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Advances in Spiral fMRI: A High-resolution Study with

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Single-shot Acquisition

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Highlights

This work reports the first fMRI study at 7T with high-resolution spiral readout
gradient waveforms.

- We achieve spiral fMRI with sub-millimeter resolution (0.8 mm, FOV 230 mm),
 acquired in a single shot (36 slices in 3.3 s).
- Spiral images exhibit intrinsic geometric congruency to anatomical scans, and
 spatially specific activation patterns.
- Image reconstruction rests on a signal model expanded by measured trajectories and
 static field maps, inverted by cg-SENSE.

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We assess generalizability of the approach for spiral in/out readouts, providing two
 images per shot (1.5 mm resolution).

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Abstract

Spiral fMRI has been put forward as a viable alternative to rectilinear echo-planar imaging, in particular due to its enhanced average k-space speed and thus high acquisition efficiency. This renders spirals attractive for contemporary fMRI applications that require high spatiotemporal resolution, such as laminar or columnar fMRI. However, in practice, spiral fMRI is typically hampered by its reduced robustness and ensuing blurring artifacts, which arise from imperfections in both static and dynamic magnetic fields.

Recently, these limitations have been overcome by the concerted application of an expanded signal model that accounts for such field imperfections, and its inversion by iterative image reconstruction. In the challenging ultra-high field environment of 7 Tesla, where field inhomogeneity effects are aggravated, both multi-shot and single-shot 2D spiral imaging at sub-millimeter resolution was demonstrated with high depiction quality and anatomical congruency.

41 In this work, we further these advances towards a time series application of spiral readouts, namely, single-shot spiral BOLD fMRI at 0.8 mm in-plane resolution. We 42 demonstrate that high-resolution spiral fMRI at 7 T is not only feasible, but delivers both 43 excellent image quality, BOLD sensitivity, and spatial specificity of the activation maps, 44 with little artifactual blurring. Furthermore, we show the versatility of the approach with 45 a combined in/out spiral readout at a more typical resolution (1.5 mm), where the high 46 acquisition efficiency allows to acquire two images per shot for improved sensitivity by 47 48 echo combination.

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50 **1** Introduction

Functional MRI (fMRI) is presently the most prominent technique to study human brain 51 function non-invasively, owing to its favorable spatiotemporal resolution regime with 52 appealing functional sensitivity. Within this regime, specific research questions require 53 different trade-offs between spatial and temporal resolution. On the one hand, ultra-high 54 spatial resolution fMRI (with sub-millimeter voxel size) successfully targets smaller 55 organizational structures of the brain, such as cortical laminae (Fracasso et al., 2016; 56 Huber et al., 2017a; Kashvap et al., 2018; Kok et al., 2016; Lawrence et al., 2018; Martino et 57 al., 2015; Muckli et al., 2015; Siero et al., 2011) and columns (Cheng et al., 2001; Feinberg 58 et al., 2018; Yacoub et al., 2008). For subcortical sites, due to the limited signal-to-noise 59 60 ratio (SNR), high-resolution (1-1.5 mm) fMRI is more prevalent (but see (Wang et al., 2020)) to characterize, for example, the superior (Savjani et al., 2018; Singh et al., 2018) 61 and inferior colliculi (De Martino et al., 2013; Sitek et al., 2019), as well as the subthalamic 62 nucleus (de Hollander et al., 2017) and midbrain (D'Ardenne et al., 2008). However, both 63 high and ultra-high spatial resolution fMRI require compromises on field of view (FOV) 64 coverage or temporal bandwidth, i.e., volume repetition time (TR). On the other hand, 65 66 fast sequences with TRs on the order of 0.5 seconds and below are important for 67 advanced analysis approaches, for example, to adequately sample physiological fluctuations (Lewis et al., 2016; Smith et al., 2013; Uğurbil et al., 2013), at the expense of 68 lowering spatial resolution (2-4 mm). 69

One means to simultaneously advance the spatial and temporal resolution boundaries of fMRI is to maximize acquisition efficiency, i.e., sampled k-space area (or volume) per unit time. Therefore, fMRI nowadays almost exclusively relies on rectilinear echo-planar imaging (EPI, (Cohen and Schmitt, 2012; Mansfield, 1977; Schmitt et al., 2012)), where acquisition efficiency is favorable due to optimal acceleration and high terminal velocity along the straight k-space lines traversed.

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To expand spatiotemporal resolution beyond the capabilities of EPI alone, the main strategy has been parallel imaging acceleration (Griswold et al., 2002; Pruessmann et al., 1999; Sodickson and Manning, 1997), in combination with simultaneous multi-slice or 3D excitation (Breuer et al., 2006; Larkman et al., 2001; Poser et al., 2010; Setsompop et al., 2012). In terms of k-space coverage per unit time, the benefit of parallel imaging lies in expanding the cross section of the k-space neighborhood covered along the readout trajectory (Pruessmann, 2006), i.e., a band in 2D or tube in 3D.

However, another key determinant of acquisition efficiency or speed of coverage is
average velocity along the trajectory, i.e., instantaneous gradient strength. On this count,
EPI is wasteful because it includes many sharp turns traversed at low speed due to the
limited gradient slew rate.

87 Substantially higher average k-space speed and thus acquisition efficiency for fMRI is achieved with spiral trajectories (Barth et al., 1999; Glover, 2012; Noll et al., 1995), which 88 avoid sharp turns by distributing curvature more evenly (Ahn et al., 1986; Likes, 1981; 89 Meyer et al., 1992). Typically, single-shot variants winding out of k-space center, e.g., on 90 an Archimedean spiral, are prevalent (Glover, 1999; Meyer et al., 1992; Weiger et al., 91 2002), but different acquisition schemes, such as spiral-in (Börnert et al., 2000) or 92 combined in/out readouts (Glover and Law, 2001; Glover and Thomason, 2004) have been 93 proposed. High-resolution fMRI studies have occasionally employed spirals as well (Jung 94 et al., 2013; Singh et al., 2018), including first applications of laminar fMRI (Ress et al., 95 2007) and regionally optimized acquisitions, e.g., for the hippocampus (Preston et al., 96 2010) or superior colliculus (Katyal et al., 2010; Savjani et al., 2018). Common to these 97 98 approaches is a reduction of acquisition efficiency in favor of robustness by acquiring kspace in multiple shots with shorter spiral readouts. 99

Despite these efforts, routine use of spiral fMRI has not been established, due to the following three challenges (Block and Frahm, 2005; Börnert et al., 1999): First, spirals are sensitive to imperfect magnetic field dynamics (drifts, eddy currents and other gradient

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imperfections) which lead to blurring and image distortions. Secondly, non-uniformity of
the static B_o field, caused by varying susceptibility of the imaged tissues, likewise causes
blurring (Bernstein et al., 2004, Chap. 17). Finally, in combination with parallel imaging,
spirals pose a somewhat greater reconstruction challenge than Cartesian trajectories
(Pruessmann et al., 2001).

Recently, these obstacles have been overcome (Engel et al., 2018; Kasper et al., 2018; Wilm 108 et al., 2017) by (1) employing an expanded signal model that incorporates coil sensitivity 109 encoding as well as independently measured static and dynamic field imperfections 110 (Wilm et al., 2011), and (2) the inversion of this model by an accompanying iterative 111 image reconstruction (Barmet et al., 2005; Man et al., 1997; Pruessmann et al., 2001; 112 Sutton et al., 2003). This approach enabled the use of long spiral readouts (on the order of 113 50 ms at 7 Tesla), while maintaining high image quality and anatomical fidelity. In 114 particular, such enhanced spiral acquisition efficiency was demonstrated by 115 accomplishing T₂*-weighted images with a nominal in-plane resolution of 0.8 mm in a 116 single shot. Ultimately, these findings hold promise that spiral fMRI can now indeed 117 profit from the theoretical benefits of enhanced acquisition efficiency to expand the 118 spatiotemporal boundaries of fMRI. 119

Based on these advances in expanded signal modeling and inversion, in this work, we explore the feasibility and utility of sub-millimeter single-shot spiral fMRI. Specifically, we first assess image quality and temporal stability of fMRI time series obtained with the expanded signal model and algebraic reconstruction. We further evaluate the resulting functional sensitivity and spatial specificity of reference activation patterns, elicited by an established visual quarter-field stimulation paradigm.

Finally, we explore the versatility of the approach with a combined in/out spiral readout at a more typical resolution (1.5 mm). Here, two images per shot can be acquired, translating the high acquisition efficiency of the spiral into enhanced functional

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- sensitivity by echo combination (Glover and Law, 2001; Glover and Thomason, 2004; Law
- 130 and Glover, 2009).

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132 **2 Methods**

133 **2.1 Setup**

All data was acquired on a Philips Achieva 7 Tesla MR System (Philips Healthcare, Best,
The Netherlands), with a quadrature transmit coil and 32-channel head receive array
(Nova Medical, Wilmington, MA, USA).

Concurrent magnetic field monitoring was performed using 16 fluorine-based NMR field 137 138 probes, which were integrated into the head setup via a laser-sintered nylon frame positioned between transmit and receive coil (Fig. 1 in Engel et al., 2018). Probe data were 139 recorded and preprocessed (filtering, demodulation) on a dedicated acquisition system 140 (Dietrich et al., 2016a). The final extraction of probe phase evolution and projection onto 141 a spherical harmonic basis set (Barmet et al., 2008) was performed on a PC, yielding 142 readout time courses of global phase k_0 and k-space coefficients k_x, k_y, k_z with 1 MHz 143 bandwidth. 144

For the fMRI experiments, visual stimulus presentation utilized VisuaStim LCD goggles
(Resonance Technology Inc., Northridge, CA, USA). A vendor-specific respiratory bellows
and finger pulse plethysmograph recorded subject physiology, i.e., respiratory and cardiac
cycle.

149 2.2 fMRI Paradigm and Subjects

Seven healthy subjects (4 female, mean age 25.7 +/- 4.1 y) took part in this study, after written informed consent and with approval of the local ethics committee. One subject was excluded from further analysis due to reduced signal in multiple channels of the head receive array. Thus, six subjects were analyzed for this study.

The paradigm, a modified version of the one used in (Kasper et al., 2014), comprised two blocks of 15 s duration that presented flickering checkerboard wedges in complementary

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pairs of the visual guarter-fields. In one block, upper left and lower right visual field were 156 stimulated simultaneously (condition ULLR), while the other block presented the wedges 157 in the upper right and lower left quarter-fields (condition URLL). These stimulation 158 blocks were interleaved with equally long fixation periods. To keep subjects engaged, they 159 had to respond to slight contrast changes in the central fixation cross via button presses 160 of the right hand. A single run of the paradigm took 5 min (5 repetitions of the ULLR-161 162 Fixation-URLL-Fixation sequence). For both of the spiral sequence designs (highresolution spiral-out and combined spiral in/out, see next section), a single run of the 163 paradigm was performed per subject. 164

165 2.3 Spiral Trajectories and Sequence Timing

Spiral fMRI was based on a slice-selective multi-slice 2D gradient echo sequence (Fig. 1) with custom-designed spiral readout gradient waveforms. For every third slice, i.e., a TR of 270 ms, concurrent field recordings were performed on the dedicated acquisition system (Dietrich et al., 2016a), with NMR field probes being excited a few milliseconds prior to readout gradient onset (Fig. 1, bottom row, (Engel et al., 2018)).

For the spiral trajectories, we selected two variants that had previously provided highquality images in individual frames (Fig. 2 in (Engel et al., 2018)): a high-resolution case winding out of k-space center on an Archimedean spiral (spiral-out, Fig. 1, black gradient waveform), and a combined dual-image readout first spiraling into k-space center, immediately followed by a point-symmetric outward spiral (spiral in/out (Glover and Law, 2001)), Fig. 1, blue gradient waveform).

