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EVEnt-Recurring (EVER) MB-SWIFT fMRI with 200-ms temporal resolution during deep brain stimulation and isoflurane-induced burst suppression in rat

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Abstract

Purpose

To develop a high temporal resolution functional MRI (fMRI) method for tracking repeating events in the brain.

Methods

We developed a novel fMRI method using Multi-Band SWeep Imaging with Fourier Transformation (MB-SWIFT), termed EVEnt-Recurring SWIFT (EVER-SWIFT). The method is able to image similar repeating events with sub-second temporal resolution. Here, we demonstrate the use of EVER-SWIFT for detecting fMRI responses during deep brain stimulation (DBS) of the medial septal nucleus (MSN) and during spontaneous isoflurane-induced burst suppression in the rat brain at 9.4 T with 200-ms temporal resolution.

Results

EVER-SWIFT showed that the shapes and time-to-peak values of the response curves to DBS stimulation significantly differed between downstream brain regions connected to the MSN, resembling findings obtained with traditional 2-s temporal resolution. In contrast, EVER-SWIFT allowed for detailed temporal measurement of a spontaneous isoflurane-induced bursting activity pattern, which was not achieved with traditional temporal resolution.

Conclusion

EVER-SWIFT enables sub-second 3-dimensional imaging of both stimulated and spontaneously recurring brain activities, and thus holds great potential for studying the mechanisms of neuromodulation and spontaneous brain activity.

Keywords: DBS, MSN, MB-SWIFT, fMRI, fast imaging, HRF

Introduction

To understand normal and abnormal brain function, it is important to monitor whole-brain activity with high spatial and temporal resolution. Functional magnetic resonance imaging (fMRI) is frequently used for studying brain activity[1,2]. The temporal capabilities of the conventional fMRI pulse sequences are limited, however, and improving the time resolution to a millisecond time scale is a current challenge in the field of fMRI. Advances in this field are particularly motivated by previously developed imaging modalities that allow for whole-brain fMRI with high spatial resolution, as well as by the existence of faster recording methods such as electroencephalography or magnetoencephalography.

Multiple strategies are used to speed up the MRI acquisition process. Parallel imaging utilizes multicoil radiofrequency arrays, which provide an additional source of spatial information for image reconstruction[3–6]. In humans, for example, magnetic resonance-encephalography (MREG) uses multiple small receiver coils to achieve simultaneous multi-channel acquisition[7,8], and later versions of the method were improved by applying highly undersampled trajectories[9] to reach a temporal resolution of 100 ms with an isotropic 5 – 6 mm spatial resolution. These imaging approaches are less efficient in small animals than in humans, however, due to the small space in the preclinical magnet bore, which can typically accommodate only 2 to 8 receiver radiofrequency coils. Therefore, the fastest fMRI sequences for small animal imaging rarely achieve a temporal resolution of less than 1 s. Another way to decrease the acquisition time is to use a multiband approach in which several slices are excited and acquired simultaneously[10]. One more set of methods relies on different k-space trajectory strategies. Compressed sensing methods are based on the recognition of MRI data sparsely represented in the transform domain. Therefore, it can be reconstructed from randomly undersampled k-space trajectories[11], such as radial[12,13], spiral[14–16], and stack-of-spirals[17] trajectories. The keyhole method samples k-space densely in the center and sparsely on the edges, and uses previous volumes to estimate sparsely sampled parts of the k-space[18]. This method is sensitive to motion, however, as information about the edges is fully updated only once in several volumes. Another approach is to repeat the same measurement several times when measuring just one line of the k-space and then combining the measurements[19] from several repeated events. Finally, the line-scanning method[20] and its modification based on FLASH sequence[21] were recently introduced[22].

