ratio of subcortical-to-cortical activity.



Figure 20: Signal amplitudes (blue sinewaves) in the five experimental levels used in simulation sets 1-2, relative to variance of noise (shaded region). The variance of the signal in level three was scaled to be equal to the variance of the noise.

The hippocampus was modeled as an open source with dipoles oriented perpendicular to its surface, and with a current density weight that was 1.5 times larger than an equivalent cortical current source (Attal et al. 2007b). The amygdala was modeled as a closed field current source with an unconstrained net current dipole orientation relative to its surface. Each dipole in the amygdala was represented by a 3dimensional vector with the same orientation and a current density weight that was 4 times larger than an equivalent cortical current source (Berretta et al., 2007; Dumas et al., 2011; García-Amado and Prensa, 2012).

The cortical signal was simulated as a 300 ms, 4Hz sinewave. Each subcortical current source (ROI #5 for the hippocampus, orientation # 16 for the amygdala) was separately forward-projected to the EEG electrodes, and a weighted minimum-norm

source localization constrained to the cortical surface was performed to create a distributed cortical current source with the same scalp topography as the subcortical current sources (Figure 17 C-E). To restrict the cortical activity to a focal distribution an amplitude threshold (p < 0.05) and vertex cluster threshold resulting in a corrected mapwise threshold of p < 0.05 were applied to define a focal region that approximated the spatial distribution of each respective subcortical source

The same scaled signal for each experimental level was applied to all the vertices within a region of interest (ROI), and the vertices outside the ROIs were left empty. The signal was forward projected onto the EEG electrodes, and the electrode with the largest amplitude of subcortical signal was identified and recorded. Trials for each experimental level were created by adding the forward projected signals to the experimentally derived noise at the level of the electrodes.

## 4.2.5 FMRI signal generation

The cortical and subcortical fMRI signals for each experimental level were generated by scaling the variance relative to the voxel-wise noise. The variance of the signal at the middle level was scaled to equal that of the noise so that signal variance of the two lower experimental levels were less than the noise while the signal variance of the two higher experimental levels were greater than the noise. Silent trials were simulated to use as a baseline that consisted of the experimentally-derived noise only.

## 4.2.6 Structure of Analyses

The detection of subcortical sources with jICA-fMRI/EEG was compared to ICA-EEG and TA-EEG. For jICA-fMRI/EEG and ICA-EEG, level-wise averages were used as input, and for TA-EEG averages across all levels were entered. For JICA-EEG/fMRI and ICA-EEG, the level-wise EEG average time course was concatenated across electrodes (64 electrodes x 800 time points) and combined into an observation matrix with rows corresponding to the vectorized level-wise EEG (Arumana, 2012). For JICA-EEG/fMRI, the voxel-wise fMRI for the entire volume (475,136 voxels) was vectorized for each level and concatenated with the corresponding EEG electrode-time course to form a single joint observation matrix. Prior to ICA, dimension reduction using principle component analysis was performed in fusion toolbox v 2.0d (http://trendscenter.org/software/fit/), using an automated estimate for the number of independent signals to reduce over parsing.

For JICA-EEG/fMRI and ICA-EEG, components containing activity varying with experimental level were identified in each imaging modality as those exceeding an amplitude threshold of p<0.05 relative to the distribution of activity across all components in that modality (Heugel et al., 2019). For TA-EEG, the entire epochs were averaged across all trials to produce an average time series for the electrode ensemble.

### 4.2.7 Subcortical signal detection

Signal detection theory was used to determine the receiver operator characteristic (ROC) associated with the detection of a signal in the presence of noise. The area under the ROC curve (AUC) was used as a summary statistic to compare the detection of subcortical sources from EEG across simulations. To estimate the ROC, the EEG time series from the channel most sensitive to the subcortical signal was used. One hundred amplitude thresholds, ranging from 0 to the maximum value of the signal, was applied

above and below the baseline and the suprathreshold time points in the EEG were counted during the 300 ms period that the subcortical source was active and during a subsequent 300 ms period with no subcortical or cortical activity. Hits and false positives were marked if the number of suprathreshold time points in the subcortical active and subcortical inactive periods, respectively. The process was repeated 1000 times for each amplitude threshold to construct the ROC and calculate the AUC. If the AUC exceeded 0.7, the subcortical signal was considered successfully detected (Attal et al., 2007a).