The spiral-out gradient waveform was designed to deliver the highest spatial resolution possible under several constraints. First, targeting maximum acquisition efficiency in 2D commands a single-shot 2D readout, because the sequence overhead, i.e., time spent without sampling k-space, accrues for each new excitation. Second, the parallel imaging capability of our receiver array at 7 T allowed for an in-plane acceleration factor of R = 4

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(determining the spacing of the spiral revolutions, i.e., FOV). We based this choice on 182 previous experience with spirals of such undersampling using this setup (Engel et al., 183 2018; Kasper et al., 2018), which were free of aliasing artifacts or prohibitive g-factor 184 noise amplification. Third, the requirement of concurrent field recordings for the whole 185 spiral readout limited its maximum duration to below 60 ms. This is the approximate 186 187 lifetime of the NMR field probe signal, after which complete dephasing occurs in a subset of probes for this specific setup, governed by their T_2^* decay time of 24 ms (Engel et al., 188 2018) and distance from iso-center when applying higher-order shims. Finally, the 189 gradient system specifications constrain the maximum possible resolution (or k-space 190 excursion) of an Archimedean spiral with prescribed FOV and duration. Here, we used 191 the optimal control algorithm by (Lustig et al., 2008) to design time-optimal spiral 192 gradient waveforms of 31 mT/m maximum available gradient amplitude, and a 160 193 mT/m/ms slew rate limit, chosen for reduced peripheral nerve stimulation. 194

Overall, these requirements led to a spiral-out trajectory with a nominal in-plane resolution of 0.8 mm (for a FOV of 230 mm), at a total readout acquisition time (TAQ) of 57 ms. BOLD-weighting was accomplished by shifting the readout start, i.e., TE, to 20 ms.

For the spiral in/out, we followed the same design principles, targeting a minimum dead time after excitation, and a symmetric readout centered on a TE of 25 ms, slightly shorter than reported T₂* values in cortex at 7 T (Peters et al., 2007). This resulted in a gradient waveform lasting 39 ms, with a nominal resolution of 1.5 mm for each half-shot of the trajectory.

All other parameters of both spiral sequences were shared, in order to facilitate comparison of their functional sensitivity. In particular, slice thickness (0.9 mm) and gap (0.1 mm) were selected for near-isotropic sub-mm resolution for the spiral-out case, while still covering most of visual cortex. For each slice, the imaging part of the sequence (Fig. 1) was preceded by a fat suppression module utilizing Spectral Presaturation with Inversion Recovery (SPIR, (Kaldoudi et al., 1993)).

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The sequence duration totaled 90 ms per slice for the spiral-out sequence (TE 20 ms + TAQ 60 ms + SPIR 10 ms), which was maintained for the spiral in/out, even though a shorter imaging module would have been possible. To arrive at a typical volume repetition time for fMRI, we chose to acquire 36 slices (TR 3.3 s). Each functional run comprised 100 volume repetitions, amounting to a scan duration of 5.5 min.

214 2.4 Image Reconstruction

Image reconstruction rested on an expanded model of the coil signal s_{γ} (Wilm et al., 2011), that – besides transverse magnetization m – incorporates coil sensitivity c_{γ} , as well as phase accrual by both magnetostatic B_o field inhomogeneity (off-resonance frequency $\Delta \omega_0$) (Barmet et al., 2005) and magnetic field dynamics k_l expanded in different spatial basis functions b_l (Barmet et al., 2008):

$$s_{\gamma}(t) = \int_{V} c_{\gamma}(\mathbf{r}) \cdot m(\mathbf{r}) \cdot e^{i \sum_{l} k_{l}(t) b_{l}(\mathbf{r})} \cdot e^{i \Delta \omega_{0}(\mathbf{r})t} \cdot dV$$
(1)

with coil index γ , sampling time t, imaging volume V, and location vector $\mathbf{r} = [x \ y \ z]^T$.

For 2D spiral imaging without strong higher order eddy currents (e.g., as induced by 221 diffusion encoding gradients), this model can be computationally reduced (Engel et al., 222 2018) to facilitate iterative inversion. To this end, we (1) considered only field dynamics 223 contributing to global phase k_0 (such as B_0 drifts and breathing modulation) and spatially 224 linear phase, i.e., k-space $\mathbf{k} = [k_x k_y k_z]$, as provided by the concurrent field recordings, 225 and (2) restricted the integration to the excited 2D imaging plane by shifting the 226 coordinate origin to the slice center r_0 , effectively factoring slice-orthogonal field 227 dynamics out of the integral: 228

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 $s_{\gamma}(t)$

$$= \int_{V} c_{\gamma}(\mathbf{r}) \cdot m(\mathbf{r}) \cdot e^{i(k_{0}(t) + \mathbf{k}(t) \cdot \mathbf{r})} \cdot e^{i\Delta\omega_{0}(\mathbf{r})t} \cdot dV$$

$$= e^{i(k_{0}(t) + \mathbf{k}(t) \cdot \mathbf{r}_{0})} \int_{V} c_{\gamma}(\mathbf{r}) \cdot m(\mathbf{r}) \cdot e^{i\mathbf{k}(t) \cdot (\mathbf{r} - \mathbf{r}_{0})} \cdot e^{i\Delta\omega_{0}(\mathbf{r})t} \cdot dV$$
(2)

For the demodulated coil signal $\tilde{s_{\gamma}}(t) = s_{\gamma}(t) \cdot \exp(-i(k_0(t) + \mathbf{k}(t) \cdot \mathbf{r_0})))$, the discretized version of eq. (2) – respecting finite spatial resolution and dwell time of the acquisition system – reads as a system of linear equations

$$\tilde{s}_{(\gamma,\tau)} = \sum_{\rho} E_{(\gamma,\tau),\rho} m_{\rho} \tag{3}$$

with sampling time index τ , voxel index ρ , $\tilde{s}_{(\gamma,\tau)} = \tilde{s}_{\gamma}(t_{\tau})$, encoding matrix element $E_{(\gamma,\tau),\rho} = c_{\gamma}(\boldsymbol{r}_{\rho}) \cdot e^{i\boldsymbol{k}(t_{\tau})\cdot(\boldsymbol{r}_{\rho}-\boldsymbol{r}_{0})} \cdot e^{i\Delta\omega_{0}(\boldsymbol{r}_{\rho})t_{\tau}}$, and $m_{\rho} = m(\boldsymbol{r}_{\rho})$.

The matrix-vector form of eq. (3) is a general linear model,

$$\tilde{s} = E m$$
 (4)

and can be efficiently solved iteratively by a conjugate gradient (CG) algorithm (Pruessmann et al., 2001; Shewchuk, 1994). As mentioned above, the restriction to first order field dynamics enables acceleration of the ensuing matrix-vector multiplications by (reverse) gridding and fast Fourier transform (FFT) (Beatty et al., 2005; Jackson et al., 1991). Off-resonance effects are also efficiently approximated by FFT using multifrequency interpolation (Man et al., 1997).

This image reconstruction algorithm was applied equivalently to the spiral-out and spiral in/out data with a fixed number of 10 iterations and no further regularization (e.g., Tikhonov). Note, however, that for the latter both field recordings and coil data were split into their in- and out-part and reconstructed separately, yielding two images per shot.

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Taken together, the in-house Matlab R2018a (The MathWorks, Natick, MA, USA) implementation of this algorithm led to total reconstruction times on a single CPU core of about 10 min per slice for the high-resolution spiral-out image and 1.5 minutes for the spiral-in or -out image. In order to reconstruct the 3600 2D images per fMRI run, reconstruction was parallelized over slices on the university's CPU cluster. Depending on cluster load, reconstructions typically finished over night for the high-resolution spiral out, and within 2 h for the spiral in/out data.

The auxiliary input data for the expanded signal model, i.e., spatial maps for static B_0 field inhomogeneity $\Delta \omega$ and coil sensitivity c_{γ} , were derived from a separate fully sampled multi-echo (ME) Cartesian gradient echo reference scan of 1 mm in-plane resolution with 6 echoes, $TE_1 = 4$ ms, $\Delta TE = 1$ ms (Kasper et al., 2018), and slice geometry equivalent to the spiral sequences. Image reconstruction proceeded as described above for this scan, albeit omitting the sensitivity and static B_0 map terms. The latter was justified by the high bandwidth of the Cartesian spin-warp scans (1 kHz).

259 Sensitivity maps were then computed from the first-echo image, normalizing single coil 260 images by the root sum of squares over all channels, while the B_o map was calculated by 261 regressing the pixel-wise phase evolution over echo images. Both maps were spatially 262 smoothed and slightly extrapolated via a variational approach (Keeling and Bammer, 263 2004).

264 2.5 Data Analysis

265 2.5.1 Image Quality Assessment

The suitability of the raw imaging data for high-resolution fMRI was assessed in terms of both sensitivity and spatial specificity. No smoothing was performed for any analysis in this section.

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For sensitivity, we evaluated the temporal statistics of the images, i.e., signal-tofluctuation noise ratio (SFNR), standard deviation (SD) and coefficient of variation (CoV) maps (Welvaert and Rosseel, 2013), defined as

$$SFNR(\boldsymbol{r}_{\rho}) = \frac{\overline{m(\boldsymbol{r}_{\rho})}}{SD(m(\boldsymbol{r}_{\rho}))},$$

$$CoV = \frac{1}{SFNR},$$
(5)

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where the bar denotes averaging over volumes of a run.

Our assessment of spatial specificity was based on the ME reference scan, which exhibits a high geometric veracity due to its spin-warp nature, i.e., high bandwidth. We overlaid the contour edges (intensity isolines) of the mean (over echoes) of the ME images onto the mean spiral images $\overline{m(r_{\rho})}$ to inspect the congruency of anatomical boundaries between the scans.

To reduce the impact of subject motion on both assessments, the volumes of the fMRI 279 280 time series were first realigned to each other using a 6-parameter rigid-body within-281 contrast registration, as implemented in SPM (Friston et al., 1996). Then, the mean ME 282 scan was co-registered to the resulting mean realigned fMRI scan, Importantly, both 283 operations were limited to six-parameter rigid-body registration, such that nonlinear 284 geometric distortions between sequences were not corrected through this preprocessing 285 step. Furthermore, to facilitate visual comparison and contour edge creation, mean ME 286 and spiral images were bias-field corrected using unified segmentation (Ashburner and 287 Friston, 2005).

Furthermore, for quantitative assessment, we extracted contour lines from the thresholded gray matter tissue probability maps ($p \ge 90\%$) retrieved by unified segmentation for both structural and functional images. To have highest contrast and

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resolution congruence, we compared the last echo of the 1 mm ME scan (TE 10 ms) to the 291 o.8 mm spiral-out scan (TE 20 ms). We computed histograms and contour distance maps, 292 i.e., contours from the structural data whose color coding per voxel reflects their distance 293 to the corresponding contour in the functional image. For the histograms, we evaluated 294 the contour distance both over the whole imaging FOV and within an ROI of early visual 295 cortex, the primary site of expected activation for our functional paradigm. Specifically, 296 the ROI mask was created using the SPM Anatomy Toolbox Version 2.2b (Eickhoff et al., 297 2007, 2006, 2005) and combined probabilistic maps of human occipital cortex V1, V2 298 (Amunts et al., 2000), V3, V4 (ventral (Rottschy et al., 2007) and dorsal (Kujovic et al., 299 2013)), lateral occipital cortex (Malikovic et al., 2016) and V5/MT (Malikovic et al., 2007). 300 The combined mask was warped into the individual subject geometry by the inverse 301 deformation field retrieved through the unified segmentation mentioned above, and 302 slightly dilated by 3 voxels to account for any inter-subject variability in visual cortex. 303

All computations were performed in Matlab R2019b, using the Unified NeuroImaging Quality Control Toolbox (UniQC, (Bollmann et al., 2018; Frässle et al., 2021)), and SPM12 (Wellcome Centre for Human Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/).

