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Multi-echo EPI of human fear conditioning reveals improved BOLD detection in ventromedial prefrontal cortex

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ABSTRACT

Standard T_2^* weighted functional magnetic resonance imaging (fMRI) performed with echo-planar imaging (EPI) suffers from signal loss in the ventromedial prefrontal cortex (vmPFC) due to macroscopic field inhomogeneity. However, this region is of special interest to affective neuroscience and psychiatry. The Multi-echo EPI (MEPI) approach has several advantages over EPI but its performance against EPI in the vmPFC has not yet been examined in a study with sufficient statistical power using a task specifically eliciting activity in this region. We used a fear conditioning task with MEPI to compare the performance of MEPI and EPI in vmPFC and control regions in 32 healthy young subjects. We analyzed activity associated with short (12 ms), standard (29 ms) and long (46 ms) echo times, and a voxel-wise combination of these three echo times. Behavioral data revealed successful differentiation of the conditioned versus safety stimulus; activity in the vmPFC was shown by the contrast "safety stimulus > conditioned stimulus" as in previous research and proved significantly stronger with the combined MEPI than standard single-echo EPI. Then, we aimed to demonstrate that the additional cluster extent (ventral extension) detected in the vmPFC with MEPI reflects activation in a relevant cluster (i.e., not just non-neuronal noise). To do this, we used resting state data from the same subjects to show that the time-course of this region was both connected to bilateral amygdala and the default mode network. Overall, we demonstrate that MEPI (by means of the weighted sum combination approach) outperforms standard EPI in vmPFC; MEPI performs always at least as good as the best echo time for a given brain region but provides all necessary echo times for an optimal BOLD sensitivity for the whole brain. This is relevant for affective neuroscience and psychiatry given the critical role of the vmPFC in emotion regulation.

Introduction

In the last two decades, functional magnetic resonance imaging (fMRI) has become one of the most popular imaging tools to study brain function in a variety of applications like surgical planning (Vlieger et al., 2004), basic neuroscience (Poldrack, 2012) and clinical neuropsychiatric research (Zhan and Yu, 2015; Mitterschiffthaler et al., 2006; Etkin and Wager, 2007; Groenewold et al., 2013). Gradient-echo echo-planar imaging (EPI) is the most commonly used and accepted pulse sequence for fMRI because of its relative robustness to motion, its high temporal resolution and its good sensitivity to blood-oxygen-level dependent (BOLD) effect (Mansfield, 1977; Ogawa et al., 1990). However, there are considerable issues with this pulse sequence mainly due to the susceptibility-induced field gradients (Koch et al., 2009; Farzaneh et al., 1990), which lead to severe signal and BOLD sensitivity loss (Deichmann et al., 2002) especially pronounced in the ventromedial prefrontal cortex (vmPFC) at 3.0 T. In particular, Deichmann et al. (2002) showed that in susceptibility affected brain regions such as the most ventral parts of the vmPFC, the local echo time (i.e. local to a given voxel or brain region) is shifted to lower or higher values, possibly leading to a signal void when the echo occurs outside of the EPI readout window. This implies that a whole range of echo times (*TE*) are needed to properly sample the BOLD response in the vmPFC. Additionally, still in the vmPFC, the more ventral the considered voxel is, the more shifted is the local echo time, meaning that the vmPFC is not uniformly affected by susceptibility induced gradient fields. In the most ventral parts of the vmPFC, the BOLD signal is expected to be better sampled by a short echo time (*TE* < 15 ms), while in the upper

Abbreviation: BOLD, Blood-Oxygen-Level Dependent; dACC, dorsal Anterior Cingulate Cortex; DMN, Default Mode Network; EPI, Echo Planar Imaging; FWE, Family-wise Error; MEPI, Multi-echo EPI; PET, Positron Emission Tomography; PTSD, Post-Traumatic Stress Disorder; MDD, Major Depressive Disorder; mPFC, medial Prefrontal Cortex; vmPFC, ventromedial Prefrontal Cortex

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part of the vmPFC it is expected to be better sampled by a longer ($TE \geq 30$ ms).