The results of the simulations, using AUC as a measure of subcortical source detection, were compared between the three analyses (jICA-fMRI/EEG, ICA-EEG, TA-EEG) using ANOVA with additional factors of ROI (in the hippocampus), dipole orientation (in the amygdala), or open field strength, as appropriate for each set of simulations. The third set of simulations included separate ANOVAs for the two additional measures of subcortical detection.

## 4.2.8 Simulation 1: Detection of an open field subcortical source

The first set of simulations was designed to examine jICA-EEG/fMRI relative to ICA-EEG and TA-EEG in the detection of an open field subcortical signal. To test the effect of current source orientation on hippocampal source detection, the entire surface of the left hippocampus was subdivided into 8 equally-sized ( $\sim 2cm^2$ ) ROIs (Figure 21), each with a different net current dipole orientation.



Figure 21: ROIs in left hippocampus used to simulate eight sources with different net current dipole orientations. (A) Medial view looking from the right side of the head. (B) Anterior view looking head on. L-lateral, M-medial, A-anterior, P-posterior, D-dorsal, and V-ventral.

# 4.2.9. Simulation 2: Detection of a closed field subcortical source

The second set of simulations was designed to examine jICA-EEG/fMRI relative to ICA-EEG and TA-EEG in the detection of a closed field subcortical source. The amygdala was modeled as a closed field current source by scaling it between 0.1 and 9% of the net current source density of an open field, and the effect of source strength on detection was tested for dipole orientation 2 (0° zenithal, 45° azimuthal). To test the effect of orientation of the amygdala net current dipole on detection, 17 amygdala dipole orientations were simulated that covered the top half of a sphere in 45° increments of azimuth ( $\theta$ ) and zenith ( $\phi$ ) angles (Figure 22). Current dipoles oriented toward the bottom hemisphere are equivalent in terms of signal detection, and were not simulated. For the orientation simulations, the amygdala open field strength was set to 1%.



Figure 22: Simulated amygdala dipole orientations, shown in (A) 3D perspective, (B) posterior view, and (C) dorsal view. Red lines denote orientations in the X-Y plane  $(0^{\circ}$  zenithal), blue lines denote orientations extending 45° from the X-Y plane (45° azimuth), and the black line denotes the dipole oriented along the Z-axis (90° zenithal). The dipoles were numbered from 1 to 16, starting from 90° zenithal and 0° azimuthal and continuing clockwise in the X-Y plane before decreasing the zenithal angle.

4.2.10 Simulation 3: Detection of a subcortical source in presence of a simultaneous cortical source

The third set of simulations examined the detection of the subcortical current source with jICA-fMRI/EEG relative to TA-EEG in the presence of temporally and spatially overlapping cortical activity. The subcortical and cortical current sources overlapped for 150ms of their 300 ms activations (Figure 23).



Figure 23: Characteristics of spatiotemporally overlapping cortical and hippocampal (#5) simulated sources. (A) Time course of the simulated 4 Hz cortical, and 12 Hz subcortical, signals. The light gray shading denotes the time intervals containing only cortical (576-725 ms), or only subcortical (876-1025 ms) activity. The dark gray shading denotes the time interval when the cortical and subcortical activity overlapped (726-875 ms). (B) Change in cortical and subcortical signal amplitudes with experimental level. (C) Topographic map of the simulated subcortical activity at the scalp electrodes. (D) Topographic map of the simulated cortical activity at the scalp electrode.

For this set of simulations, the number of experimental levels was increased to 10 to optimize the separation of current sources using within-subject jICA-EEG/fMRI (Mangalathu-Arumana et al., 2018). Four conditions were tested: In the first two, the cortical and subcortical (amygdala or hippocampus) sources co-varied linearly as a function of experimental level. In the last two, the subcortical sources varied nonlinearly with experimental level, whereas the cortical source varied linearly (Figure 23 B). The

variance of the experimentally derived noise was set to be equal to the average power across all 10 levels.

