Comparison of EEG microstates with resting state fMRI and FDG-PET measures in the default mode network via simultaneously recorded trimodal (PET/MR/EEG) data

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Abstract

Simultaneous trimodal positron emission tomography/magnetic resonance imaging/electroen-cephalography (PET/MRI/EEG) resting state (rs) brain data were acquired from **10** healthy male volunteers. The rs-functional MRI (fMRI) metrics, such as regional homogeneity (ReHo), degree centrality (DC) and fractional amplitude of low-frequency fluctuations (fALFFs), as well as **2-[18**F**]**fluoro-**2**-desoxy-D-glucose (FDG)-PET standardised uptake value (SUV), were calculated and the measures were extracted from the default mode network (DMN) regions of the brain. Similarly, four microstates for each subject, showing the diverse functional states of the whole brain via topographical variations due to global field power (GFP), were estimated from artefact-corrected EEG signals. In this exploratory analysis, the GFP of microstates was nonparametri-cally compared to rs-fMRI metrics and FDG-PET SUV measured in the DMN of the brain. The rs-fMRI metrics (ReHO, fALFF) and FDG-PET SUV did not show any significant correlations with any of the microstates. The DC metric showed a significant positive correlation with microstate C(r_s = 0.73, p = .01). FDG-PET SUVs indicate a trend for a negative correlation with microsta-tes A, B and C. The positive correlation of microstate C with DC metrics suggests a functional relationship between cortical hubs in the frontal and occipital lobes. The results of this study suggest further exploration of this method in a larger sample and in patients with neuropsychiat-ric disorders. The aim of this exploratory pilot study is to lay the foundation for the development of such multimodal measures to be applied as biomarkers for diagnosis, disease staging, treat-ment response and monitoring of neuropsychiatric disorders.

Keywords

18F-FDG, biomarkers, electroencephalography, fMRI, multimodal imaging, positron emission tomography

Introduction

Recent developments in medical imaging technologies have made the simultaneous measurement of the three modalities, magnetic reso-nance imaging (MRI), positron emission tomography (PET) and electro-encephalography (EEG), feasible (Shah et al., 2017). The main advantage of such technology is that structural and functional (via MRI), metabolic (via PET) and electrophysiological (via EEG) signatures can be confined simultaneously under the same physiological and psychological conditions (Shah et al., 2013). Exploitation of such simulta-neous multimodal neuroima-ging technology has enabled neuroscientists to explore the functioning of the human brain using the diverse information provided by each modality with different temporal and spatial resolutions. The complementary value of the information provided by each modality is considerably increased by the simultaneous

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execution of MR, PET and EEG. The physiological information provided by each modality is as follows:

- Functional MRI (fMRI) measures brain activity in an indirect fash-ion via the blood oxygenation level-dependent (BOLD) contrast (Ogawa, Lee, Kay, & Tank, 1990).
- PET provides quantitative molecular information (Tomasi, Wang, & Volkow, 2013).
- EEG, a direct measure of neuronal activity records the electro-physiological signals of the brain with high temporal resolution. Electrical activity that occurs at synapses of neurons and changes in neuronal cell membrane permeability create EEG signals (Davidson, Jackson, & Larson, 2000).

A number of image and signal analysis methods (Abreu, Leal, & Figueiredo, 2018; Bai, Xia, & Li, 2017; Boellaard, 2008; Bowman, Guo, & Derado, 2007) are available to process, either qualitatively or quantitatively, the data obtained from each imaging modality. Com-bined analysis of the complimentary information provided by each modality can help in understanding the complex relationships between the various physiological mechanisms of the brain. The rela-tionship between simultaneously recorded bimodalities, such as fMRI/PET (Aiello et al., 2015; Riedl et al., 2014, 2015), fMRI/EEG (Goldman, Stern, Engel, & Cohen, 2000; Huster, Debener, Eichele, & Herrmann, 2012; Ritter & Villringer, 2006) and PET/EEG (Hur, Lee, Lee, Yun, & Kim, 2013), has already been reported by a number of groups. Fur-thermore, other research has shown the feasibility and application (Golkowski et al., 2017; Del Guerra et al., 2017; Shah et al., 2017) of simultaneous trimodal (MR/PET/EEG) measurements. Even though various functional relationships between simultaneously recorded bimodal and trimodal data have already been investigated and reported on, an exploratory analysis on the neuroelectric (electrophys-iology as measured by EEG) metrics and its relationship with neuro-vascular (hemodynamic response as measured by BOLD fMRI) and neurometabolic (metabolic activity as measured by PET) metrics on a simultaneously recorded resting state (rs) trimodal data set has not yet been reported. In this work, we performed an exploratory analysis on simultaneously recorded rs-trimodal data in order to elucidate the relationship between neuroelectric measures with neurovascular and neurometabolic measures.