Recently, we performed fMRI by Multi-Band SWeep Imaging with Fourier Transform (MB-SWIFT) pulse sequence that has zero acquisition delay and high excitation and readout bandwidths[23]. These features of MB-SWIFT are essential for minimizing motion and magnetic susceptibility artefacts from implanted electrodes[23,24]. We demonstrated that MB-SWIFT provides an excellent fMRI activation contrast in the brain[25]. SWIFT collects k-space data radially in 3 dimensions and is thus optimally suited for an approach in which k-space lines (or spokes in case of radial acquisition) for a single image are combined from several acquisitions, as each line contains information from the center of the k-space.

Here, we present a new EVEnt-Recurring MB-SWIFT fMRI (EVER-SWIFT fMRI) approach based on combining and resampling data acquired with the MB-SWIFT sequence from several repeated events to improve temporal resolution. We tested our novel, fast fMRI approach for mapping activation patterns and time courses in response to deep brain stimulation (DBS) of the medial septal nucleus (MSN) in the rat brain. The MSN was selected because of its high potential to activate the hippocampal formation, as connections between the MSN and hippocampus have an important role in regulating hippocampal theta oscillations, with the MSN acting as a pacemaker for the hippocampus. In particular, this area is an important therapeutic target for restoring memory dysfunction during aging and in patients with Alzheimer's disease[26,27], as well as for inducing neurogenesis in the dentate gyrus (DG) of the hippocampal formation[28,29]. Furthermore, MSN stimulation produces stable responses[30], allowing us to compare the proposed method with traditional temporal resolution strategies.

To test the applicability of the new method to other types of recurring events, we also applied EVER-SWIFT to randomly occurring events during isoflurane-induced spontaneous burst suppression. This state is characterized by alternating high-amplitude and low-amplitude periods of electrical activity, resulting from the interaction of thalamocortical networks [31]. Electrical activity during isoflurane-induced bursting activity is coupled with fMRI signal fluctuations[32]. As anesthesia is an important part of many imaging protocols, studying the phenomenon with a finer temporal resolution is of great interest.

Methods

DBS experiments. All surgical and experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Minnesota. Ten male Sprague-Dawley rats (Envigo; Madison, WI, USA; 260–320 g) were used for this study.

Surgery. Animals were anesthetized with isoflurane for the surgery (5% for induction, then decreased to 2%–3%) with O_2/N_2O (30%/70%) carrier gas. The respiration rate was monitored throughout the study. The temperature was monitored using a rectal thermometer and maintained at 37°C. The anesthesia was then switched to urethane (1.25 – 1.50 g/kg, i.p.). The animal was placed in a stereotactic frame and a hole was drilled through the skull over the right hemisphere. Before making the incision, 2% lidocaine was applied to the scalp for local anesthesia, and before cauterizing vessels of the scalp and skull. A tripolar lead comprising 3 twisted polyimide-insulated tungsten wires (PlasticsOne, MS333T/2C-A/SP; Roanoke, VA, USA) with tip-contact diameters of 127 μm, and a 150-μm insulation layer (total diameter of the 3-electrode bundle is ~350 μm) was implanted in the MSN (anterior-posterior = +0.1 mm, mediolateral = +0.4 mm and dorsoventral = 5.8 mm. The precision of implantation in the MSN was monitored with anatomical T_2-weighted fast spin-echo (FSE) images before fMRI acquisitions, and localization of the electrodes in the MSN was confirmed by histology after the MRI study. The remaining hole in the skull around the electrode was filled with gelatin

foam (SPONGOSTAN™, Søborg, Denmark), and covered with dental acrylic (Lang Dental, Jet Acrylic, Wheeling, IL, USA). Finally, an Ag/AgCl wire (5 cm long, 0.5 mm in diameter) acting as a ground electrode was inserted below the skin of the neck. For a more detailed description of the procedures, see [25].

Stimulation paradigm. The DBS paradigm consisted of 10 stimulation trains followed by rest periods. Each stimulation train lasted 10 s, and the resting time was randomized between 55 and 65 volumes (110 – 130 s) to avoid amplification of cyclic physiological noise in the resampled data. A stimulation frequency of 130 Hz at 1-2 mA was used. A single 3-dimensional (3D) k-space consisted of 2060 spokes and the total time for volume acquisition was 2 s. This measurement was repeated 3 times for each animal without a delay between acquisitions, resulting in a total of 30 stimulation periods.