Unfortunately, the vmPFC is strongly affected by susceptibility-induced field gradients while being a key region for many affective processes. The medial part of this region has been repeatedly associated with fear conditioning and extinction (Milad and Quirk, 2012; Groenewold et al., 2013; Hayes et al., 2012; Milad and Rauch, 2007). Fear extinction is impaired in anxiety disorders and post-traumatic stress disorder (PTSD) (Duits et al., 2015) and hypoactivity in vmPFC during fear extinction learning and recall has been observed in patients with PTSD as well (Milad et al., 2009). The most ventral parts of the mPFC (overlapping with the medial orbitofrontal cortex) have direct projections to amygdala, ventral striatum, lateral hypothalamus, and hippocampus (Milad and Rauch, 2007), which are also involved in affective processing and stress response integration, making the vmPFC ideally posed as a mediator of circuitry subserving in emotional responses. The role of the vmPFC can extend to more cognitive processes as well, as demonstrated by one study showing that cognitive emotion regulation (i.e., subjects trying to modulate their own emotional responses to stimuli) is also mediated by the vmPFC (Delgado et al., 2008). Interestingly, studies on fear learning using standard EPI generally do not show involvement of the most ventral parts of mPFC in fear learning (Fullana et al. 2015), whereas an anatomical study (that uses acquisitions less prone to signal loss and distortion) focusing on thickness of vmPFC in relation to extinction learning reported the strongest correlation in the most ventral part of the mPFC (Milad et al., 2005).

Furthermore, a general emotion and stress regulation function of the vmPFC might also help understand why this region, at least the more subgenual parts, showed differences in functional connectivity during the resting-state in major depressive disorder (MDD) patients (Greicius et al., 2007). Particularly its contribution to the default mode network (DMN) was heightened in patients, which was found generally plausible as the DMN is associated with an internal mode of information processing including episodic memory processing (Buckner et al., 2008). Additionally, positron emission tomography (PET) imaging has highlighted a role of the subgenual mPFC in MDD (Drevets et al., 1997). There are over 2000 PubMed listed fMRI publications on the DMN in the last decade, and interestingly, PET studies reported integration of the most ventral parts of mPFC in the DMN (Buckner et al., 2008) whereas this is less clear for fMRI studies (Andrews-Hanna et al., 2014), even though the medial but not the lateral parts of the ventral parts of the PFC have been found to correlate with the DMN (Zald et al., 2014).

We propose that inconsistencies in the literature on the involvement of the vmPFC in task activity or resting state functional connectivity may be due to technical limitations of standard EPI pulse sequences even though other potential influences (e.g., study design, statistical analysis choices, sample sizes) cannot be excluded.