308 2.5.2 BOLD fMRI Analysis

The main goal of this analysis was to assess the functional sensitivity and spatial specificity of the spiral fMRI sequences at the single-subject level under standard paradigm and preprocessing choices. Note that, unless explicitly stated otherwise, all activation maps and their quantification (e.g., cluster extent, peak t-values) are therefore reported after smoothing.

Equivalent preprocessing steps were applied to all spiral fMRI runs using SPM12. After slice-timing correction, we employed the pipeline described in the previous section (realignment, co-registration, bias-field correction via unified segmentation). Finally, the

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functional images were slightly smoothed with a Gaussian kernel of o.8mm FWHM, i.e.,
the voxel size of the high-resolution scan.

The general linear model (GLM) contained regressors of the two stimulation blocks (ULLR and URLL) convolved with the hemodynamic response function (HRF), as well as nuisance regressors for motion (6 rigid-body parameters) and physiological noise (18 RETROICOR (Glover et al., 2000) regressors, as specified in (Harvey et al., 2008)), extracted by the PhysIO Toolbox (Kasper et al., 2017).

To characterize functional sensitivity, we evaluated the differential t-contrasts +/- (ULLR-URLL) and report results at an individual voxel-level threshold of p < 0.001 (t > 3.22). For quantification in the results tables, we report activations under whole-brain family-wise error (FWE) correction at the cluster level (p < 0.05), given this voxel-level threshold (p < 0.001) for cluster definition. If not noted otherwise in the figure, we omitted multiple-comparison correction in the visualization of the activation maps, to study their spatial extent and specificity.

Spatial specificity of the activation was gualitatively assessed by overlaying the 331 thresholded t-contrast maps for both contrasts onto the anatomically veridical mean ME 332 image. We checked whether activation patterns were restricted to gray matter regions of 333 visual cortex, as well as whether the spatial separation and symmetry of activations were 334 linked to distinct guarter-field stimulation patterns, as expected by the retinotopic 335 organization of visual cortex (Engel et al., 1997; Wandell et al., 2007; Warnking et al., 336 2002). Furthermore, we evaluated the individual contrasts for the ULLR and URLL 337 stimulation blocks to assess the spatial overlap of their activation patterns as an 338 alternative measure of functional specificity (since the differential contrasts cannot 339 overlap by design). 340

The quantification of functional spatial specificity relied on the tissue probability maps extracted via unified segmentation from the structural scan (mean ME). To reduce the number of uncategorized voxels, we chose a liberal exceedance threshold of 60 % to

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define the individual tissue classes (gray matter (GM), white matter (WM), cerebrospinal 344 fluid (CSF)). Of the remaining voxels, those that exceeded 30 % probability for two tissue 345 classes were categorized as gray/white matter boundary (GM/WM interface) or pial 346 surface (GM/CSF interface). All other voxels were labeled as ambiguous. We then 347 evaluated the share of significantly activated voxels for the differential t-contrasts +/-348 (ULLR-URLL) after multiple comparison correction (p < 0.05 cluster-level FWE corrected 349 with a cluster-forming voxel threshold of p < 0.001). This analysis was performed for both 350 the whole imaging FOV and within the ROI of early visual cortex, as defined at the end of 351 the previous section (2.5.1). We repeated this analysis for activation maps derived from 352 unsmoothed data to study the impact of smoothing on spatial specificity. 353

This overall analysis procedure was performed for the spiral-out as well as the individual 354 spiral-in and spiral-out image time series reconstructed from the spiral in/out data. As 355 spiral in/out sequences are predominantly selected for their potential gain in functional 356 sensitivity when combining spiral-in and spiral-out images (Glover and Law, 2001), we 357 additionally repeated the BOLD fMRI analysis for such a surrogate dataset ("in/out 358 combined"), but omitted the quantitative analysis of spatial specificity. We chose a signal-359 weighted combination per voxel (Glover and Thomason, 2004), which is considered the 360 361 most practical approach for echo combination (Glover, 2012):

$$m_{combined} = w \cdot m_1 + (1 - w) \cdot m_2,$$

$$w = \frac{\overline{m_1}}{\overline{m_1} + \overline{m_2}},$$
(6)

with m_1 and m_2 being the in-part and out-part voxel time series, respectively.

2.6 Code and Data Availability

Image reconstruction was performed by an in-house custom Matlab implementation of
 the cg-SENSE algorithm (Pruessmann et al., 2001). A demonstration of that algorithm is
 publicly available on GitHub (https://github.com/mrtm-zurich/rrsg-arbitrary-sense),

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with a static compute capsule for reproducible online re-execution on CodeOcean (Patzig 367 et al., 2019), which were created in the context of the ISMRM reproducible research study 368 group challenge (Maier et al., 2021; Stikov et al., 2019), albeit without the multi-frequency 369 interpolation employed here. An example reconstruction pipeline including static Bo 370 correction for the spiral data presented here is available on GitHub as well 371 (https://github.com/mrikasper/julia-recon-advances-in-spiral-fmri), utilizing MRIReco.jl 372 (Knopp and Grosser, 2021), an MRI reconstruction framework written in Julia (Bezanson 373 et al., 2017). 374

fMRI analyses performed Image and using SPM12 were 375 (https://www.fil.ion.ucl.ac.uk/spm, distributed under GPLv2) and the in-house developed 376 UniQC Toolbox (Bollmann et al., 2018), publicly available under a GPLv3 license as a beta 377 release 378 within the TAPAS software collection (https://www.translationalneuromodeling.org/tapas, (Frässle et al., 2021)). 379

All custom analysis and data visualization scripts for this publication are available on https://github.com/mrikasper/paper-advances-in-spiral-fmri. This includes both a oneclick analysis (main.m) to rerun all image statistics and fMRI analyses, as well as the automatic re-creation of all figure components found in this manuscript (main_create_figures.m), utilizing the UniQC Toolbox. More details on installation and execution of the code can be found in the README.md file in the main folder of the repository.

387 Data from this study is publicly available as part of the ETH Research Collection 388 (doi:10.3929/ethz-b-000487412, (Kasper et al., 2021)) and described in more detail in the 389 accompanying Data in Brief Article, according to the FAIR (Findable, Accessible, 390 Interoperable, and Re-usable) data principles (Wilkinson et al., 2016). For one subject 391 (SPIFI_0007), this includes both the reconstructed images in NIfTI format with 392 behavioral and physiological logfiles, to validate the analysis scripts, as well as raw coil

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and trajectory data in ISMRMRD format (in the patient coordinate system), together with
 the corresponding B_o and sensitivity maps (NIfTI).

For the other datasets, we did not obtain explicit subject consent to share all raw data in the public domain. However, we do provide the magnetic field evolution time series as ISMRMRD files (in the scanner coordinate system) within the ETH Research Collection. Mean spiral fMRI images with corresponding activation t-maps for all subjects are also made available on NeuroVault for interactive viewing ((Gorgolewski et al., 2015), https://neurovault.org/collections/6086/).

Finally, for further data dissemination, montage views of the presented image quality
metrics and statistical map overlays containing all slices and subjects are included in the

403 supplementary materials (high-resolution spiral-out: SM 1, spiral in/out: SM 2).

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405 **3 Results**

406 3.1 Spiral Image Quality, Congruency and Stability

407 In the following, we mainly present images from individual subjects (S7: Figs. 2,3, S2: Figs.

408 4,6,9, S₃: Fig. 5). However, as illustrated by Fig. 7, as well as supplementary materials SM 1
409 and SM 2, results were comparable for all six analyzed datasets.

The mean images (one run of subject S7, after realignment) of the high-resolution spiral-410 out sequence exhibit good image quality, rich in T_2^* contrast and anatomical detail 411 (Fig. 2A). In the center of the brain, no blurring is apparent, and anatomical boundaries 412 can be clearly delineated, e.g, the optic radiation, down to the single-voxel extent. 413 Moderate residual imaging artifacts (local ringing, blurring) are visible in the 414 orbitofrontal areas, at some brain/skull boundaries, and in the vicinity of larger muscles 415 and fat deposits, e.g., the temporal muscles. For more inferior slices, signal dropouts can 416 be identified at typical sites of through-plane dephasing, e.g., in the temporal lobe above 417 418 the ear canals (SM 1, subject 6) or in the orbitofrontal cortex (SM 1, subject 5). Individual frames of the time series exhibit similar features (Fig. 2B), though somewhat noisier, as 419 expected because of the reduced SNR. 420

Interestingly, the mean of the corresponding raw phase images also contains high
anatomical detail and few phase wraps (Fig. 2C), which are again located at the interface
between brain and skull or close to air cavities. Note that the unwrapped appearance of
the phase image is a feature of the B_o-map based correction (Kasper et al., 2018) and does
not require any postprocessing.

426 Mapping the temporal statistics of the spiral image time series (Fig. 3, Table 1) proves its 427 sufficient stability for functional imaging in all slices. The SFNR images (Fig. 3A) are 428 rather homogeneous, with mean values of 15.3 +/- 1.1 in cortical gray matter, averaged over 429 subjects (Table 1). A slight reduction for central brain regions is visible due to the

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diminished net sensitivity of the receiver array. Notably, no structured noise
amplification through bad conditioning of the undersampled reconstruction problem (gfactor penalty) is discernible in this area.

The SD images (Fig. 3B) corroborate this impression, showing peak values in CSF-filled 433 (lateral ventricles) and highly vascularized areas (insula, ACC). These noise clusters 434 presumably stem from fluctuations through cardiac pulsation and are not specific to 435 spiral acquisitions. However, for the raised SD values in voxels close to the cortex borders, 436 it is unclear whether also CSF fluctuations, the BOLD effect itself, or rather time-varying 437 blurring due to unaccounted magnetic field fluctuations contribute. This is scrutinized in 438 the GLM analysis below. Additionally, for the CoV images (Fig. 3C), the internal capsule 439 appears prominently, presumably due to its reduced average signal level. 440

In terms of spatial specificity, overlaying contour edges of the anatomical reference (mean ME spin-warp image, subject S₂) (Fig. 4A) onto the mean spiral-out image suggests a geometrically very faithful depiction of the anatomical interfaces (Fig. 4B,F). Boundaries of the ventricles and gray to white matter are congruent in general, also for the visual cortex relevant to the later fMRI analyses. Some regions of the spiral-out images suffer from ringing (yellow arrow) or signal dropout (white arrow), most likely due to throughplane dephasing and incomplete correction of in-plane B_o inhomogeneity(Fig. 4E).

Incorporating the mean images of the spiral in/out sequence into the comparison 448 confirms the nature of these artifacts (Fig. 4C,D,G,H). The in-part images (Fig. 4C) are 449 devoid of these artifacts and match the anatomical reference almost completely in terms 450 of edge contours (Fig. 4G). Only CSF/skull interfaces, for example, in frontal regions, are 451 slightly compromised by a more global ringing, presumably from residual fat or high-452 intensity signal right after slice excitation, and the reversed T₂* weighting in k-space for 453 spiral-ins, amplifying high spatial frequencies of the image. The out-part of the spiral-454 in/out (Fig. 4D,H) constitutes a compromise between spiral-in and high-resolution spiral-455

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out in terms of artifact-level. Its shorter readout of only 20 instead of 60 ms alleviates
through-plane dephasing or incomplete B_o correction through inaccurate mapping.