In addition, 10 minutes of resting-state were measured in one animal to study the temporal signal-to-noise ratio (tSNR) of the method.

MRI acquisition. MRI scans at the University of Minnesota were conducted in a 9.4-tesla (T) 31-cm horizontal-bore magnet equipped with Agilent Direct DRIVE console (Palo Alto, CA, USA) using an in-house made quadrature transmit-receive radio frequency volume coil with full rat brain coverage made of materials that do not give a 1H NMR signal. Shimming was performed inside an approximate cerebrum-sized voxel (10 x 10 x 6.5 mm^3) using a field mapping-based shimming protocol included in the Agilent VNMRJ 4.0 package.

Prior to fMRI acquisitions, high-resolution anatomical images were obtained using the FSE pulse sequence: repetition time TR=3 s, echo time TE=48 ms, number of echoes = 8, matrix size = 192 x 192, field of view FOV = 32 x 32 mm^2, slice thickness = 1 mm and number of slices = 15 from anterior-posterior -4.5 mm to 9.5 mm^{33}. The following parameters were used in MB-SWIFT fMRI: TR=0.97 ms, 2060 spokes per volume, resulting in a radial undersampling factor of 6.2 and a temporal resolution of 2 s without reshuffling of spokes, bandwidth = 192 kHz, matrix size = 64^3, FOV = 3.5 x 3.5 x 6.4 cm, using 4 gaps and flip angle = 5°.

Burst suppression measurements. Animal procedures were approved by the Animal Experiment Board in Finland and conducted in accordance with the European Commission Directive 2010/63/EU guidelines. Three male Wistar rats (RccHan®:WIST; Envigo RMS B.V., Horst, Netherlands; 420–470 g) were used in the experiments.

Data acquisition is described in [34]. Briefly, the rats were anesthetized with isoflurane in a mixture of N_2/O_2 70%/30%, implanted with silver wire polytetrafluoroethylene-insulated electrodes (0.2 mm bare wire diameter, outer diameter of coated wire 0.27 mm; AG549511, Advent Research Materials, Oxford, UK) on top of the somatosensory cortex and imaged under isoflurane anesthesia (1.4 – 2.0 %) with simultaneous electroencephalography (EEG) and fMRI. EEG was required to know the exact timings of the isoflurane-

induced bursts. The isoflurane anesthesia was adjusted to achieve typical EEG burst-suppression pattern consisting of high-voltage bursts with low-voltage suppression periods[35].

MRI scans at the University of Eastern Finland were conducted in a 9.4 T 31-cm bore magnet interfaced with an Agilent DirectDRIVE console (Palo Alto, CA, USA) using a custom-made (either in-house made or by Neos Biotec, Pamplona, Spain) surface transmit-receive radio frequency coil with a 22-mm inner diameter (ID), made of materials that do not give a 1H NMR signal. The following parameters were used for MB-SWIFT fMRI measurements: TR 0.97 ms, 2000 spokes per volume resulting in a temporal resolution of ∼2 s, bandwidth = 192 kHz, matrix size 64^3, FOV 3.5 × 3.5 × 6.4 cm, and flip angle = 6°. Each animal underwent two 10-min scans.

For EEG measurement, an MRI-compatible BrainAmp MR system (5 kHz sampling rate; Brain Products GmbH, Gilching, Germany) with a preamplifier (10x amplification; Multi Channel Systems, Reutlingen, Germany) was used.

Data resampling and reconstruction.

DBS experiments. The EVER-SWIFT resampling approach relies on the recognition that similar repeating events can be tracked with higher temporal resolution than a single event by retrospectively combining data from several events[19]. Assuming that the repeating events are approximately the same, one full k-space can be filled by using spokes from several events. To fill the whole k-space, the timing of the events must be shifted relative to the acquisition so that different portions of the k-space are measured during each event. In DBS experiments, the starts of the stimuli were shifted by varying amounts of spokes relative to the first spoke in volume, in random order.