Analysis of simultaneously recorded trimodal data can advance the understanding of the brain functions in general. The main future advantage of multimodal analysis techniques lies in the definition of image-based biomarkers for neurological and psychiatric disorders with the help of machine learning approaches (Polikar, Tilley, Hillis, & Clark, 2010). The simultaneous approach is especially valuable for the prediction of response to a given medication based on a pharmacolog-ical challenge during trimodal scanning (Bayouth et al., 2011). This would also prevent cofounding effects inevitable with separate scan-ning sessions (Laruelle et al., 1997). Also, by utilising the multimodal data, the accuracy in early diagnosis of neurological and psychiatric disorders could be improved. Furthermore, possibilities with regard to the potential applications of multimodal neuroimaging are already well reviewed and discussed in literature (Liu et al., 2015; O'Halloran, Kopell, Sprooten, Goodman, & Frangou, 2016; Uluda g & Roebroeck, 2014). A study has shown potential in vivo markers for neocortical neuronal loss in Alzheimer's disease by utilising multimodal evidence from MRI, PET and EEG (Hampel et al., 2002). A recently published pilot study has shown the feasibility of simultaneous trimodal data acquisition in schizophrenic patients (Del Guerra et al., 2017). The potential of utilising rs-fMRI data as biomarker in neurodegenerative disorders is also discussed in the literature (Hohenfeld, Werner, & Reetz, 2018). rs-fMRI is an fMRI technique that measures the low-frequency fluctuations in the BOLD signal while the subject is in the resting condition (not actively performing any task). Since the discov-ery of rs-fMRI (Biswal, Yetkin, Haughton, & Hyde, 1995), several methods have been developed to analyse rs-fMRI data (Lee, Smyser, & Shimony, 2013) and the possibility of deriving various rs-fMRI metrics has also been reported (Shehzad et al., 2009; Zhang, Han, Hu, Guo, & Liu, 2013; Zuo et al., 2010, 2013). In this exploratory analysis, the fol-lowing rs-fMRI metrics were considered for comparison with other neuroelectric and neurometabolic measures:

- Regional homogeneity (ReHo) (Zang, Jiang, Lu, He, & Tian, 2004) is a voxel-based measure used to characterise the functional homogeneity of the rs-fMRI signal within a short range. ReHo weighs the degree of synchronisation between a given voxel and its nearest neighbouring voxels time series. Kendall's coefficient of concordance (KCC) (Stuart, 1956) is used as an index to mea-sure the degree of synchronisation in ReHo analysis. Since the ReHo metric considers only neighbouring voxels, it depicts the strength of functional connectivity within neighbouring voxels. A voxel with a high ReHo value is functionally well connected with neighbouring voxels. ReHo analysis has been applied considerably in rs-fMRI data analysis (Long et al., 2008; Zang et al., 2004) and changes in ReHo values have also been reported in schizophrenia (Del Guerra et al., 2017; Liu et al., 2006), Alzheimer's disease (He et al., 2007) and in several other disorders.
- Degree centrality (DC) (Buckner et al., 2009; Joyce, Laurienti, Burdette, & Hayasaka, 2010) or global functional connectivity density (Tomasi & Volkow, 2012) is a functional connectivity mea-sure, which estimates the number of direct functional connections between a given voxel and all the other voxels in the brain. Pear-son's correlation coefficient is used as the measure to estimate DC. The DC metric considers all the voxels, and thus the value shown by the DC metric is the sum of local and long-range func-tional connectivity. Since the long-range voxels are comparatively high in number, the DC metric can be considered as a long-range functional connectivity measure. A voxel with a higher DC value means that this particular voxel is functionally well connected to many other voxels. DC has been largely studied to reveal the cor-tical functional hubs in the brain (Buckner et al., 2009; Zuo et al., 2012).
- Amplitude of low-frequency fluctuations (ALFFs) (Zang et al., 2007) and fractional amplitude of low-frequency fluctuations (fALFF) (Zou et al., 2008) are interrelated measures that quantify the amplitude of low-frequency oscillations (LFO), a fundamental feature of the rs-fMRI measurements. The ALFF measure of a