We further quantified the spatial specificity of the high-resolution spiral-out images using 458 contour distance mapping (Fig. 5). This measure is visualized as colored anatomical 459 460 image contour on top of the mean spiral image (Fig. 5A, depicting subject S₃) and shows in general good congruence of functional and structural data (o to 1.5 voxel contour 461 distance in most voxels). Larger deviations occurred at tissue boundaries with large 462 susceptibility gradients, e.g., close to the frontal sinus (Fig. 5A, left inset, white arrows), as 463 well as areas with pronounced T_2^* contrast differences between the functional and 464 structural scan, such as subcortical gray matter (Fig. 5A, right inset, yellow arrows). 465

466 Overall, in most slices and subjects, the mean distance between corresponding contours of the structural and functional image varied between 0.5 and 1.5 voxels, with generally 467 better congruence for more superior slices (Fig. 5B). Prominent outliers (subject 5,6, 468 inferior slices) arose in areas with signal dropout for the spiral-out image, which was 469 more susceptible to through-plane dephasing than the structural ME scan due to the 470 difference in echo time (TE 20 ms vs 5-10 ms). For visual cortex in particular (Fig. 6B), the 471 region of interest for our functional analysis, contour congruencies between 0.5 and 1 mm 472 were most common, with fewer outliers than in the rest of the brain, driven by both 473 contrast differences (S2, slice 10) and signal dropouts close to the sagittal sinus (S2, slice 474 34). Averaged over the whole volume and all subjects, the mean gray matter contour 475 distance amounted to 1.04 ± 0.26 voxels (0.83 ± 0.21 mm), varying between 0.7 (S₃) and 476 1.4 voxels (S₅), i.e., 0.6-1.1 mm between subjects. Within visual cortex, congruence was 477 slightly higher, with mean gray matter contour distances of 0.96 ± 0.14 voxels (0.77 \pm 478 0.11 mm), varying between 0.7 (S3) and 1.2 (S2) voxels, i.e., 0.6-1.0 mm. 479

480 Summarizing the distribution of contour distances over all voxels in the acquisition 481 volume (Fig. 5D), 41 ± 7 % of gray matter contours in all subjects were strictly 482 overlapping (min (S6): 35 %, max (S3): 52 %), and 76 ± 7 % were at most 1 voxel apart

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483 (min (S6): 67 %, max (S3): 85 %), with only 11 ± 5 % of contour voxels exceeding a 484 distance of 2 voxels (1.6 mm). This distribution was near-identical within visual cortex 485 (Fig. 5E), with the exception of large outliers (3 voxels, i.e., 2.4 mm or more), which were 486 reduced for individual subjects (S5, S6) from about 10 to 5 %.

487 **3.2** Functional Sensitivity and Specificity

488 Functional sensitivity of the high-resolution spiral-out images is evident at the singlesubject level (subject S2) in a differential contrast of both stimulus conditions (+/- ULLR-489 URLL). The corresponding t-map, overlaid on the mean functional images, reveals 490 expected activation patterns in visual cortex (Fig. 6A). Hemispheric separation of the 491 complementary guarter-field stimulation blocks is visible (left slice), as well as the 492 contrast inversion from inferior to superior slices (leftmost slice vs second from left). 493 Notably, significant activation flips between neighboring voxels occur at the cerebral 494 fissure, suggesting spatial specificity at the voxel level. 495

This functional specificity is confirmed when overlaying the identical activation maps on the mean ME image as anatomical reference (Fig. 6B), again demonstrating the good alignment of functional and structural data seen in the previous subsection (Figs. 4,5). Clustered activation is almost exclusively constrained to gray matter with no extension into adjacent tissue or skull. Note that no multiple comparison correction was performed for visualization, in order to be more sensitive to such effects, at the expense of occasional false-positive voxels throughout other brain areas.

503 Gray-matter containment and retinotopic organization of the activation can be further 504 corroborated in the zoomed-in sections of visual cortex for transverse, coronal and 505 sagittal orientation (Fig. 6C). Additionally, we evaluated the ULLR and URLL blocks 506 individually (Fig. 6D), because differential contrasts, by design, do not allow for spatial 507 overlap between significant activation of both conditions. In the individual contrasts, the 508 identified portion of activated visual cortex appears larger, but is still very well restricted

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to cortical gray matter. Few overlaps exist, and, again, contrast switches between adjacent
voxels, pointing to spatial specificity at the prescribed sub-mm resolution.

These findings are reproducible over subjects (Fig. 7). Importantly, similar image quality 511 and geometric congruency are accomplished in all subjects. To verify, we show both the 512 mean spiral and the anatomical ME reference image of the corresponding transverse slice 513 as underlays for the differential activation patterns. Some subjects exhibit more frontal 514 blurring artifacts and dropouts (S₅, S₆, S₇) due to different geometry of the air cavities. 515 Still, the retinotopic organization of visual cortex is recovered in all subjects, as visualized 516 in the zoomed coronal and sagittal views. Existing differences of the specific activation 517 patterns are within the expected range of variability in subject anatomy and task 518 engagement. Quantitatively, peak t-values reach 15.1 on average for the differential 519 contrasts, with a standard deviation of 2.6, i.e. 17 %, over subjects (Table 1). Activation 520 clusters comprise 10371 +/- 2480 voxels (after FWE-multiple comparison correction at the 521 cluster level, p < 0.05), i.e., 6467 +/- 1547 mm³. 522

Because traditional Gaussian smoothing is frequently omitted in ultra-high resolution 523 fMRI studies (e.g., for laminar fMRI), we assessed its impact on our results. We repeated 524 the statistical analysis for all subjects to create a version of Figure 7 based on unsmoothed 525 data (supplementary material SM 3). For one particular subject (S2), we also juxtaposed 526 spatial characteristics of the statistical t-maps in an animated slide show by varying 527 significance thresholds for smoothed and unsmoothed data, as well as cropping the spiral 528 k-space data to 1 mm resolution before reconstruction (supplementary material SM 4). 529 Overall, spatial smoothing increased overall CNR (higher t-values) and extent of 530 activation clusters that were already discernible in the unsmoothed data. The activation 531 clusters of the smoothed data resemble those of unsmoothed data at lower thresholds, 532 but with fewer single-voxel activation sites. When overlaying activation masks of both 533 differential t-contrasts (+/- ULLR-URLL) after cluster-level multiple comparison 534 correction (p < 0.05 cluster-FWE, cluster-forming threshold: p < 0.001) for this subject 535 directly, we observed two distinct effects of the employed moderate smoothing 536

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(FWHM 0.8 mm) (Fig. 8A): on the one hand, cluster extent may increase isotropically by
about one voxel (left inset), consistent with a loss in spatial specificity. On the other
hand, clusters can expand by several voxels along the cortical ribbon after smoothing
(right inset), suggesting that increased sensitivity by averaging of thermal noise can lead
to functionally more plausible activation patterns.

To quantify functional specificity, we evaluated the tissue type of all significantly 542 activated voxels, and assessed the impact of smoothing on this measure (Fig. 8B), with 543 tissue type based on the unified segmentation results of the structural data (mean ME). 544 For smoothed data and considering the whole imaging volume (top left), 71 ± 8 % of all 545 significantly activated voxels resided in GM (mean and standard deviation over subjects 546 and whole volume), 2.2 ± 0.5 % and 1.9 ± 0.9 % at pial surface and GM/WM interface, 547 respectively, 5.7 ± 2.7 % in WM and 13 ± 3 % in CSF, while for the remaining 5.5 ± 2.5 % 548 of significant voxels, tissue type could not be determined unambiguously. Gray matter 549 containment dropped by about 2 % in the unsmoothed data (bottom left), presumably 550 due to randomly distributed false positives. This small difference is preserved when 551 restricting the analysis to the ROI of early visual cortex (right column), in which gray 552 matter containment is about 3 % higher for both smoothed and unsmoothed data. This 553 indicates that the impact of smoothing on this quantification of functional specificity was 554 small on average, and that the activation containment was comparable in early visual 555 cortex and the whole imaging volume. 556

3.3 Spiral In/Out Analysis and Echo Combination

558 We continue to present data from the same subject (S2) as in the high-resolution case, to 559 facilitate comparison. All findings are generalizable over subjects, and we provide mean, 560 SD, SFNR and t-maps of all slices for further dissemination in the supplementary material 561 (SM 2).

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562 Overall, the differential t-contrast maps for the spiral in/out data resemble the activation 563 patterns of the high-resolution spiral-out case (Fig. 9). This holds for all three derived 564 in/out time series, i.e., the separate reconstructions of the in-part and the out-part, as 565 well as their combination in the image domain via signal-weighted averaging ("in/out 566 combined").

In terms of functional sensitivity, the in/out sequence provides higher peak t-values and cluster extents in the differential t-contrasts compared to the high-resolution spiral-out, as expected due to the larger voxel size and consequential higher SFNR (Table 1). For example, the in-part itself provides a 61 % SFNR increase in gray matter (averaged over subjects), 17 % increased maximum peak t-value, and 56 % increase in significantly activated gray matter volume (Table 1, rightmost column).

573 Comparing the out- to the in-part of the spirals, SFNR is slightly decreased in the out-part 574 (8%), while the situation is reversed for the t-maps, with 2% increase in peak t-value and 575 14% increase in cluster extent, compared to the spiral-in. This suggests that higher T_2^* -576 sensitivity of the spiral-out causes both effects, by both amplifying signal dropouts and 577 BOLD signal.

The signal-weighted echo combination (eq. (6), (Glover and Thomason, 2004)) provides 578 the highest functional sensitivity of the three in/out time-series, having a 25 % increased 579 SFNR compared to the in-part, and 37 % increase compared to the out-part. This 580 translates into an average increase in peak t-value of 2 % and significant cluster extent of 581 582 21 %, compared to the out-part alone. This is in line with previous findings for highresolution multi-shot spiral data (Singh et al., 2018) at 3 T, which also reported contrast-583 to-noise ratio (CNR) increases for signal-weighted spiral in/out combinations on the 584 order of 25 %. However, it falls somewhat short of the 54 % increase in CNR reported 585 586 originally for low-resolution single-shot spiral in/out combination (Glover and Thomason, 2004, p. 866). 587

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In terms of spatial specificity, all activation patterns exhibit a good congruency to the anatomical reference, as evident from a close-up overlaid onto the mean ME image (Fig. 9D). In general, this visualization confirms the overall impression that the echo combination increases CNR throughout visual cortex, rather than just in regions of higher dephasing. Remarkably, there seem to be more false positive clusters for the spiral-in than in all other spiral variants (Fig. 9A), in particular close to the temporal muscle, presumably due to the ringing mentioned above.

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596 **4 Discussion**

597 **4.1 Summary**

In this work, we demonstrated that recent advances in high-resolution, single-shot spiral imaging (Engel et al., 2018) can be deployed to fMRI. The typical drawbacks of spiral fMRI, which have so far limited its routine use, were overcome by an expanded signal model, accurate measurement of its components, and corresponding iterative image reconstruction (Barmet et al., 2005; Pruessmann et al., 2001; Wilm et al., 2011).

503 Specifically, time series of high image quality and stability were obtained that exhibited 504 geometric congruency to anatomical scans without the need for post-hoc distortion 505 correction. Notably, also the corresponding phase images exhibit high raw data quality 506 (without any postprocessing, e.g., phase unwrapping), and suggest the suitability of spiral 507 acquisition for novel phase- or complex-value based fMRI analysis workflows (Balla et al., 508 2014; Bianciardi et al., 2014; Calhoun et al., 2002; Menon, 2002).

The functional sensitivity of spiral readouts was confirmed by observing typical activation 609 610 patterns in response to an established visual quarter-field stimulation. While a consensus on how to assess spatial specificity for fMRI is lacking, several indicators point to a 611 localization capability in the sub-mm range for our data. First, the distance of gray matter 612 contours in spiral and structural MRI data were at most one voxel (0.8 mm) apart in the 613 vast majority of voxels per subject (76 %). Second, the activation patterns of different 614 stimulus conditions could be discriminated in neighboring voxels of 0.8 mm nominal 615 resolution (Fig. 6). Third, the vast majority (75%) of significant activation sites were 616 contained within gray matter or at its boundaries, suggesting a limited impact of 617 618 artifactual blurring.