To improve temporal resolution *n* times while keeping k-space coverage the same, at least *n* repetitions of the event are needed (Figure 1 A). Therefore, to achieve 200-ms temporal resolution from 2-s temporal resolution data with spoke view order repeating every 2 s, the stimulus was repeated 10 times. Theoretically, the minimal possible temporal resolution of the method is the TR of the MB-SWIFT sequence, which was 0.97 ms in our case.

During preprocessing, the data were first Fourier-transformed from the k-space domain and correlated with the pulse function. Next, the data were transformed back to the k-space domain and chopped to obtain the radial spokes[23]. The spokes were reordered according to the resampling approach described above, and the data from each newly created volume was reconstructed using a gridding algorithm (https://www.ismrm.org/mri_unbound/).

For each animal, three 118-s-long measurements (30 s before the stimulus starts, 10-s stimulus and 78 s after the stimulus) with a 200-ms time resolution were composed from each of the 3 repeated 10-min acquisitions with 10 stimulus periods. These 3 measurements were then averaged and used for further analysis.

Next, the 2-s time resolution data were preprocessed for comparison with the 200-ms data. Due to shifting of the DBS onset, the stimulus typically started in the middle of the conventional 2-s volume acquisition. Therefore, the time series of 2-s temporal resolution data were linearly interpolated so that new data points matched the 200-ms temporal resolution data points and therefore, the starts of the stimuli.

For the resting-state measurement, the same resampling was performed, though no stimulus was applied.

Burst suppression experiments. EEG data were notch-filtered with a band-stop at 50 Hz, Hilbert transformed, and absolute values were analyzed. Bursts were automatically marked in the EEG data using MATLAB's *findpeaks* function using the 5-s constraint for the minimum distance between peaks.

Data resampling for spontaneous events. Resampling of the data during the spontaneously occurring events was performed the same way as for the DBS data. The main challenge was to get all the spokes needed to reconstruct the event with the desired time resolution, as we could no longer control the timing of the events. The reordering of the spokes was based on the EEG data (Figure 1 B). A detailed description of the method can be found in Supporting Information Text 1. Briefly, the algorithm divided events into 3 sub-groups (to resemble 3 repetitions in DBS experiments), so that events in each group covered full k-space and groups had as few events in common as possible. Each group resulted in one 200-ms temporal resolution fMRI dataset, and an average was calculated across the datasets.

For comparison purposes, the same groups of events were used to reconstruct data with 2-s temporal resolution. Similarly to the DBS experiments, time series with 2-s temporal resolution were interpolated so that the temporal data points matched the start of bursting activity, and the data were averaged across the events.

Preprocessing and data analysis. The preprocessing pipeline is depicted in Figure 2. The data (200-ms temporal resolution and original 2-s temporal resolution data for both datasets) was preprocessed using in-house written MATLAB code, Aedes software v217 (http://aedes.uef.fi), ANTs (http://stnava.github.io/ANTs/), SPM8, MATLAB R2017b (Mathworks) and Python 3.6.9 (https://www.python.org/). The images were converted to NIfTi format, motion-corrected, and coregistered to one of the animals chosen as a reference using ANTs software. A brain mask was manually created for the anatomical image of the reference animal.

tSNR was compared between spoke-reordered and original versions of resting-state data measurement inside the brain mask.

For each animal, first volumes of the resampled and original datasets were compared using the structural similarity index (SSIM) with *multissim* MATLAB function.

To make an initial estimate of the mean activation pattern from DBS, a general linear model (GLM) analysis with temporal and dispersion derivatives as implemented in SPM software was performed for the preprocessed data with 2-s temporal resolution using a standard rat hemodynamic response function (HRF)[36]. The acquired group activation map was thresholded at $p < 0.0001$, uncorrected for multiple comparisons. A hippocampal region of interest (ROI) was chosen to test the stability of activation. Amplitudes of activation during the 10 stimulation periods from that ROI were compared between animals and for each animal between 3 runs of the experiment to ensure the stability of activation throughout the scans (Figure 3). The Mann-Kendall test was used to test the null hypothesis regarding the trend presence in the vector of activation amplitudes.