The ROC analysis was used to test the effect of the spatiotemporally overlapping cortical source on detection of the subcortical source with each of the analyses. Two additional measures were used to quantify how well the subcortical current source was parsed from the cortical current source during the time period that the signals overlapped. First, the ratio of the power at the subcortical frequency (12Hz +/- 1 frequency steps) to the total power across all frequencies over the 1600 ms trial interval was calculated. Second, the correlation coefficient between the simulated and retrieved subcortical signals during the period of cortical and subcortical overlap was calculated.

### 4.3 Results

4.3.1 Simulation 1: Detection of an open field subcortical source

The detection of a hippocampal current source with the three analyses (jICA-EEG/fMRI, ICA-EEG, and TA-EEG) is shown in Figure 24, for the eight hippocampal ROIs. A two-way ANOVA revealed significant main effects of analysis type (F(2,144) =253, p<0.001) and ROI (F(7,144) = 28.6, p<0.001)), and an interaction between analysis type and ROI (F(14,144) =13.1, p<0.001). Post-hoc tests revealed that the effect of analysis type was due to increased detection of hippocampal sources with TA-EEG compared to jICA-EEG/fMRI (t(55) =6.18, p<0.001) and ICA-EEG (t(55) =20.6, p<0.001), and with jICA-EEG/fMRI compared to ICA-EEG (t(55) =6.74, p<0.001). The effect of ROI was due to increased detection of hippocampal sources in ROIs 2, 6, 7 and 8 versus 1, 4, and 5 (t(20)>2.33, p<0.05), and overall lower detection of the source in ROI 3 (t(20)>3.25, p<0.01). For jICA-fMRI/EEG and ICA-EEG, the subcortical signals in less detectable ROIs were parsed to more than one component, suggesting that the ICA analyses over estimated the number of independent signals in the data.



Figure 24. Average area under the curve (AUC) for detecting hippocampal activity with jICA-EEG/fMRI, ICA-EEG, and TA-EEG, as a function of the hippocampal ROI (ROI locations shown in Figure 15). The breakout plot shows the TA-EEG more clearly. Error bars denote one standard deviation from the mean of the seven simulated subjects.

The strength of the net current dipole and the angle between the net current dipole, and the vector from the ROI center of mass to the sensor most sensitive to the hippocampal source are shown in Figure 25A and B respectively. The correlation coefficient between the net dipole strength and the AUC for jICA-EEG/fMRI (r=0.767),

TA-EEG (r=0.584), and ICA-EEG (r=0.749) were calculated. Additionally, the correlation coefficient was calculated between the AUC and the vector from the ROI center of mass to the electrode most sensitive to the hippocampal source for jICA-EEG/fMRI (r=0.7301), TA-EEG (r=0.785), ICA-EEG (r=0.489).



Figure 25. Strength of the net current dipoles for each of the hippocampal ROIs (A) and angle between the net current dipole and the vector from the ROI center of mass to the sensor most sensitive to the hippocampal source.

4.3.2 Simulation 2: Detection of a closed field subcortical source

Figure 26 shows the detectability of an amygdala current source with dipole orientation 2 (0° zenithal, 45° azimuthal), as a function of its electrical field strength (defined as a percentage of the open field strength). JICA-EEG/FMRI outperformed ICA-EEG and TA-EEG at all field strengths except the smallest (0.3% of an open field), and ICA-EEG outperformed TA-EEG at field strengths greater than 3% of an open field. A two-way repeated measure ANOVA revealed significant main effects of analysis type (F(2,108) =147.65, p<<0.001) and field strength (F(5,108)=63.44, p<<0.001), and an interaction between these factors (F(10,108)=4.833, p<<0.001). Post hoc tests showed that the effect of analysis type and the interaction with field strength were due to significantly greater amygdala current source detection with jICA-EEG/fMRI relative to ICA-EEG for field strengths greater than 0.3% (t(6)>17.29, p<<0.001) and for ICA-EEG relative to TA-EEG for field strengths greater than 1% (t(6)>2.60, p<0.05).



Figure 26. Area under the curve (AUC) for jICA-EEG/fMRI, ICA-EEG, and TA-EEG detection of an amygdala current source, as a function of the strength of the source. The electrical field of the amygdala was varied from 0.3% to 9% of an open field current source. Error bars denote ±1 standard deviation from the mean of the simulated subjects.

