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Vascular-metabolic and GABAergic Inhibitory Correlates of Neural Variability Modulation. A Combined fMRI and PET Study

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Abstract—Neural activity varies continually from moment to moment. Such temporal variability (TV) has been highlighted as a functionally specific brain property playing a fundamental role in cognition. We sought to investigate the mechanisms involved in TV changes between two basic behavioral states, namely having the eyes open (EO) or eyes closed (EC) *in vivo* in humans. To these ends we acquired BOLD fMRI, ASL, and [^{18}F]-fluoro-deoxyglucose PET in a group of healthy participants (n = 15), along with BOLD fMRI and [^{18}F]-flumazenil PET in a separate group (n = 19). Focusing on an EO- vs EC-sensitive region in the occipital cortex (identified in an independent sample), we show that TV is constrained in the EO condition compared to EC. This reduction is correlated with an increase in energy consumption and with regional $GABA_A$ receptor density. This suggests that the modulation of TV by behavioral state involves an increase in overall neural activity that is related to an increased effect from GABAergic inhibition in addition to any excitatory changes. These findings contribute to our understanding of the mechanisms underlying activity variability in the human brain and its control.

Key words: temporal variability, brain state, cerebral blood flow, visual cortex, GABAA receptor, flumazenil, FDG.

INTRODUCTION

Neural activity varies continually from moment to moment. Such neuronal temporal variability (TV) is the target of increasing amounts of research and has been measured through a number of techniques, including blood-oxygen-level-dependent (BOLD) fMRI (Garrett et al., 2013). Recent work has shown that TV in different brain regions can be been linked to individual differences in, for example, visual discrimination thresholds (Wutte et al., 2011), task accuracy (Armbruster-Genc et al., 2016; Mennes et al., 2011), and peripersonal space

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Abbreviations: ASL, arterial spin labeling; BOLD, blood-oxygen-level-dependent; CSF, cerebrospinal fluid; EC, eyes closed; EO, eyes open; FDG-PET, [^{18}F]-fluoro-deoxyglucose PET; FMZ-PET, [^{18}F]-flumazenil PET; GM, gray matter; PET, positron-emission-tomography; rCBF, regional cerebral blood flow; TV, temporal variability; WM, white matter.

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(Ferri et al., 2015). As well as this, TV has been reported to be altered in a number of psychiatric and neurological disorders, including Alzheimer's disease (Takahashi, 2013) and bipolar disorder (Martino et al., 2016). Importantly, TV is not a fixed property of the brain but is instead modulated by different tasks and stimuli (Garrett et al., 2012, 2014). Taken together, this evidence suggests that TV is a functionally specific brain property that plays a fundamental role in cognition. Despite this apparent importance, the mechanisms underlying TV and its change between specific behavioral contexts remain to be fully explored *in vivo* in humans.

Previous work has shown that neural TV, as measured with BOLD fMRI, correlates well with the amount of energy consumed locally, as measured through glucose consumption (Aiello et al., 2015; Nugent et al., 2015). This link presents an opportunity for gaining insight into what mechanisms are related to the modulation of TV according to behavioral state. For example, it has been observed that switching from an eyes closed (EC) to eyes open (EO) condition results in a reduction in TV (Bianciardi et al., 2009; Jao et al., 2012; Zou et al., 2015). Given this, the first aim of this study was to use these EC to EO changes to investigate the energetic processes supporting the neural changes reflected in TV modulation, asking whether changes in TV lead to concurrent changes in local energy usage. BOLD fMRI was used to quantify TV while [^{18}F]-fluorodeoxyglucose PET (FDG-PET) was used as a measure of regional glucose, and as such energy, consumption (rMRGlu). Regional cerebral blood flow (rCBF), as measured with arterial spin labeling (ASL), was used as an additional proxy measure of energy consumption due to the known coupling between rCBF and glucose uptake during both rest and task states (Cha et al., 2013; Galazzo et al., 2016; Newberg et al., 2005). This additional measure was used to circumvent issues relating to scanning participants in two different states with PET. The three types of data were acquired in the same participants (Dataset 1 – see Fig. 1).