Several unilateral ROIs, ipsilateral to the implantation site, were chosen based on the mean activation pattern obtained with SPM and an anatomical atlas[33] (Supporting Information Figure S1). For each ROI, the data were averaged among all voxels. The stability of activation was also checked for each of those ROIs with the Mann-Kendall test. The time series trend was estimated using smoothness priors with $\lambda = 10$ as implemented in Aedes software. The activation peak was detected, and the onset time and time-to-peak were calculated in each ROI and finally compared between the ROIs (Figure 4) using a one-sample t-test with false discovery rate (FDR) correction for multiple comparisons.

To estimate fMRI activation during isoflurane burst suppression, a group independent component analysis (ICA) with 20 components was performed for original data (2-s temporal resolution, no spoke reordering). A component corresponding to the burst suppression was chosen based on correspondence to EEG data. This component's spatial map thresholded at $z = 2.08$ was taken as an ROI to estimate fMRI activation. Mean data signal from this ROI was visually compared between the 2-s interpolated and 200-ms temporal resolution resampled data. The peak value was calculated and compared between the 2-s interpolated and resampled data using one-sample t-test.

Results

The location of DBS electrodes in the MSN was confirmed with histology (not shown). Raw MB-SWIFT data are shown in Supporting Information Figure S2. DBS electrode artefacts were minimal and there were no visible artefacts from background signal or movement. There were no visually detectable differences in image quality after the resampling approach, SSIM was ≥ 0.997 for the first volumes of all datasets, when comparing original and resampled data. The tSNR was calculated for resampled and original data of the resting-state measurement, and the mean values of tSNR inside the brain mask were 68.6±12.3 for original data and 66.4±11.4 for resampled data.

DBS of the MSN caused activation of a network including the ventral (temporal) hippocampus, mammillary nuclei, lateral hypothalamus, amygdala, piriform and insular cortices, and also prelimbic (PL) and infralimbic

(IL) cortices, and these areas were chosen for the ROI analysis. (Supporting Information Figure S1) To exclude possible habituation to the stimulus (Figure 3), we verified the consistency of the response and activation amplitudes for each animal. The ROI selected in the hippocampus based on the activation map showed a clear activation pattern with stable amplitude of the response throughout the measurement. The results were consistent for each animal for all the ROIs, and for the 3 repeated scans. No habituation to the stimulus was observed (all $p > 0.05$, Mann-Kendall test), during the 1-h experiment, allowing us to combine data for high temporal resolution analysis.

Time-to-peak and amplitude of fMRI activation acquired from 200-ms temporal resolution data varied between the different brain regions (Figure 4). No correlation between the time-to-peaks across animals was present. The method provided stable results across 3 averages: mean (averaged across animals) time-to-peak variation from 3 averages from 0.57 s for Pir&Ins ROI (with time-to-peak 6.8 s, 8% coefficient of variation), to 1.44 s for MamN ROI (with time-to-peak 10.8 s, 13% coefficient of variation). In the IL/PL (5.70 ± 1.56 s) and amygdala (7.58 ± 2.30 s), the peak occurred before the end of the stimulus, while in the lateral hypothalamus (8.96 ± 2.49 s), ventral hippocampus (10.04 ± 1.78 s), and mammillary nuclei (10.50 ± 1.71 s) the peak tended to occur towards the end of the stimulus. The differences were statistically significant, and the statistically significant pairs are indicated in Figure 4C. However, there were no differences in the onset time of the activation (all $p > 0.5$).

The differences in 200-ms temporal resolution data were similar to those acquired from the 2-s temporal resolution interpolated data (Figure 5). The difference in the time-to-peak between the lateral hypothalamus and mammillary bodies was significant in 2-s data ($p = 0.033$), but not in 200-ms data ($p = 0.088$); otherwise, significance levels of the differences were similar.