In the literature, many solutions have been proposed to mitigate signal dropouts in fMRI. These can be classified in three categories: (i) shimming techniques including z-shimming (Constable and Spencer, 1999; Deichmann et al., 2002; Weiskopf et al., 2006), 2D/3D x/y/z-shimming (Glover, 1999; Weiskopf et al., 2007), passive shimming (Cusack et al., 2005; Koch et al., 2006) and active shimming (Hsu and Glover, 2005; Juchem et al., 2014); (ii) tailored RF pulses (Cho and Ro, 1992; Stenger et al., 2000; Wastling and Barker, 2015; Yip et al., 2006) and through-plane phase precompensated RF pulses (Chen and Wyrwicz, 1999; Yang et al., 2010; Yang et al., 2011; Yang et al., 2012; Yip et al., 2009) and; (iii) other pulse sequence and reconstruction techniques including parallel imaging (Preibisch et al., 2003; Preibisch et al., 2008), improved k-space sampling strategies like spiral in/out (Glover and Law, 2001) combined gradient and spin-echo EPI (Schwarzbauer et al., 2010) and Multi-echo EPI (MEPI) (Poser et al., 2006; Posse, 2012; Posse et al., 1999) which can easily take advantage of parallel imaging (Schmiedeskamp et al., 2010). Active and passive shimming techniques usually require additional hardware that is not always compatible with a full fMRI setup (e.g. 32 channel coil, video screen, goggles, electroencephalography, electrooculography, eye-tracker and so on) and can lead to subject discomfort. Slice shimming techniques have the disadvantage of significantly lengthening the repetition time (TR). Tailored and phase precompensated RF pulses have unclear effects on BOLD sensitivity (Yip et al., 2009) and temporal signal-to-noise ratio (Wastling and Barker, 2015). The combined gradient and spin-echo EPI approach (Schwarzbauer et al., 2010) might possibly be difficult to use in resting state as it implies mixing two different types of signals with different origin and sensitivity which might not be correlated (i.e. gradient-echo and spin-echo). The use of parallel imaging such as SENSE and GRAPPA (Griswold et al., 2002; Pruessmann et al., 1999) is now well established in fMRI (Lütcke et al., 2006; Schmidt et al., 2005) and fits particularly well with MEPI as previously reported (Schmiedeskamp et al., 2010). Moreover, recent advances in analysis strategies based on MEPI showed the possibility of separating BOLD from non-BOLD components and improving specificity (Kundu et al., 2012; Kundu et al., 2013; Kundu et al., 2015). It is worth noting that a TE of 30 ms is typically used at 3T which is lower than the optimum for gray matter but represents a good compromise between BOLD sensitivity, image quality and temporal resolution (Norris, 2006). All these previous results on MEPI and on the BOLD sensitivity gave additional motivation to further develop MEPI and its associated analysis pipeline (Posse et al., 1999). Another motivation for MEPI is that T_2^* varies across the brain (Peters et al., 2007) and consequently, the optimal TE varies accordingly (Gati et al., 1997).

In the present study, we are seeking a generic methodology that allows for whole brain acquisition with reasonable spatial and temporal resolution (i.e. whole brain coverage at 3–4 mm isotropic spatial resolution in 2–2.5 s acquisition time per volume) and a better BOLD sensitivity in the vmPFC without compromising the BOLD sensitivity in B0-homogeneous brain regions. Since the methodology is intended to be used routinely in fMRI, it should be not more complicated to use than the standard EPI. Consequently, we chose to develop and evaluate MEPI associated with parallel imaging and the weighted sum combination approach (Poser et al., 2006). This approach has the advantages of including the standard EPI and of being compatible with the latest advanced development like multiband EPI with blipped CAIPI (Setsompop et al., 2012). Several papers showed that MEPI had a tendency to perform better than the standard EPI approach (Poser et al., 2006; Posse et al., 1999; Weiskopf et al., 2005; Posse, 2012; Schmiedeskamp et al., 2010), and a recent study indicated an enhanced sensitivity of MEPI in the orbitofrontal cortex using an emotional learning and a reward based learning task (Kirilina et al., 2016). However, according to several meta-analyses, the emotional learning and reward based learning tasks employed do not seem to specifically elicit activity in the ventral part of the mPFC (Garrison et al., 2013; Hayes et al., 2014; Sabatinelli et al., 2011; Zhang et al., 2013). Consequently, what is needed to remove uncertainty about the superior performance of MEPI in vmPFC is a whole brain, statistically robust comparison between MEPI data and standard EPI data with appropriate statistical power using a task specifically eliciting activity in vmPFC. We aimed to do this by using a fear conditioning task which is known to elicit activity in the vmPFC, the target region, the dorsal anterior cingulate cortex (dACC) and the bilateral insula as control regions (Fullana et al. 2015). We hypothesized that MEPI with the weighted sum combination approach would yield a statistically stronger effect in the vmPFC for the contrast safety stimulus > conditioned stimulus ($CS^- > CS^+$) than standard EPI, particularly in the most ventral parts. As a second hypothesis, we expect the anticipated differences in vmPFC to be anatomically and neurophysiologically relevant, meaning that the tentative vmPFC cluster should be connected to the bilateral amygdala in a separate data-set of resting-state data, among other regions.