The effect of net dipole orientation on the detection of an amygdala current source with 1% of open field strength is shown in Figure 27. A two-way ANOVA showed significant main effects of analysis type (F(1,204)=770.77, p<<0.001) and dipole orientation (F(16,204)=5.48, p<<0.001). There was also a significant interaction between analysis type and dipole orientation (t(118)=21.77, p<<0.001), with amygdala current source detection higher for jICA-EEG/fMRI than ICA-EEG for dipoles oriented toward the ipsilateral hemisphere (i.e., dipoles 1,2,3,5,6,7,8,9,10,11,15,16, and 17) (t(6)> 6.2471, p< 0.00078).



Figure 27. (A)Area under the curve (AUC) indexing detection of an amygdala current source, as a function of net dipole orientation. Error bars represent one standard deviation from the mean of the simulated subjects. (B) Spatial representation of AUC detection performance with jICA-fMRI/EEG (top) and ICA-EEG (bottom). The sector polar angle denotes the net dipole azimuth angle and eccentricity decreases as zenith angle increases. The color scale codes the AUC.

3.3.3 Simulation 3: Detection of a subcortical source with a spatiotemporally overlapping cortical source

The effects of analysis type and dependence of subcortical and cortical activity across experimental level, on the detection of sources in the hippocampus or amygdala, are summarized in Figure 28 for the three source detection metrics (AUC, power ratio (PR), and time series correlation (TC)). For the hippocampal source, a two-way ANOVA of PR showed main effects of analysis type (F(1,24)=12.89, p=0.001), dependence on level (F(1,24)=5.39, p=0.029), and the interaction between analysis type and dependence
on level (F(1,24)=5.35, p=0.03), a two-way ANOVA of TC showed main effects of analysis type (F(1,24)=0.038, p<0.038), and the interaction between analysis type and dependence on level (F(1,24)=4.71, p=0.04), and a two-way ANOVA of AUC showed a main effect for analysis type (F(1,24)=121.48, p<0.001).

For the amygdala source, a two-way ANOVA of PR showed main effects of analysis type (F(1,24)=17.9, p<0.001), dependence on level (F(1,24)=24.6, p<0.001), and the interaction between analysis type and dependence on level (F(1,24)=13.6, p<0.001), a two-way ANOVA of TC showed main effects of analysis type (F(1,24)=255.2, p<0.001), of dependence on level (F(1,24)=194.2, p<0.001) and the interaction between analysis type and dependence on level (F(1,24)=179.6, p<0.001), two-way ANOVA of AUC showed a main effect for analysis type (F(1,24)=219.3, p<0.001).



Figure 28. Detectability of hippocampus and amygdala current sources with jICAfMRI/EEG and TA-EEG, in the presence of a spatiotemporally overlapping cortical current source with either the same or different dependence on experimental level as the subcortical source. Subcortical source detection was assessed with (A) area under the curve (AUC), (B) ratio of the power at the subcortical signal frequency relative to the total power (Spower/Tpower), (C) time series correlation between the retrieved and simulated subcortical signals (CorrRet-Sim). Asterisks denote statistically significant differences (p<0.05).

Figure 29 shows example EEG components obtained from jICA-fMRI-EEG of a simulation containing amygdala and cortical current sources with different activation patterns as a function of experimental level. For the component containing the subcortical current source (Figure 29A), the simulated 12 Hz sinewave can be seen in both the periods with, and without, overlapping cortical activity. The component with the cortical current source (Figure 29B), contained the simulated 4 Hz sinewave and a residual 12 Hz sinewave corresponding to the simulated subcortical signal. The TA-EEG signal (averaged across trials from all levels) and the simulated subcortical and cortical signals added together, are shown in Figure 29 C and D, respectively.



Figure 29. EEG components resulting from jICA-EEG/fMRI and containing the (A) amygdala (876-1025 ms) and (B) cortical current sources (575-875 ms). (C) The EEG resulting from TA-EEG and (D) the simulated subcortical and cortical signals from Figure 16 are shown for comparison. Panels A-C depicts the activity from the most sensitive electrode to the subcortical amygdala source, T7 electrode.