619 Finally, we demonstrated the versatility of this approach to spiral fMRI with a combined
620 in/out readout at a more typical resolution (1.5 mm). Here, the high acquisition efficiency

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of the spiral allowed to measure two images per shot, increasing CNR by about 20 %. The 621 observed discrepancy to previously reported gains of more than 50 % for signal-weighted 622 echo combination (Glover and Thomason, 2004) is in line with recent spiral fMRI studies 623 (Singh et al., 2018). It might result from higher target resolution and static off-resonance 624 correction employed in our study and (Singh et al., 2018), compared to the original work. 625 626 The increased image congruency and smaller dephasing effects between the in- and out-627 part compared to low-resolution spirals may reduce the impact of echo combination. Still, 628 more sophisticated combination of echo images (Glover and Thomason, 2004), or of kspace data during reconstruction (Jung et al., 2013) could result in further SNR increases. 629

In summary, the presented advances render spiral fMRI an attractive sampling scheme that delivers on the long-time postulate of high acquisition efficiency without compromising image quality. Here, the spatiotemporal application domain of fMRI on a standard gradient system was enhanced by acquiring a 230x230x36 mm FOV brain image at 0.8 mm nominal in-plane resolution (i.e., a matrix size of 288x288x36) while maintaining a TR typical for high-resolution fMRI (3.3 s). This corresponds to an acquisition efficiency of about 900,000 resolved voxels per second.

To our knowledge, this is the highest acquisition efficiency reported for 2D spiral fMRI to 637 638 date (see Table SM 5 for a comparison of sequence parameters in several spiral fMRI studies), as well as the first high-resolution spiral fMRI study at ultra-high field. In 639 combination with the presented evidence for geometric accuracy, this makes the 640 presented spiral-out sequence an attractive candidate for high-resolution applications of 641 fMRI, studying the functional sub-organization of cortex, e.g., in laminae or columns 642 643 (Cheng et al., 2001; Feinberg et al., 2018; Fracasso et al., 2016; Huber et al., 2017a; Kok et al., 2016; Koopmans et al., 2010; Lawrence et al., 2018; Martino et al., 2015; Muckli et al., 644 2015; Siero et al., 2011; Uğurbil et al., 2013; Yacoub et al., 2008). 645

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646 4.2 Effective Resolution, Spatial Specificity and Congruency

The claim of high acquisition efficiency for fMRI hinges on whether the acquired voxels effectively resolve distinct activation. This question of *effective* functional resolution arises for any fMRI protocol and comprises global aspects, such as PSF broadening, as well as more localized effects concerning geometric congruency and spatial specificity of the activation mapping.

The circular k-space coverage of spirals leads to a broadening of the PSF main lobe by 652 17 % compared to Cartesian k-space coverage in EPI (1.4 vs 1.2 times the voxel size (Qin, 653 2012)). Furthermore, any sequence with long readout duration encounters considerable 654 T_2^* signal decay along the trajectory, which manifests as a filter in image domain. For 655 656 spiral-in images, this emphasizes higher spatial frequencies, while the effect on spiral-out 657 images is reversed, leading to blurring. Based on typical brain tissue relaxation times at 7T, we adapted previous simulations of this effect for a similar high-resolution spiral-out 658 protocol (Fig. 7 in Engel et al., 2018). There are diminishing returns for investing more 659 660 acquisition time to achieve higher in-plane resolution, but a net gain remains at our chosen readout duration of 60 ms. Effectively, the FWHM of the PSF due to T_2^* blurring 661 corresponds to a voxel size smaller than 1 mm for the targeted 0.8 mm nominal 662 resolution, while at 40 ms readout duration actual voxels are larger than 1.1 mm for a 663 664 targeted 1 mm nominal resolution. Still, choosing shorter readouts with slightly coarser resolution in favor of sampling more slices within the given TR might deliver overall 665 666 higher acquisition efficiency in this case. Finally, static B₀ inhomogeneity also manifests 667 as spatially varying blurring or ringing in spiral imaging, because off-resonance induces broadening of the PSF main lobe, as well as amplification of its side lobes (Bernstein et 668 al., 2004, Chap. 17; Fig. 6 in Engel et al., 2018; Man et al., 1997). As long as Bo 669 670 inhomogeneity is properly mapped and included in the signal model, this effect is 671 mitigated by the iterative image reconstruction utilized in this work.

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In our experimental data, we found that the spatial specificity of spiral fMRI is very high 672 in about 75-80 % of the voxels, as indicated by both contour distance mapping (Fig. 5) 673 and gray matter containment of activation (Fig. 8). While these quantifications provide 674 rough estimates of functional spatial specificity in fMRI, there is no consensus on such 675 676 quantification in the community, and the absolute values reported here are hard to compare to previous work. We hope that through our sharing of the code, this 677 678 methodology may provide future reference points. Furthermore, the utilized measures are in themselves imperfect assessments of spatial specificity, and might underestimate the 679 68o achieved spatial specificity in our data. First of all, both analyses relied on unified 681 segmentation (Ashburner and Friston, 2005) to extract tissue probability maps, which in 682 principle should work contrast-independently. However, the employed default parameter 683 settings may not be optimal to model bias fields at 7 T or voxel intensity distributions of 684 multi-echo GRE scans with only partial brain coverage. Additionally, because the contrast 685 in our functional and structural scans were not equivalent (e.g., TE 20 vs 10 ms), contour 686 distance mapping reflects, to a certain extent, differences in contrast rather than 687 geometry.

Finally, relying on a perfect retinotopic organization of visual cortex for assessing functional spatial specificity has also limitations. For example, receptive fields can cross the vertical meridian (especially in higher visual areas), such that differential contrasts of quarterfield stimulation may not flip between adjacent voxels (Fig. 6C). Similarly, overlapping voxel activation or single-voxel "false positives" (Fig. 6D) may indicate imperfections in the visual field leading to non-compact retinotopic representations, rather than losses in spatial specificity.

695 Another contentious point concerning spatial specificity is our choice of moderately 696 smoothing the data (FWHM 0.8 mm) before statistical parametric mapping. While 697 smoothing is a standard preprocessing step in the majority of fMRI studies, high-698 resolution applications, such as retinotopic mapping or layered fMRI analyses, frequently

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abstain from it or use more spatially informed averaging *methods* (Blazejewska et al., 699 2019). From a conceptual point of view, smoothing alters the target PSF of the imaging 700 process in multiple ways that affect the effective resolution: On the one hand, a Gaussian 701 filter, as employed here, broadens the PSF main lobe (PSF) reducing spatial specificity. 702 On the other hand, it suppresses PSF side lobes and thus contamination by remote 703 locations, which enhances spatial specificity. The opposite is true for an edge or high-pass 704 filter, as implemented, for example, by multiplying the inverse of the T₂^{*} decay curve onto 705 the k-space data. Overall, resolution can be re-negotiated by appropriate filtering, which 706 has to be adapted to the specific application, in order to provide optimal specificity. 707

For our spiral data in particular, the decision to smooth was governed by another goal of 708 filtering, namely, recovering sensitivity. Theoretically, sensitivity is maximized by a 709 matched filter resembling the spatial activation extent, which is traditionally assumed to 710 be a Gaussian for fMRI (Friston, 2007, Chap. 2; Kasper et al., 2014), but has, to our 711 knowledge, not been determined for the ultra-high-resolution regime in question here. 712 Our choice of smoothing with an FWHM equivalent to the voxel size (instead of 2-3 times 713 714 the voxel size as in standard fMRI) therefore constitutes a compromise between sensitivity and specificity, motivated by the noise levels in our raw data, the short run 715 duration (5.5 min) and by having only one run acquired per subject and spiral sequence. 716 This hampered our ability to quantify whether the investment into longer readouts of 717 nominal 0.8 mm resolution, compared to 1 mm, translated into more spatially specific 718 activation (supplementary material SM 4). More temporal averaging via longer and more 719 numerous functional runs would allow to address this important research question in 720 future studies. 721

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722 4.3 General Applicability and Limitations of Spiral Imaging Advances

723 **4.3.1** Rationale

Increasing acquisition efficiency for high-resolution single-shot spirals while maintaining depiction quality, as presented here, resulted from the favorable interplay of the expanded signal model components: the encoding field dynamics with long-readout spirals, static B_0 inhomogeneity characterization, and parallel imaging with iterative reconstruction enabling undersampling.

For deploying this advanced spiral functional imaging to other sites and systems, it is important to evaluate how individual aspects of the approach contribute to its overall performance, and to assess the generalizability of our findings. This includes both the impact of model and system components, as well as the utilized methodology for their characterization, in relation to possible alternatives and extensions.

734 4.3.2 Magnetic Field Monitoring

In terms of availability, the concurrent field monitoring hardware employed in our
approach (Barmet et al., 2008; Engel et al., 2018; Kasper et al., 2018; Wilm et al., 2017,
2011), is probably the scarcest resource across sites. It serves to characterize both the
reproducible and irreproducible imperfections of the encoding magnetic fields.

For reproducible field effects, such as the actual spiral trajectory performed by the system 739 and its induced eddy currents, previous work has shown that their characterization is 740 often required to avoid severe image artifacts (Engel et al., 2018, Fig. 6; Vannesjo et al., 741 2016). This, however, might vary between systems, as successful spiral image 742 reconstructions based on nominal trajectories have been reported (Kurban et al., 2019; 743 Singh et al., 2018). If image artifacts arise from reproducible trajectory imperfections, they 744 could be measured without concurrent field monitoring hardware by calibration 745 approaches in a separate scan session (Bhavsar et al., 2014; Duyn et al., 1998; Robison et 746

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al., 2019, 2010). For more flexibility, the gradient impulse response function (GIRF) to 747 arbitrary input trajectories can be modelled from such data under linear-time invariant 748 system assumptions (Addy et al., 2012; Campbell-Washburn et al., 2016; Rahmer et al., 749 2019; Vannesjo et al., 2014, 2013). The required field measurements for these calibrations 750 may either rely on dedicated NMR-probe based field cameras (Barmet et al., 2008; 751 Vannesjo et al., 2014, 2013; Zanche et al., 2008) or on off-the-shelf NMR phantoms (Addy 752 et al., 2012; Duyn et al., 1998; Rahmer et al., 2019), with certain trade-offs to measurement 753 precision and acquisition duration (Graedel et al., 2017). 754

For the dynamic field effects, induced by the system (e.g., drifts through gradient 755 heating), as well as the subject (e.g., fluctuations with the breathing cycle or limb 756 motion), few studies have analyzed their impact on spiral fMRI time series (Pfeuffer et al., 757 2002). In principle, the concurrent field monitoring and reconstruction employed here 758 incorporated changes of global off-resonance and k-space with the bandwidth of the 759 trajectory measurement of about 4 Hz (monitoring every third slice). As we did not 760 observe any conspicuous problems in the time series statistics, for example, SFNR drops, 761 nor any indication of time-dependent blurring, which would be the spiral equivalent to 762 apparent motion in phase encoding direction observed in EPI (Bollmann et al., 2017; 763 764 Power et al., 2019), this approach presumably addressed the majority of field fluctuations 765 present in our data. This is in line with previous results of breathing-induced field 766 fluctuations reported at 7T in spiral fMRI of only a few Hz for healthy subjects and normal breathing (Pfeuffer et al., 2002). An in-depth analysis of these effects is beyond 767 the scope of this paper, as it would, for example, entail quantitative comparisons with 768 nominal or GIRF reconstructions (Vannesjo et al., 2016), as well as simulating the impact 769 of different measured field components on image time series, similar to work previously 770 conducted for EPI (Bollmann et al., 2017; Kasper et al., 2015). As we do believe that this 771 investigation is relevant to the neuroimaging community, we provide the field dynamics 772of all spiral-out fMRI runs in ISMRMRD format for further scrutiny. 773

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Note, however, that the dataset in itself might not be representative for assessing the 774 utility of concurrent field monitoring for spiral fMRI. In terms of system fluctuations, we 775 did have a challenging gradient duty-cycle (with gradients switched on during 70 % of the 776 sequence, 50 % of the time at amplitude maximum), leading to substantial heating of 15 777 degrees throughout the 5.5 min high-resolution spiral-out sequence, as measured using 5 778 optical sensors cast into the gradient coil (Dietrich et al., 2016b). This actually limited the 779 780 duration of our functional runs. While system fluctuations might thus be particularly pronounced in our data, the subject-induced fluctuations will be moderate, because all 781 782 volunteers were young, healthy individuals instructed to lie still throughout the session. 783 This is reflected in the small mean framewise displacement (FD) encountered in all subjects (mean FD and standard deviation over subjects 0.09 ± 0.04 mm, see SM 6 for 784 785 motion and FD traces). For a comprehensive assessment, instructed limb motion and 786 deep breathing, a range of BMIs and body shapes would have to be included in the design of the study, similar to evaluations of field effects on structural T_2^* imaging (Duerst et al., 787 788 2016). Finally, in terms of the chosen imaging FOV covering the visual cortex, dynamic 789 field effects will be at an intermediate level, with maximum fluctuations expected in inferior regions closer to the chest (brainstem, cerebellum) and minimum effects near 790 791 the top of the head (e.g., motor cortex).

