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Resting State fMRI in the moving fetus: A robust framework for motion, bias field and spin history correction

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ABSTRACT

There is growing interest in exploring fetal functional brain development, particularly with Resting State fMRI. However, during a typical fMRI acquisition, the womb moves due to maternal respiration and the fetus may perform large-scale and unpredictable movements. Conventional fMRI processing pipelines, which assume that brain movements are infrequent or at least small, are not suitable. Previous published studies have tackled this problem by adopting conventional methods and discarding as much as 40% or more of the acquired data.
In this work, we developed and tested a processing framework for fetal Resting State fMRI, capable of correcting gross motion. The method comprises bias field and spin history corrections in the scanner frame of reference, combined with slice to volume registration and scattered data interpolation to place all data into a consistent anatomical space. The aim is to recover an ordered set of samples suitable for further analysis using standard tools such as Group Independent Component Analysis (Group ICA).
We have tested the approach using simulations and *in vivo* data acquired at 1.5 T. After full motion correction, Group ICA performed on a population of 8 fetuses extracted 20 networks, 6 of which were identified as matching those previously observed in preterm babies.

Introduction

Resting State Networks (RSNs) are consistently mapped in different human populations with functional MRI (fMRI) and are the topic of extensive Neuroscience research (Van Den Heuvel and Hulshoff Pol, 2010). RSNs are characterized by low frequency temporal fluctuations of the blood-oxygen-level-dependent (BOLD) signal which are correlated between distinct anatomical regions when a subject is imaged at rest, or at least with no prescribed activity or stimulus (Biswal et al., 1995; Buckner et al., 2008). Spatial mapping of RSNs in adults suggests that involved areas are functionally relevant, and include regions involved in motor, visual, auditory, executive and memory functioning (Damoiseaux et al., 2006). RSNs have also been described in infants, and include many of those regions seen in the mature brain (Damaraju et al., 2010; Fransson et al., 2007, 2009, 2011; Gao et al., 2009).

The emergence of RSNs during the preterm period was explored by Smyser et al. (2010) and Doria et al. (2010), who were able to map a full repertoire of networks encompassing the visual, auditory, somatosensory, motor, and executive control areas. These infant studies have identified a maturational trend during this period (equivalent to the third trimester of gestation) consisting of a progression from lateralized networks to bilateral patterns at full term equivalent post-menstrual age (PMA).

The studies on preterm babies suggest that it is of great interest to look at the development of RSNs directly *in utero*. However, this is a challenge, as during the several minutes taken to acquire a typical fMRI dataset, the fetal brain undergoes large-scale motion caused by changes in fetal position within the womb and also as a result of maternal respiration.

Fetuses move sporadically and in an unpredictable fashion (Malamateniou et al., 2013). These movements take place in both the in-plane and the out-of-plane directions. Motion, particularly head rotations and nodding, can be rapid. The quality and duration of periods of motion vary with gestational age, such that, as the fetuses get larger later in pregnancy, they may have longer quiet periods and body motion is more constrained (Hayat et al., 2011).

Some preliminary studies have explored fetal RSNs using conventional processing pipelines. Schöpf et al. (2012) acquired fMRI data from 87 healthy fetuses and used single subject Probabilistic ICA (Beckmann and Smith, 2004) to identify RSNs. However, because of large motion levels, 71 datasets couldn't be processed. Thomason et al. (2013) analyzed a set of 25 healthy subjects in the second and third trimesters of gestation using Group ICA (Calhoun et al., 2009) and correlation analysis. In this study, individual time frames were rejected, with

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single volumes removed from the time series when there was judged to be excessive motion. The reported rejection rate was 41.28%.

Fig. 1 illustrates an example of changes in fetal position for a 28 week old fetus over a period of 4 min. The figure shows 3 images taken from a real-time balanced steady state free precession (bSSFP) cine sequence acquired at 3.3 frames per second. The fetal head position changes in a complex series of 3 dimensional movements that cause the anatomical content within a slice at a fixed location in the scanner to change substantially. Within any single stack of slices that provide whole brain coverage the fetus may therefore change position significantly, so that the conventional approach of correcting motion by realigning whole imaging volumes is likely to result in registration errors (Kim et al., 1999).

This work proposes a framework for processing fetal fMRI data that is designed to operate when there is large-scale and frequent movement. The approach seeks to directly accommodate movement on a slice-by-slice timescale and to correct for signal variations due to changes in position of the fetal head with respect to a spatially varying receiver coil sensitivity distribution. A consequence of fetal motion is that anatomical locations are sampled at irregular time intervals introducing spin history effects that are likely to be variable (Bhagalia and Kim, 2008; Yancey et al., 2011). The proposed method seeks to model and correct for these, before rendering the now scattered data samples back onto a regular coordinate system, enabling further analysis by standard methods such as Group ICA. The aim is to achieve a robust framework that allows as much as possible, ideally all, of the acquired data to be retained and used as part of the Resting State Network analysis.