Group ICA found a component related to the burst suppression from original 2-s temporal resolution fMRI data (Figure 6). This component covered most of the cortex and was taken as an ROI for further analysis. Mean signals from this ROI were acquired for 200-ms temporal resolution resampled data and 2-s interpolated data. The activation curve acquired with 200-ms temporal resolution was consistent over all rats and followed typical HRF activation pattern, while the shape of the response could not be determined with 2-s temporal resolution. The amplitude of the peak was significantly lower with 2-s temporal resolution ($p = 0.03$).

Discussion

In this study, we aimed to establish a framework for a high temporal resolution EVER-SWIFT fMRI method using the MB-SWIFT technique for monitoring the fMRI response to repeated events. The method was shown to work on controlled stimuli, but it does not yield significant benefits with long stimuli. EVER-SWIFT, however, does provide significant improvement for uncontrolled and short stimuli, such as in spontaneous

brain activity. DBS of the MSN was used to explore the performance and reliability of the method. Isoflurane-induced burst suppression state was chosen for testing the algorithm in case of spontaneously recurring events.

Prior studies demonstrated that the blood oxygenation level-dependent (BOLD) effect closely reflects single- and multi-unit neural activity on laminar resolution[19], and distinct events separated by a few tens of milliseconds could be monitored. Here, we further investigated the possibility of detecting short temporal events using fMRI. This was possible by using MB-SWIFT, which differs from conventional MRI pulse sequences in that it has essentially no acquisition delay. Because we demonstrated that fMRI responses detected with SWIFT are governed primarily by a blood inflow effect during neural activation[25], we anticipated monitoring the temporal interrelationship between cerebral blood flow and neural activation using MB-SWIFT.

A method closely resembling the EVER-SWIFT approach was proposed by Silva and Koretsky (2002). It measures the same line of the Cartesian k-space trajectory for all images and then repeats the measurement with another k-space line. The hemodynamic response to the somatosensory stimulus was tracked with a 40-ms time resolution. Switching from a Cartesian trajectory to a radial trajectory, as we did in our approach, allows for more flexibility in the timing of events, as each spoke is acquired in less than a millisecond. This also allows us to collect data from detectable random events replacing the stimuli. Moreover, as the center of the k-space is measured for each spoke, the method is not sensitive to small movement.

In this work, we tested our method first for detecting brain activation in response to electrical DBS. fMRI measures neuronal activity indirectly, based on an increase in blood flow, blood volume, and/or blood oxygenation changes caused by neuronal activation. The HRF characterizes the shape of the activation response to a single impulse, and usually takes several seconds to peak. In rats, the time-to-peak is approximately 2 s under α-chloralose anesthesia[36], and varies with the type of anesthesia and brain region[37].

In the DBS study, we acquired similar results using 200-ms and interpolated 2-s temporal resolution, which demonstrates the reliability of the method. The reason for the finer temporal resolution providing little additional information is that responses after a relatively long DBS stimulation are slow and long-lasting, and with enough repetitions, can be measured with close to similar accuracy with 2-s temporal resolution.

We determined that the time-to-peak and shapes of DBS responses differ between brain regions. Noticeably, cortical areas, which are connected by several synapses, exhibited the fastest time-to-peak interval, while the areas directly connected to the area of stimulation, such as the hippocampus, exhibited the longest time-to-peak response. The most likely explanation for this discrepancy is antidromic stimulation at the MSN of fibers of passage from these cortical areas. However, no differences in onset times were detected. The differences in the time-to-peaks are likely related to the hemodynamic response, not neural activity, as the

electrical potential propagation happens in the millisecond range, and even with 200-ms time resolution, it would be impossible to see the difference related to neural activity. Recent work revealed that cortical and subcortical fMRI responses to visual stimuli differ significantly in humans[38] and cats[39], with subcortical responses being narrower and faster. The differences our results might be due to differences in the type of stimulation used, activation sites and/or type of anesthesia. It has been proposed that neurovascular coupling is altered in subcortical structures of the rat compared with cortical areas[40]. Interestingly, in most regions, we see the activation peak before the stimulation is complete, which might indicate the nonlinearity of the response function or intra stimulation block habituation.