#### **4.4 Discussion**

In this paper, simulations were used to quantify the detection of subcortical signals in the hippocampus and amygdala using within-subject jICA of simultaneous fMRI and EEG. The first two sets of simulations quantified the detection of open field (hippocampus) and closed field (amygdala) subcortical current sources with jICA-EEG/fMRI in the presence of experimentally derived EEG noise. The third set of simulations quantified their detectability in the presence of EEG noise and a spatiotemporally overlapping cortical current source. Overall, the simulation results indicate that the detection of weaker current sources approximated by a closed field was better with jICA-EEG/fMRI relative to the other methods.

For the detection of the hippocampal open field current source, the simulation results showed no benefit for jICA-EEG/fMRI or ICA-EEG relative to TA-EEG. This may be due in part to a ceiling effect on detection related to the relative strength of the hippocampal source (250% of a cortical source), and the 14-fold reduction in noise associated with averaging across 200 trials. Previous simulation studies have added Gaussian noise, an approximation of MEG instrumental noise, to the hippocampal signal and shown that TA-EEG can detect the presence of hippocampal sources with as few as 40 trials (Attal et al., 2007b; Dumas et al., 2013). These studies focus on varying the patch size of the subcortical sources, and determining what the smallest patch size is that can produce a detectable signal. Our approach applies the same AUC threshold of 0.7 as these studies, however, there are two major differences in the design of our simulations and previous studies. First, we modeled experimentally derived noise to account for confounding non-task related neural activity as well as instrumental noise, rather than just

the later. Second, we explored the detectability of subcortical sources when a task related cortical source was simultaneously active, rather than considering only subcortical sources. Finally, this study expands upon previous work that used ICA to link epileptiform discharges recorded from intracranial electrodes to scalp recordings, by using fMRI along with scalp recordings to establish a non-invasive blind source separation approach for measuring subcortical signals (Pizzo et al., 2019).

The strength of the net current dipole seems to be the primary factor in how detectable subcortical signals are. For the hippocampal simulations, the AUC for ICA-EEG and jICA-fMRI/EEG were both correlated to the strength of the net current dipole more than to the orientation of the net current dipole. Likewise, the amygdala source showed far greater sensitivity to the strength of the net current dipole, compared to the dipole orientation. While the strength of the net current dipole cannot be known *a priori*, experimental protocols designed to directly elicit a response from subcortical structures will allow for easier detection and separation of subcortical sources. Spontaneous activity has been shown to be detectable with intracranial recordings and EEG (Pizzo et al., 2019), as well as with intracranial recordings and fMRI (Sharma et al., 2019). This suggests the possibility that our approach using EEG and fMRI could be used to extract spontaneous activity noninvasively.

In the presence of a spatiotemporally overlapping cortical current source, the hippocampal or amygdala sources were detected and separated better with jICA-EEG/fMRI than with the other methods when the subcortical and cortical patterns of activity differed across experimental levels. If spatiotemporally overlapping subcortical and cortical sources co-varied across experimental levels, the sources were grouped into the same component and could not be separated using within-subject jICA-EEG/fMRI. Future research could examine whether group jICA-EEG/fMRI (Calhoun et al., 2009) could provide improved detection and separation of subcortical sources based on differences in the ratios of subcortical and cortical activity across subjects.

The simulations performed here have several limitations. Within-subject jICA detects covarying fMRI and EEG signals across experimental levels. If the fMRI and EEG responses vary differently across levels, the fMRI and EEG signals will be split between separate components. Nevertheless, components containing a split signal can be linked back together to reconstitute the source based on residual activity, either spatial or temporal, that each component retains (Mangalathu-Arumana et al., 2018). Other data driven approaches such as independent vector analysis (IVA), which loosen the constraint that the activity of both imaging modalities must vary identically across experimental conditions, could also be used (Adali et al., 2015; Du et al., 2017; Ma et al., 2013). With IVA, the likelihood that EEG and fMRI activity would be split into separate components is reduced, but detection performance could also be reduced as jICA is maintains performance better at lower SNR, due to the constraint of an identical mixing matrix (Adali et al., 2015).