Materials and methods

Acquisition

The data used in this study were from 16 fetuses (mean gestational age: 30.37 ± 4.35 weeks) who had been assessed as normal and were scanned on a Philips Achieva 1.5 T scanner with a 32 channel receiver coil using single shot EPI ($T_R = 4000$ ms, $T_E = 50$ ms with an in-plane resolution of $2.5 \cdot 2.5$ mm^2 and slice thickness of 5 mm). During each T_R interval, 35 slices were acquired with interleaved slice ordering (1–3–5–7…2–4–6–8…). We denote the time to acquire a single slice as T_S.

To make the sampling as dense as possible, the slice positions were overlapped by up to 2.5 mm, with the overlap selected to ensure a large enough stack volume to encompass the fetal brain with a margin for motion.

A SENSE factor of 2 was used for all EPI acquisitions with calibration scans obtained at the beginning of the examination. Since the receiver coil used was fixed relative to the maternal anatomy, fetal movements within the womb changed only local anatomical content, with no substantial effects on coil sensitivity maps. The SENSE calibration scans were rerun if the mother changed her position substantially with respect to the scanner bore during the examination. This was easily detected as all fetal images also contain substantial information about the maternal anatomy.

A complete fMRI acquisition consisted of 100 volumes acquired in a single dynamic time series. We also acquired a smaller number of volume stacks of slices in the coronal and sagittal planes to assist the registration algorithm by providing spatial information from different orientations. The phase encoding direction for transverse and coronal views was Anterior–Posterior, so that spatial distortions were nominally in the same direction for these acquisitions. The number of acquired frames in the coronal and sagittal directions was chosen depending on the available scanning time. Single shot Fast Spin Echo (ssFSE) images were also acquired in 3 nominally orthogonal anatomical planes for all subjects ($T_R = 15000$ ms, $T_E = 180$ ms, 5 packages with a resolution of $1.25 \cdot 1.25$ mm^2, 2.5 mm slice thickness overlapped by 1.25 mm).

Functional studies employ prolonged data acquisitions, in this case almost 7 min for the transverse view. This is longer than routinely used for purely anatomical imaging, which in our practice consists of multiple shorter acquisitions typically lasting 1–2 min each. There is thus an increased risk that fetuses may change position substantially in the womb during an fMRI acquisition. Despite prescribing imaging stacks with larger anatomical coverage than the actual fetal brain dimensions, there were 3 subjects that moved sufficiently to cause part of the brain to be outside the field of view, resulting in unrecoverable data loss (Fig. 2a). In a further 2 subjects there was substantial localized signal loss in part of the brain caused by gas bubbles in the maternal gut (see example in Fig. 2b). These 5 cases were excluded from this study.

Table 1 summarizes gestational age, slice overlap and the number of frames that were acquired in the coronal and sagittal directions for every subject that was imaged. Those subjects that were excluded because of incomplete data are shaded in blue.

The remaining 11 datasets constituted the study population upon which the methods were tested; in these instances subjects labeled 1–8 could be fully processed, and those labeled 9–11 couldn't be corrected because of excessive motion not recoverable by the registration algorithm.

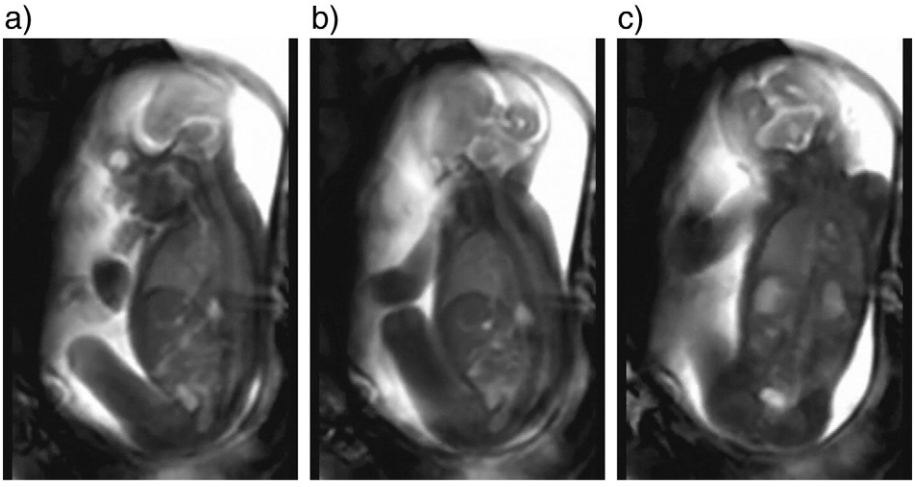

Fig. 1. Three different frames taken from a real-time cine MR sequence showing significant motion in a fetal subject at 28 weeks of gestation. The frames were extracted approximately at 18, 36 and 90 s from the beginning of the acquisition.