If dynamic field effects constitute a significant artifact and noise source for spiral fMRI time series, in lieu of field monitoring, alternative correction methods comprise dynamic off-resonance updates or higher-order field navigators (Pfeuffer et al., 2002; Splitthoff and Zaitsev, 2009), as well as gradient response models that incorporate time-courses of gradient coil temperature (Dietrich et al., 2016b; Stich et al., 2020) or current measurements (Nussbaum et al., 2019; Rahmer et al., 2021).

798 4.3.3 Static B₀ Inhomogeneity

To characterize static B_0 inhomogeneity, we acquired a Cartesian multi-echo gradient echo scan with rather high resolution (1 mm). Including this information in the signal

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801 model has previously been crucial to maintain spatial specificity in spiral imaging at 7T 802 (Engel et al., 2018, Fig. 6; Kasper et al., 2018, Fig. 7).

The B_o maps obtained in this work exhibited considerable inhomogeneity, even after 3rd order shimming of the targeted 4 cm oblique-transverse slab of the brain including the visual cortex. For the B_o map of a single subject (SPIFI_0007) provided in the accompanying Data In Brief article (see "Code and data availability" section), 20 % of brain voxels were more than 50 Hz off-resonant, which – if uncorrected for – would incur blurring with FWHMs of several voxels.

809 Thus, some form of static B_o inhomogeneity correction seems indispensable for providing 810 high spiral image quality, and to correct this at the reconstruction stage via inclusion into the expanded signal model proved sufficient for most of the imaged brain slices. 811 However, localized blurring, distortion and ringing artifacts remained at cortex 812 boundaries close to the skull or air cavities, most prominently in orbitofrontal regions, 813 and in the temporal lobe, above the ear canals, as well as in more inferior slices, 814 particularly in the brainstem. Consequently, such regions might exhibit less sensitive and 815 816 spatially less defined activation patterns than the ones in visual cortex evaluated here.

We did not evaluate whether our particular choice of B_0 map resolution or processing 817 818 contributed to the accomplished image quality or its limitations. Alternative methods to 819 determine B_0 may provide similar results at reduced scan time, for example, slightly 820 varying TEs during a spiral image time series to estimate the B_o map from their phase 821 differences directly (Glover and Law, 2001; Singh et al., 2018) or joint estimation of B_0 and image from the spiral data itself (Fessler, 2010; Hernando et al., 2008; Patzig et al., 2020). 822 These methods also allow to regularly update B_0 maps during long fMRI runs, increasing 823 the alignment to the spiral acquisition geometry in case of subject motion. 824

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825 4.3.4 Iterative Parallel Imaging Reconstruction

To enable single-shot imaging for maximum acquisition efficiency, we also relied on the coil sensitivity profiles for spatial encoding, i.e., parallel imaging. Spiral trajectories are particularly suited for this form of acceleration, because they possess favorable behavior in terms of spatial noise amplification by the coil geometry factor, allowing for higher kspace undersampling (Larkman, 2007; Lee et al., 2021).

For our data with in-plane acceleration factors of 4 using a 32-channel receive array at 7 T
this was confirmed through the SD maps of the time series data, which did not exhibit
spatially structured residual aliasing or noise patterns. This also points to the robustness
of the reconstruction to motion-induced mismatch of measured and actual coil
sensitivities.

836 Compared to Nyquist-sampled spiral data, which could be reconstructed via gridding and 837 conjugate phase correction for static off-resonance effects (Singh et al., 2018 and references therein), parallel imaging of non-Cartesian trajectories typically necessitates 838 iterative reconstruction schemes (Heidemann et al., 2006; Lustig and Pauly, 2010; 839 Pruessmann et al., 2001; Weiger et al., 2002; Wright et al., 2014). Depending on the 840 number of iterations and precision of the off-resonance correction, these algorithms are 841 842 one or two orders of magnitude slower than direct reconstruction methods. Note, however, that the reconstruction times reported here will not present a general hurdle for 843 844 deployment, because our Matlab code was not optimized for speed. The numerous 845 matrix-vector multiplications (eq. 5) burden the CG algorithm most, and an implementation on graphical processing units (GPUs) will significantly accelerate 846 reconstruction. High-performance implementations of the conjugate gradient iterative 847 848 reconstruction algorithm, including off-resonance correction, are publicly available in different MR reconstruction packages, and we have successfully tested reconstruction of 849 the example data presented here in MRIReco.jl (Knopp and Grosser, 2021), written in the 850 851 modern scientific programming language Julia (Bezanson et al., 2017).

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852 4.3.5 Ultra-high field Magnet (7T) and Gradients

Finally, the availability of an ultra-high field system may be seen as a limitation for the 853 advances presented here. We implemented the spiral sequences at 7T, which has shown 854 855 particular utility for high-resolution functional MRI due to its superlinear increase in 856 BOLD CNR (Uludağ and Blinder, 2018). From an image reconstruction perspective, this is 857 a challenging scenario, because both static and dynamic field perturbations are 858 exacerbated at ultra-high field and deteriorate conditioning of the expanded signal model. Thus, the adoption of the presented advances in spiral fMRI to lower field 859 strengths (e.g., 3T) not only seems straightforward and worthwhile, but also offers 860 861 benefits. For example, spiral readouts could be prolonged in light of the more benign field 862 perturbations, mitigating the lower CNR while maintaining high image quality.

863 Our gradient system, on the other hand, had standard specifications, available on most sites (utilized gradient amplitude 31 mT/m, slew rate 160 T/m/s). Already here, spiral 864 trajectories offered reduced readout times of 19 % compared to EPI due to their higher 865 866 average speed covering k-space. Because the last 80 % (45 ms) of our high-resolution 867 spiral gradient waveform were amplitude-limited (Fig. 1, black waveform), this 868 acceleration could be considerably increased by dedicated gradient hardware with higher maximum gradient strength, e.g., high-performance whole-body "connectome" gradient 869 870 coils (Kimmlingen et al., 2012) or insert gradients for head imaging (Foo et al., 2018; 871 Weiger et al., 2018).

872 **4.4 Translation to other fMRI applications**

873 This work focused on two-dimensional, slice-selective spiral BOLD imaging.
874 Simultaneous multi-slice (SMS) or 3D excitation schemes offer a complementary means
875 of acceleration, by extending sensitivity encoding to the third encoding (slice) dimension,
876 as, e.g., in stack-of-spiral trajectories (Deng et al., 2016; Engel et al., 2021; Zahneisen et al.,
877 2014), which also provides SNR benefits (Poser et al., 2010). The expanded signal model

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and image reconstruction framework employed here, apart from the 2D-specific
simplifications, are equally applicable to this scenario (Engel et al., 2021; Pruessmann et
al., 2001; Zahneisen et al., 2015).

Furthermore, the successful deployment of the in/out spirals here suggests the feasibility of other dual-echo variants, such as out-out or in-in acquisition schemes. In particular, recent correction methods for physiologically or motion-induced noise that rest on multiecho acquisition (Kundu et al., 2012; Power et al., 2018) could profit considerably from spiral-out readouts: compared to EPI, the shorter minimum TE provides first-echo images with reduced T_2^* - weighting and should enhance disentanglement of BOLD- and non-BOLD related signal fluctuations.

Beyond BOLD, the adaptation of single-shot spiral acquisition for other time series readouts seems promising. In particular fMRI modalities with different contrast preparation (Huber et al., 2017b), such as blood-flow sensitive ASL (Detre et al., 2012, 1992), and blood-volume sensitive VASO (Huber et al., 2018; Lu et al., 2013, 2003) benefit from the shorter TEs offered by spiral-out readouts. These sequences do not rely on T_2^* decay for functional sensitivity, and thus minimizing TE leads to considerable CNR gains (Cavusoglu et al., 2017; Chang et al., 2017).

895 Acknowledgments

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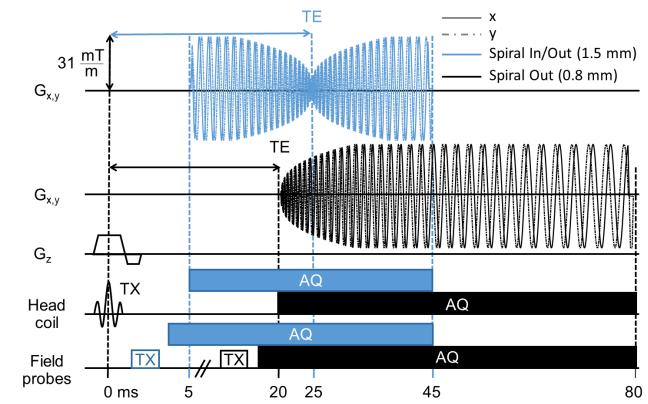
208 Conflicts of Interest

At the time of submission, Christoph Barmet and Bertram J. Wilm are employees of Skope Magnetic Resonance Technologies. Klaas P. Pruessmann holds a research agreement with and receives research support from Philips. He is a shareholder of Gyrotools LLC.