In addition to DBS, we tested the EVER-SWIFT method for detecting the activation during isoflurane burst suppression as a model for short-duration spontaneous brain activity. During isoflurane anesthesia, fMRI data shows activation in the cortical area synchronous with EEG[35]. We acquired a consistent typical gamma response curve from all 3 animals, and 200-ms temporal resolution allowed us to define an accurate response curve for brain events lasting 2 – 3 s, while responses could be seen only in one time-point of a time series with 2-s temporal resolution. In contrast to external stimuli, spontaneous events are not anymore exactly similar. However, averaging between many events provides us with the mean activation curve. Application of the method to spontaneous events requires more data to be collected, as some parts of the k-space are imaged more than others.

It is important to note that the contrast of fMRI with the MB-SWIFT method is different from the more frequently used BOLD contrast. Even though not characterized in detail, the contrast in MB-SWIFT-fMRI has been demonstrated to originate primarily from the inflow effect as it depends on the flip angle and is substantially reduced by saturation of the inflowing spins[25]. The shapes and timings of response curves obtained in this study both for long- and short-lasting brain activity are consistent with cerebral blood flow dominating as contrast mechanism. Furthermore, the contribution of physiological noise (heart and breathing pulsation) to MB-SWIFT fMRI has not been characterized, however we assume that to be smaller than that of EPI-based fMRI as the contribution of physiological noise has been shown to be echo time-dependent[41]. We observed strong vascular contributions in the lower part of the brain, for example, in the mammillary nuclei ROI (not shown). However, as the pause durations between the stimuli were randomized, vascular signals were not amplified in the resampled images.

EVER-SWIFT method relies on the assumption of the similarity of the recurring events. When the events are not similar, the differences will be averaged, and if the differences are symmetrically distributed, the results will not be biased. However, the approach should not be used in case of the highly different events.

Based on the results of the current study, we conclude that EVER-SWIFT is expected to be helpful for detecting fast dynamics in either stimulus-induced or spontaneously recurring events, including, for example,

hippocampal ripples or dentate spikes that can be independently recorded due to small artefact that MB-SWIFT causes to electrical recordings[24]. That analysis would require finer temporal resolution, which means acquiring more data and potentially using more sophisticated reconstruction for a partially sampled k-space. In addition, though the method is not sensitive to small motion, bigger movement might require correction before the reordering of spokes.

Conclusions

A novel EVER-SWIFT fMRI method allows for 3D imaging of repeating events in the brain with higher temporal resolution than the conventional techniques used for fMRI acquisition. The method is easily applicable and useful for DBS studies, where the responses are stable and different between brain regions. In addition, this method can be used for characterizing the fast dynamics of spontaneously recurring events with superior accuracy compared with conventional, low time-resolution approaches.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Figure legends

Figure 1. Schematic representation of the resampling method applied to a sequence with radial k-space sampling. A. Application to stimuli data. A part of the k-space is taken for each time-point from different events, resulting in a higher temporal resolution in the combined event. The starts of the events are shifted so that a different portion of k-space is acquired each time (marked with blue double-headed arrows). B. Resampling scheme when spontaneous events are present. As we do not control the starting place of the event, the aim of the algorithm is to choose events combining which we achieve full coverage of the k-space with desired temporal resolution.

Figure 2. Data processing pipeline. First, the data were transformed to radial spokes, then both spoke reordered and original data underwent image reconstruction, motion correction and coregistration to the reference image. General linear model (GLM) analysis was performed for DBS data and independent component analysis (ICA) for burst suppression data to determine the regions of interest (ROIs). Original data were interpolated, and spoke reordered data were averaged before the ROI analysis.

Figure 3. Evoked response to the MSN stimulation. A. Group fMRI activation maps. $p < 0.0001$ thresholded at $z = 3.7$. B. Original time series from a representative animal with 2-s time resolution from 3 repetitions, including ten 10-s stimulus blocks each. Data are averaged from the hippocampal ROI marked in A with an arrow and a circle. Red line represents smoothed signal curve.