In summary, we performed a series of simulations to determine whether informing EEG signal detection with simultaneous fMRI, in the context of jICA-EEG/fMRI, would improve the detection of the subcortical activity. The results indicate an advantage to using within-subject jICA-EEG/fMRI over ICA-EEG and TA-EEG when the subcortical signal is weak, e.g. for detection of signals from nearly-closed field current sources such as the amygdala. JICA-EEG/fMRI is also effective for resolving simultaneous subcortical and cortical activity when the patterns of activity differ between the two sources. Within-subject jICA-EEG/fMRI could be used to enhance the detection of subcortical sources in heterogeneous populations that are less amenable to traditional group analyses (e.g., Alzheimer's disease, Autism, Cushing's disease etc.). Thus, withinsubject jICA-EEG/fMRI can be used to characterize the dynamics of cortical and subcortical networks noninvasively and at high spatial and temporal resolution.

## CHAPTER 5: SUMMARY OF RESULTS AND FUTURE DIRECTIONS

#### 5.1 Summary of Results

The overarching goal of this dissertation was to apply joint independent component analysis (jICA) as a tool to characterize the relationship between fMRI and EEG within subject. We have presented analytical approaches to optimize the spatial correspondence between fMRI and EEG sources, identify brain areas in a syllable detection task with nonlinear correspondence between EEG and fMRI, and used simulations to demonstrate the efficacy of using jICA to improve the detection of subcortical sources of brain activity using EEG. This dissertation was among the first studies to leverage blind source separation to characterize the neuroimaging relationship between simultaneously acquired fMRI and EEG signals, and to demonstrate the advantage of incorporating jICA for the detection of subcortical sources. The combined approaches can be used within subject to investigate the temporal interactions between cortical networks and subcortical structures across experimental conditions that support perception and cognition. The remainder of this chapter provides an overall summary of the work and outlines directions for future research.

5.1.1 Specific Aim 1: Develop a Method for Spatial Overlap Estimation of Electroencephalography and Functional Magnetic Resonance Imaging Responses.

We proposed a data-driven approach, fMRI and ERP spatial overlap estimation (fMRI-ERP SOE), to estimate the spatial overlap between maps of brain activity generated from fMRI and ERP measurements that assumes overlapping, but not identical, sources of neural activity contribute to each measurement. By representing both fMRI and ERP signals in a common 'nonnative' source imaging space, fMRI-ERP SOE maximized the ability to spatially correlate fMRI and ERP sources of activity while minimizing assumptions regarding neuroimaging coupling. FMRI-ERP SOE of sources of the auditory oddball response revealed regions of consistent activity overlap in the insula, superior temporal, and inferior parietal cortices, in-line with previously reported auditory odd-ball experiments. It also showed less consistent activation in the right inferior frontal cortex which is associated with attention. This approach provides a way to quantitatively measure how well fMRI and EEG signals correspond, and can be used to inform whether the assumption of approaches like fMRI constrained EEG localization are being met.

# 5.1.2 Specific Aim 2: Characterization of the Neuroimaging Coupling between EEG and FMRI in a Syllable Detection Task.

A data-driven method for the integration of fMRI and EEG recordings of brain function was proposed. The approach was applied to a syllable detection task with a known nonlinear relationship between fMRI and EEG to characterize brain function with high spatial and temporal resolution. The approach leveraged jICA's creation of mixing matrices associated with each component to characterize how the activity within each component varied between EEG and fMRI across task levels. The results revealed two brain networks associated with the task that responded differently across task levels. The activity of the first network, involving the bilateral Heschel's gyrus and lateral superior temporal cortex, increased with syllable presentation rate for both EEG and fMRI, consistent with the obligatory auditory response to sound stimuli. The activity of the second network included distributed activity in perisylvian regions, with the largest clusters seen in the left supramarginal and precentral gyri, decreased with syllable presentation rate in EEG but had had only a weak response with fMRI, consistent with the orienting response. The nonlinearity in the second response was a result of activity that was captured by the EEG, but undetected by the fMRI. The areas in the primary component represent parts of a neural network that responds to increased stimulus rate, while those in the secondary component respond to the onset of stimuli, whose strength increases the longer it has been since a previous auditory stimulus. These results demonstrate the ability for this analysis approach to characterize the neuroimage coupling between fMRI and EEG in a condition where there are two different networks driving the recorded activity.