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913 Figures

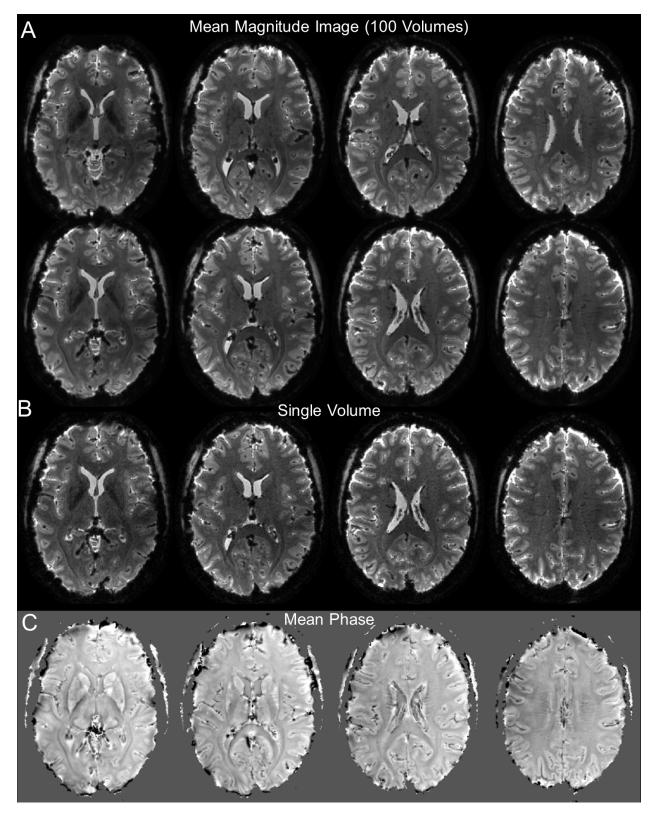
914 Figure 1



915 0 ms 5 20 25 45 80 916 Utilized 2D single-shot spiral acquisitions (R = 4 undersampling): High-resolution single-917 shot spiral-out (nominal resolution 0.8 mm, black) and spiral in/out trajectory (1.5 mm 918 resolution, blue). Depicted are the gradient waveforms (G_x, G_y, G_z) as well as RF excitation 919 (TX) and ADC sampling intervals (AQ) for both the ¹H head coil and the ¹⁹F field probes 920 used to monitor the trajectories and other concurrent encoding fields. Field probe 921 excitation and acquisition start a few milliseconds before the spiral readout gradient 922 waveforms.

Advances in Spiral fMRI

924 Figure 2

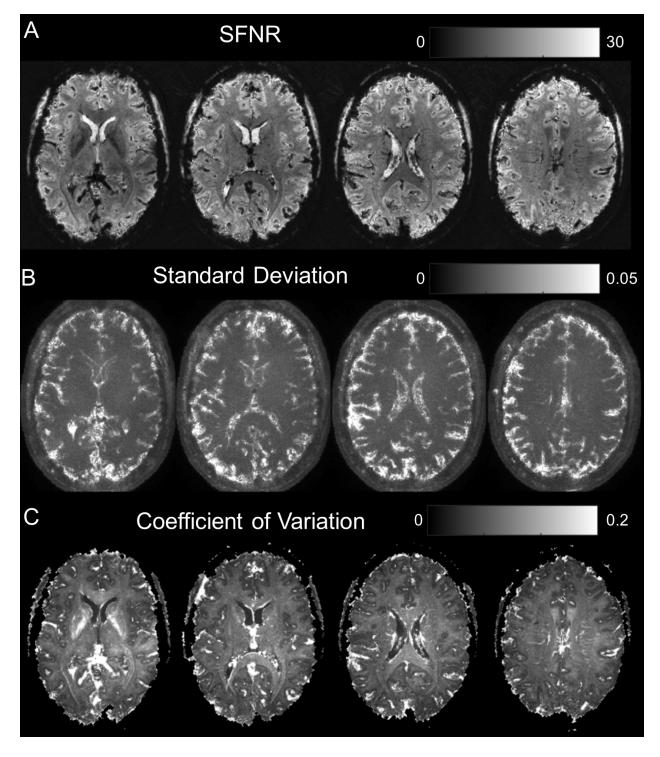


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- 926 Overview of image quality for high-resolution (0.8 mm) single-shot spiral-out acquisition.
- 927 (A) 8 oblique-transverse slices (of 36) depicting the time-series magnitude mean of one
- 928 functional run (subject S7, 100 volumes). (B) Single-volume magnitude images for slices
- orresponding to lower row of (A). (C) Mean phase image over one run, without any post-
- 930 processing, for slices corresponding to lower row of (A).

Advances in Spiral fMRI

932 Figure 3



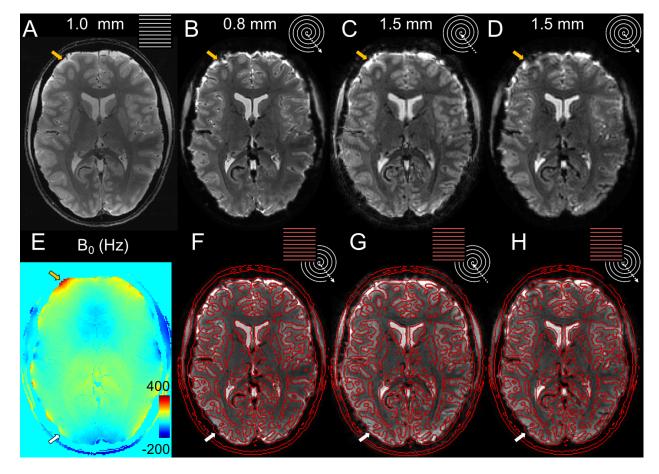
934 Characterization of image time series fluctuations over 1 spiral-out run (95 volumes,
935 discarding first five). (A) Signal-to-Noise Fluctuation Ratio (SFNR) image for same slices

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- as in Fig 2. Rather homogeneous, exhibiting sufficient SFNR levels. (B) Standard deviation
- 937 (SD) image over time. Regions of high fluctuation mainly include pulsatile areas close to
- 938 ventricles or major blood vessels, and cortex/CSF interfaces. (C) Coefficient of Variation
- 939 (CoV) image. Inverse of (A), highlighting regions of high fluctuations relative to their
- 940 respective mean. Vascularized/CSF regions appear prominently, as well as the internal
- 941 capsule, due to its reduced average signal level.

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943 Figure 4



944

Image quality and geometric accuracy of spiral images, reconstructed with the expanded
signal model. (A) Anatomical Reference: Mean multi-echo (ME) spin-warp image (1 mm
resolution) (B) High-resolution (o.8 mm) spiral-out; (C) In-part of spiral in/out (1.5 mm);
(D) Out-part of spiral in/out (1.5 mm). (E) B_o-map computed from (A). (F-H) Overlay of
isoline contour edges from (A) onto (B)-(D).

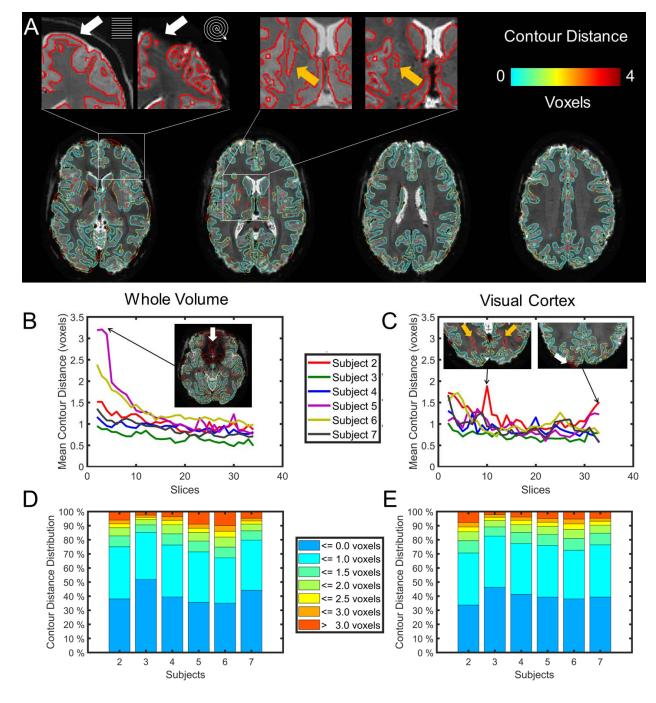
950 Depicted are the mean images of a single run (subject S₂, top row, B-D). The mean ME 951 image (A), used to compute SENSE- and B_o -map (E) for the expanded signal model, 952 provides the anatomical reference via its contours (red lines), overlaid onto the different 953 spiral variants (bottom row, F-H). Arrows indicate residual geometric incongruence by 954 through-plane dephasing (white) or incomplete B_o mapping and correction (yellow) in

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- 955 the spiral-out, which are reduced in the out-part and absent in the in-part of the spiral-
- 956 in/out sequence.

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958 Figure 5



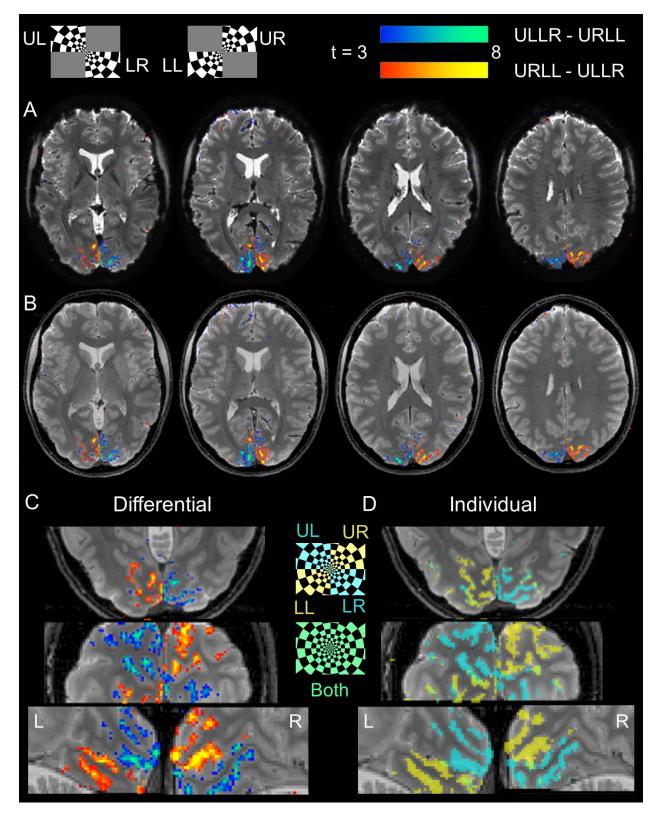
960 Quantification of spatial specificity in spiral images via contour distance mapping. 961 (A) Gray matter contours extracted from tissue probability maps (threshold 90 %) of the 962 T_2^* -weighted structural image (TE 10 ms, echo 6 of ME scan), overlaid onto mean high-

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resolution spiral-out image (subject S₃). Color coding reflects distance to corresponding 963 contour in segmented spiral image. Contour discrepancies are prevalent at tissue 964 interfaces with high susceptibility gradients (left inset, white arrows), as well as areas 965 with pronounced T_2^* contrast differences (right inset, yellow arrows). (B) Mean contour 966 distance per slice for different subjects (averaged over all contours within each slice for 967 968 the whole imaging volume). Average over subjects and slices: 1.04 ± 0.26 voxels $(0.83 \pm 0.21 \text{ mm})$. Prominent outliers (subjects S5, S6) arose in inferior slices with 969 considerable signal loss due to through-plane dephasing (sphenoid sinus, ear canals). (C) 970 Mean contour distance per slice for different subjects, as in (C), but restricted to contours 971 within a mask of early visual cortex. Average over subjects and slices: 0.96 ± 0.14 voxels 972 $(0.77 \pm 0.11 \text{ mm})$. Fewer outliers exist, mostly due to contrast differences and close to the 973 sagittal sinus. (D) Distribution of contour distances per subject within the whole imaging 974 volume. 41 ± 7 % of gray matter contour voxels in all subjects were strictly overlapping, 975 with 76 ± 7 % at most 1 voxel apart and only 11 ± 5 % exceeding a distance of 2 voxels 976 (1.6 mm). (E) Distribution of contour distances per subject, as in (D), but restricted to a 977 978 mask of early visual cortex. Near-identical distribution to (D), but fewer larger outliers $(\geq 3 \text{ voxels})$ in some subjects (S₅, S₆). 979