Since opening the eyes is primarily a visual stimulus, the study focussed on the occipital cortex. The relevant brain areas were identified in an independent sample using an EO/EC block-design experiment and applied to the main datasets. A region-based analysis of the EO/EC fMRI and ASL data, along with EC FDG-PET, was then conducted (He, 2011; Huang et al., 2016; Nugent et al., 2015). The validity of rCBF as a measure of energy consumption in this region was confirmed by correlating EC rMRGlu with the EC ASL data (Cha et al., 2013). It was hypothesized that TV would be reduced in the EO condition, as compared to EC (Bianciardi et al., 2009; Jao et al., 2012). At the same time, based on previous work using FDG-PET, rCBF (and thus energy consumption) was expected to increase with the opening of the eyes (Riedl et al., 2014). We thus hypothesized that changes in TV between EC and EO would be negatively correlated with rCBF changes.

The modulation in the visual cortex of the variability of excitatory responses over time by inhibitory interneurons has been studied previously in non-human animals

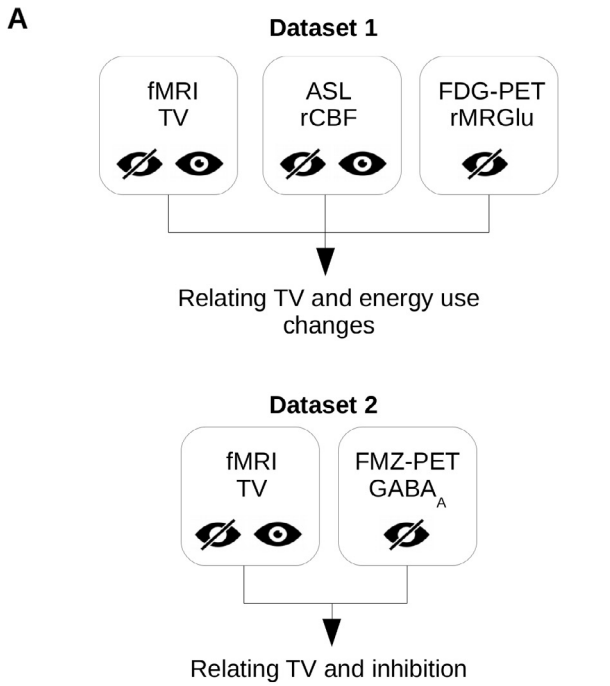

Fig. 1. (A) Two separate datasets were used in the analysis. Dataset 1 (upper section) consisted of BOLD fMRI for measuring temporal variability, ASL for measuring regional cerebral blood flow (rCBF), and FDG-PET for measuring glucose consumption. Dataset 2 (lower section) consisted of BOLD fMRI and FMZ-PET for measuring GABAA receptor density. (B) Mean values for each data type were extracted from a set of 99 ROIs located in the occipital cortex (note that four ROIs were then excluded due to high TV values).

(Fingelkurts et al., 2004; Sabolek et al., 2012; Shew et al., 2011; Xiao et al., 2012). This role for inhibition in structuring activity over time has not been studied in humans, however. Notably, though, evidence from work linking instantaneous responses, such as BOLD effect amplitudes, to GABAergic activity provides background evidence for the relationship between inhibition and neuroimaging measures in humans (Duncan et al., 2014). Accordingly, the second aim of the study was to relate TV in the occipital cortex to GABAergic activity. To do so we utilized [^{18}F]-flumazenil PET (FMZ-PET) data as a measure of $GABA_A$ receptors (Prevett et al., 1995), along with BOLD fMRI data from the same participants to quantify TV (Dataset 2 – see Fig. 1). The same region-based approach was taken as with Dataset 1. The change in TV between EC and EO was calculated and then correlated with regional $GABA_A$ receptor density. It was assumed that regions with more $GABA_A$ receptors have a greater potential for inhibitory action (see *Discussion*, below, for more on this point) and so it

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