5.1.3 Specific Aim 3: Assessment of the Impact of Within-Subject jICA on the Detection of Subcortical Signals.

In Aim 3, the performance of within-subject jICA of fMRI/EEG (jICAfMRI/EEG) relative to ICA of EEG uninformed by fMRI (ICA-EEG), and relative to simple trial averaging of EEG (TA-EEG) was examined for the detection of subcortical signals under experimentally realistic conditions. The results indicate an advantage to using within-subject jICA-EEG/fMRI over ICA-EEG and TA-EEG when the subcortical signal is weak, e.g. for detection of signals from nearly-closed field current sources such as the amygdala. JICA-EEG/fMRI was also effective for resolving simultaneous subcortical and cortical activity when the patterns of activity differed between the two sources. These simulations demonstrate how jICA can be applied to improve the detection of subcortical sources, and offer an approach to study cortical and subcortical networks non-invasively.

## **5.2 Future Directions**

#### 5.2.1 Investigation of Alternative Blind Source Separation Algorithms

In future studies there are several lines of research that could be explored to improve upon the methodological approaches presented here. Alternative blind source separation algorithms could be employed within subject to relax the strict constraint that EEG and fMRI contributions to a task are the same within a component. Independent vector analysis (IVA) would be an excellent candidate for this type of analysis due to its ability to extract signals that are present in a single modality. Independent vector analysis is similar to jICA in that it extracts EEG/fMRI signals that covary across task conditions into components that are maximally independent in space and time. IVA provides each modality with its own mixing matrix, which would allow for nonlinear relationships between the modalities without splitting the response across multiple components as jICA does. So where jICA will split activity across two or more components if EEG and fMRI signals within a brain network do not vary identically across task conditions, IVA should keep the entirety of the signal within the same component and by correlating the separate mixing matrices would then encapsulate those differences across levels. IVA seeks to find uncorrelated signals to separate into components rather than independent signals, and as such the impact that has on the methodological approaches presented here would need to be examined. This change could build upon all three aims presented within this dissertation, and would remove the current need to recombine nonlinear responses between modalities into a single component.

5.2.2 Characterization of the Detection of Additional Subcortical Sources

Another avenue that could be explored would be to build upon the simulations presented in the third aim. The current simulations focused on the amygdala and the hippocampus as two representative examples of subcortical sources spanning the range of signal strengths from open to closed field structures. However, the current results do not directly inform on all subcortical structures. The size, strength of local field potentials, and structure of the other subcortical sources are all expected to impact the detection of other subcortical sources, using EEG. By characterizing the relative detection of other types of subcortical sources, the combined simulation studies could provide guidelines about the types of EEG analyses and experimental designs that can be used to detect activity within specific subcortical structures.

## 5.2.3 Incorporation of Subcortical Sources

The ability of jICA-fMRI/EEG to improve the detection of subcortical sources using EEG, suggests a natural extension of the research to incorporate detection of subcortical sources into the fMRI source projection analysis and characterization of neuroimage coupling. The presence of a subcortical source could give rise to uncoupling in Aim 1, because the EEG activity would be localized to the cortex, but the fMRI activity from deep structures would not be captured at all, since only activity near the cortical surface is being projected onto the inflated surface. As a result, uncoupling using the fMRI-ERP SOE approach could reflect activity from subcortical sources that have been mis-localized to the cortex. Similarly, characterization of the relationship between EEG and fMRI in Aim 2 could be improved by accounting for the presence of subcortical sources as part of the jICA analysis. While it is a less pressing issue in this case, since the volumetric fMRI would capture the subcortical activity, and the EEG would localize it to the cortical surface, unless a localization technique incorporating subcortical sources was used, it would make the interpretation of the activity within a component more challenging by placing a mis-localized subcortical source onto the neocortex.

The incorporation of subcortical sources as part of the overall EEG analysis is a non-trivial task, however. Approaches to localize subcortical sources with EEG are relatively new, requiring additional assumptions, such as signal sparsity, to localize subcortical sources. Because localizing subcortical signals adds added complexity, it would be necessary to review the current methodological approaches to ensure whichever approach was chosen would not make assumptions that conflict with those made by jICA.

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