Figure 4. Response to the DBS in the selected brain regions detected with EVER-SWIFT with 200-ms time resolution. A. fMRI responses in selected ROIs normalized to the baseline. Each line shows a smoothed response with 200-ms temporal resolution from 1 animal. Red asterisks indicate peaks of activity. The stimulus was applied between the 2 dotted red lines and lasted 10 s. B. Time-to-peaks for selected ROIs and statistically significant differences between ROIs. VHipp – ventral hippocampus, Amyg – amygdala, MamN – mammillary nuclei, PrL&IL – prelimbic and infralimbic cortices, Pir&Ins – piriform and insular cortex, LHTh – lateral hypothalamus. *: p-value < 0.05, **: p-value < 0.01 (paired t-test, FDR-corrected for 15 multiple comparisons).

Figure 5. Response to the DBS in the selected brain regions reconstructed with 2-s temporal resolution. A. fMRI responses in selected ROIs normalized to the baseline. Each line shows a smoothed response with 200-ms temporal resolution from 1 animal. Red asterisks indicate peaks of activity. The stimulus was applied between the 2 dotted red lines and lasted 10 s. B. Time-to-peaks for selected ROIs and statistically significant differences between ROIs.

Figure 6. Application of EVER-SWIFT to the data acquired during isoflurane burst suppression. A. An example of Hilbert-transformed amplitude of EEG signal from a representative animal during 1.8 % isoflurane anesthesia. B. An ROI made from an ICA component related to the burst suppression from the original data. C. Mean signal around burst suppression from ROI shown in B reconstructed with 2-s and 200-ms time resolutions, respectively. Orange, green, and blue lines correspond to 3 different animals, and bold gray line corresponds to their mean. Peak values in original data and in EVER-SWIFT are compared, $p = 0.03$.

Supporting Information Figure S1. ROIs used for analysis. VHipp – ventral hippocampus, Amyg – amygdala, MamN – mammillary nuclei, LHTh – lateral hypothalamus, Pir&Ins – piriform and insular cortex, PrL&IL – prelimbic and infralimbic cortices.

Supporting Information Figure S2. Raw MB-SWIFT data indicating data quality A. MB-SWIFT data from a representative animal before and after spoke reordering. B. Electrode position from an anatomical scan of a representative animal. C. Mean signal from a hippocampal ROI (same as in Fig. 2) from 3 averages for original data, spoke-reordered data and mean of 3 averages.

Supporting Information Text 1. *Algorithm for resampling spontaneously occurring events.* Let us assume that for desired temporal resolution we need n spokes from each event to fully cover the k-space. So, if a spontaneous event starts at the time of acquisition of spoke number s, this event will be represented by spokes from s to $s + n - 1$. We used an algorithm that tried to combine events into groups, so that each group covered all the spokes and groups had as few events in common as possible, while also minimizing the number of events in each group.

1. The output group of events is initially empty. $G = \{\}$
2. All the events were arranged based on starting spoke s in ascending order $S = \{E_1, \dots, E_k\}$.
3. The algorithm examined if there was a distance between adjacent event starts longer than n spokes in S. If yes, the algorithm failed. Otherwise, the algorithm continued.
4. The algorithm chose a random event E_r from S and added it to the output group G (let's assume E_r starts from spoke m).
5. The algorithm selected all the events from S that started with spokes from $m + 1$ to $m + n$ and placed them into group R.
6. The algorithm checked if E_r is in the group R. If yes, the algorithm stopped, and group G is complete. Otherwise, the algorithm continued.
7. The algorithm chose a random event E_l from the group R, added E_l to G, updated m to E_l's starting point, emptied group R, and returned to step 5.

The algorithm produced a group of events covering all the spokes. The algorithm was repeated for 30 times, resulting in 30 groups of events, and the group with the fewest number of events was selected for further analysis. Then 2 more groups were selected so that the number of common events between the groups was minimized and did not exceed 3.

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