fMRI using a hyperpolarized tracer molecule

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Introduction:

Conventional fMRI methods are known for their extremely low contrast-to-noise ratio. This is a consequence of the fact that physiological changes due to neural activity affect only a small fraction of the water molecules compared to the entire pool, which yields a relative large background signal. Dynamic Nuclear Polarization (DNP) is a mechanism by which compounds can be polarized far beyond their thermal equilibrium magnetization leading to a detection of the injected hyperpolarized tracer with up to 10,000 times higher signal-to-noise ratio [1]. Here we introduce a new approach for fMRI, which we term hyperpolarized-fMRI (H-fMRI), based on the use of a hyperpolarized ^{13}C-labeled tracer that has the potential for significantly enhanced contrast-to-noise ratio compared to conventional fMRI techniques. The method is based on the fact that a slice selective 90º pulse destroys the hyperpolarized magnetization in the slice, which is subsequently replenished to levels beyond thermal equilibrium magnetization due to blood flow as hyperpolarized tracer unaffected by the slice-selective pulse flows into the slice. The method, thus detects blood flow and changes in this blood flow induced by neuronal activity.

Methods:

Three fasted male Sprague-Dawley rats were injected intravenously with approximately ~2.6 mL of hyperpolarized by DNP (Hypersense, Oxford Instruments, UK) ^{13}C-urea solution (50 mg of the mixture of 86 mg of urea dissolved in glycerol (0.216 g) with 15 mM OX63 and 1.5 mM $GdCl_3$) under α-chloralose anesthesia. *In vivo e*xperiments were performed using a 9.4-T/31-cm horizontal bore magnet equipped with a Varian INOVA spectrometer and using a coil assembly consisting of a ^{1}H quadrature surface coil (two loops of 14 mm diameter) and an inner ^{13}C linearly polarized surface coil (12 mm diameter). The forepaw stimulation paradigm (3 pulses with the amplitude of 1 mA at 3 Hz followed by a 2 s period without stimulation repeated to match the duration of the total time series) and the data acquisition started upon injection. The following imaging parameters for ^{13}C-detected EPI were used: 938 µm×469 µm, acquired matrix: 32×16, echo time: 12 ms, nominal flip angle 90º. Two experiments were run with a slice thickness of 5 mm, a repetition time of 1 s and 30 images. Another two experiments were performed with a slice thickness of 2.5 mm, a repetition time of 0.5 s and 60 images (Fig. 1). For each rat, a control experiment was performed with a separate injection without forepaw stimulation to confirm that no activation was detected. Prior to each injection, a standard ^{1}H BOLD fMRI experiment was performed to confirm activation. In addition, RARE images (FOV: 6 cm×6 cm, matrix: 128×256, slice thickness: 1 mm) were acquired. To avoid Nyquist ghosting in the images, even and odd echoes in all EPI time series were split, reconstructed individually, and averaged. The apparent T_1 decay in ^{13}C time series was removed by dividing a polynomial function, which was fitted to the decay of total ^{13}C signal within the slice. Activation maps were obtained by displaying the spectral component of each time series, which match the fundamental frequency of the paradigm [2].

Results:

Figure 1 shows an example of an fMRI experiment using hyperpolarized urea. In all experiments, signal changes, which correlated with the paradigm, were detected in the contralateral motor cortex in both ^{1}H BOLD (Fig. 1a) and hyperpolarized tracer experiment (Fig. 1b). Such signal changes were not detected in the corresponding experiments without stimulation. In Fig. 1c, the time courses of the total ^{13}C -signal in the slice and of the activated region (amplitude not to scale). The relative signal in the activated region averaged across all dissolution experiments was 16%, which is lower than the reported average 90% change in blood flow caused by forepaw stimulation [3]. The relative BOLD signal change in the same region averaged to 1%, which is consistent with previous reports.

At each excitation, the polarization of the tracer is fully converted to transverse magnetization (90º excitation), and the polarization in the slice is lost for the subsequent acquisition. Therefore the only signal contribution arises from hyperpolarized tracer flowing into the imaging slice [4]. Urea does not cross the blood-brain barrier. Hence, in this case, only ^{13}C signal from the blood pool is detected. The method can be significantly improved using a long-T_1 hyperpolarizable tracer that crosses the blood brain barrier, using a larger dose of tracer (which was limited by the capacity of the existing hyperpolarizer), and minimizing the delay between hyperpolarization and the injection, which can be achieved using automated and improved delivery. In these studies, this delay was ~30 s leading to more than 60% loss of the hyperpolarization.

Summary:

For the first time, fMRI utilizing a hyperpolarized tracer was performed. Despite the low tracer concentration in the blood in gray matter, focal activated regions were robustly detected in all ^{13}C fMRI experiments.

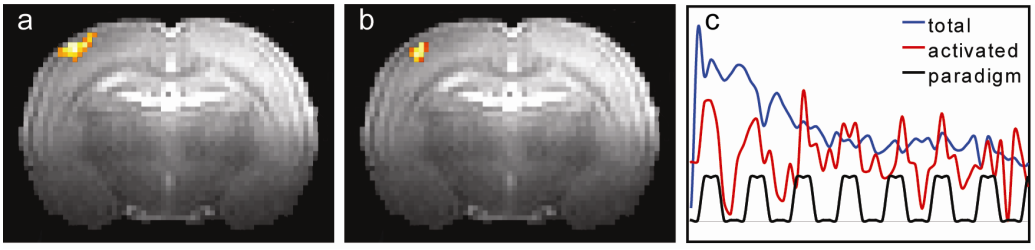

Figure 1. Activation maps derived from a ^{1}H BOLD (a) and a hyperpolarized ^{13}C tracer (b) experiments in a single rat brain superimposed on anatomical RARE images. (c) Time courses of the total ^{13}C signal in the slice (blue), the ^{13}C time course of the activated region (red), and the corresponding forepaw stimulation paradigm (black) corresponding to the data shown in (b). The amplitudes of time courses (not to scale) are shown without normalization to eliminate T_1-decay.

References and Acknowledgments:

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