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981 Figure 6

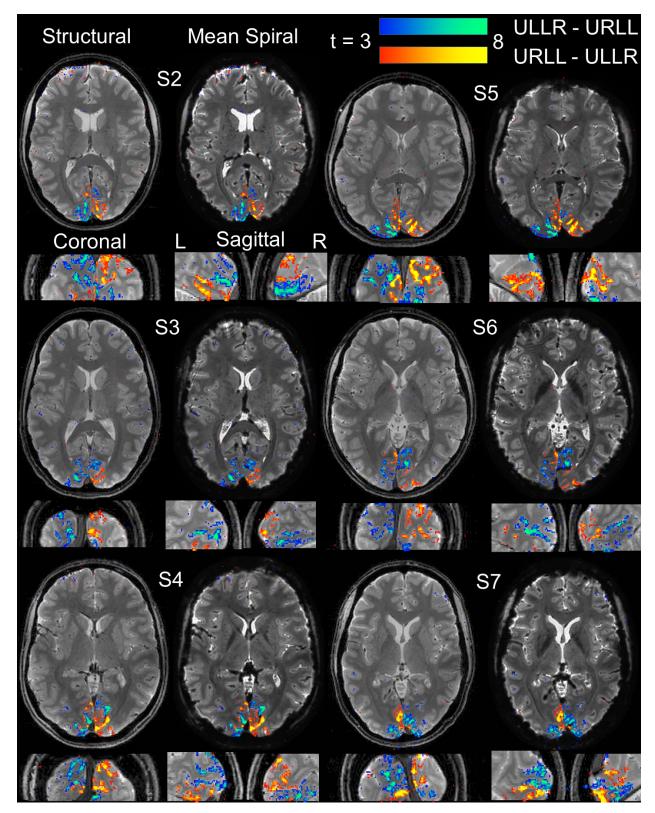


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Visual Activation Maps of high-resolution (0.8 mm) spiral-out fMRI for a single subject 983 (S₂). Representative stimuli of both conditions (ULLR and URLL) are displayed at the top. 984 (A) Overlay of differential t-contrast maps (p < 0.001 uncorrected) on transverse slices of 985 mean spiral image (hot colormap: URLL-ULLR, cool colormap: ULLR-URLL). (B) Same 986 987 contrast maps as in (A), overlaid on mean ME image as anatomical reference. (C) 988 Zoomed-in sections of differential t-contrast maps in different orientations: transverse 989 (top), coronal (middle) and sagittal (bottom, left (L) and right (R) hemisphere). (D) tcontrast maps for individual conditions (blue: ULLR, yellow: URLL), showing more 990 widespread activation and high spatial specificity, i.e., little spatial overlap (green). 991

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993 Figure 7

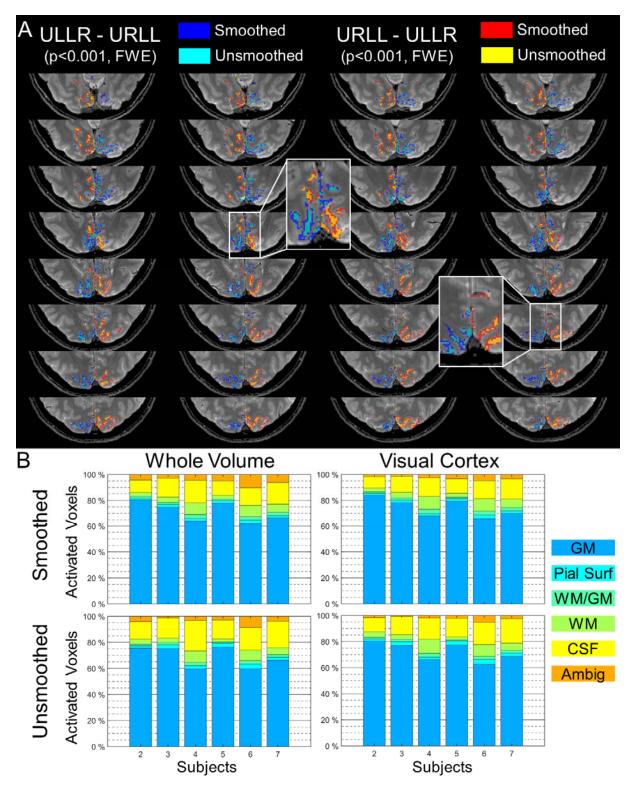


Advances in Spiral fMRI

995 Mean spiral images and activation maps over subjects (S2-S7) for high-resolution spiral-996 out fMRI. For each subject, the following 4 sections are displayed, with the mean ME 997 image as anatomical underlay: transverse, coronal and sagittal slice (for left (L) and right 998 (R) hemisphere), each chosen for the maximum number of activated voxels (over both 999 differential statistical t-contrasts, p < 0.001 uncorrected). To assess raw spiral data quality, 1000 the corresponding mean functional image is displayed side-by-side to the anatomical 1001 transverse slice as an alternative underlay.

Advances in Spiral fMRI

1003 Figure 8

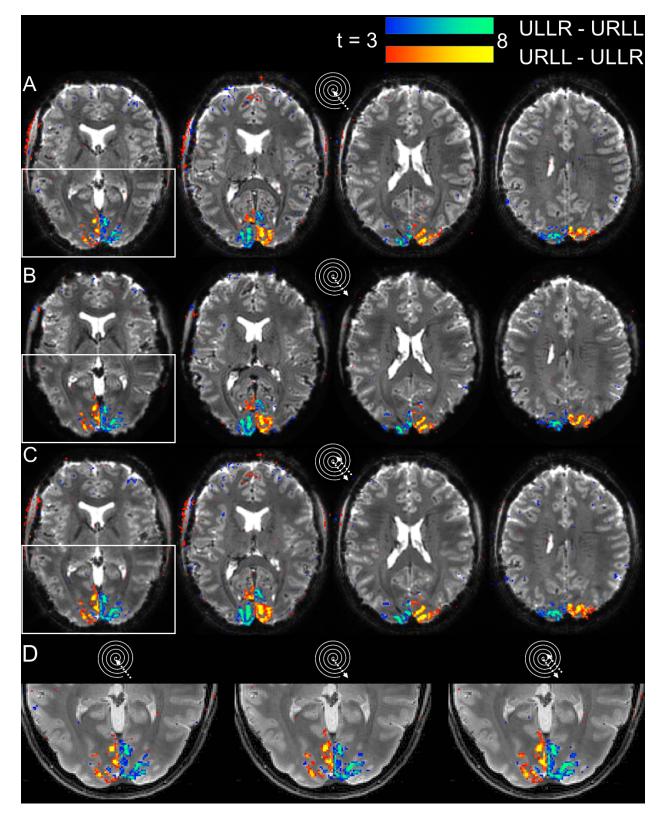


Advances in Spiral fMRI

Spatial specificity of functional activation for high-resolution spiral-out fMRI. Analyses 1005 are based on significant voxels over both differential t-contrasts (+/- ULLR-URLL, p < 0.05 1006 cluster-FWE corrected, cluster-forming threshold: p < 0.001). (A) Comparison of 1007 activation extent in smoothed (FWHM 0.8 mm) and unsmoothed data in a single subject 1008 (S₂). Masks of all significant voxels are overlaid for both t-contrasts based on smoothed 1009 data (blue/red mask) as well as unsmoothed data (cyan/yellow masks). (B) Percentage of 1010 significant voxels located in relevant tissue types, analyzed for smoothed (top row) and 1011 unsmoothed (bottom row) data, as well as within whole imaging volume (left) and 1012 restricted to a mask of early visual cortex (right). Tissue types were identified by unified 1013 segmentation of the structural (mean multi-echo) image, with 60 % exceedance threshold 1014 for individual tissue classes (GM: gray matter, WM: white matter, CSF: cerebrospinal 1015 fluid) and 30 % each for interfaces (Pial surface (GM/CSF), WM/GM surface), with the 1016 remaining voxels categorized as ambiguous. On average, irrespective of smoothing and 1017 1018 ROI, the majority (74-78%) of activation was contained in gray matter or adjacent surfaces, with 6 % and 13-17 % residing in majority white matter and CSF voxels, 1019 respectively. Gray matter containment was highest when smoothing the data and 1020 restricting the analysis to the visual cortex, and lowest in the unsmoothed data 1021 considered within the whole imaging volume. 1022

Advances in Spiral fMRI

1024 Figure 9



Advances in Spiral fMRI

1026	Visual Activation Maps of spiral in/out (1.5mm) fMRI run for a single subject (S2, as in
1027	Fig. 6). (A-C) Displayed are the differential t-contrast maps (p < 0.001 uncorrected) on
1028	transverse slices of the respective mean spiral images (hot colormap: URLL-ULLR, cool
1029	colormap: ULLR-URLL), based on: (A) Spiral Images reconstructed from in-part of the
1030	trajectory. (B) Spiral images reconstructed from the out-part of the trajectory. (C) Signal-
1031	weighted combination (eq. (6), (Glover and Thomason, 2004)) of images in (A) and (B).
1032	(D) Zoomed view of activation maps in leftmost slice of (A)-(C), overlaid on anatomical
1033	reference image (mean ME).

Advances in Spiral fMRI

1035 Tables

1036 Table 1

Quantification of temporal stability and functional sensitivity of all spiral fMRI sequences. 1037 For the signal-to-fluctuation-noise ratio (SFNR, eq. (5)), the table contains mean +/- SD 1038 in a gray matter ROI over the whole imaging volume. For the t-contrast SPMs, peak t-1039 value and number of significant voxels over both differential contrasts (+/- ULLR-URLL) 1040 are reported (p < 0.05 FWE-corrected for multiple comparisons at the cluster level with a 1041 cluster-forming threshold of p < 0.001). The last column shows relative increases to the 1042 previous sequence, i.e., the one reported in the sub-table directly above. Since resolutions 1043 differ between spiral-out (0.8 mm) and spiral in/out (1.5 mm), we compare activated 1044 volume instead of voxel count. 1045

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	Subjects								Gain vs		
			previous	high-res							
Measure	S2	S3	<i>S4</i>	<i>S5</i>	<i>S6</i>	S7	Mean	SD	spiral	spiral out	
high-resolution spiral out											
SFNR_mean	14.1	17.2	14.9	15.7	14.7	15.2	15.3	1.1	-	-	
SFNR_SD	5.0	5.4	4.6	5.0	4.7	4.9	4.9	0.3			
SPM_T_max	12.9	15.2	16.2	17.5	11.1	17.6	15.1	2.6	-	-	
SPM_T_nVoxels	10957	6157	11673	12202	8682	12553	10371	2480			
SPM_T_volume (mm³)	6832	3839	7279	7609	5414	7828	6467	1547	-	-	
in-part spiral in/out											
SFNR_mean	22.7	28.6	23.5	26.6	22.9	23.9	24.7	2.4	61%	61%	
SFNR_SD	7.3	8.2	7.6	7.8	7.3	8.2	7.7	0.4			
SPM_T_max	16.6	19.5	23.5	15.1	15.3	15.9	17.7	3.3	17%	17%	
SPM_T_nVoxels	10097	4863	10221	6470	8157	2816	7104	2953			
SPM_T_volume (mm ³)	14363	6918	14540	9204	11604	4006	10106	4200	56%	56%	
				out-par	t spiral i	n/out					
SFNR_mean	20.4	26.4	21.4	24.3	21.0	22.9	22.7	2.3	-8%	48%	
SFNR_SD	7.3	8.4	7.4	8.0	7.7	7.9	7.8	0.4			
SPM_T_max	17.8	20.2	18.2	20.1	17.2	14.4	18.0	2.1	2%	19%	
SPM_T_nVoxels	8976	6087	10661	7923	11606	3312	8094	3054			
SPM_T_volume (mm³)	12769	8659	15166	11271	16510	4711	11514	4344	14%	78%	
combined spiral in/out											
SFNR_mean	28.3	35.9	29.5	33.6	28.7	30.3	31.1	3.0	37%	103%	
SFNR_SD	9.4	10.9	10.0	10.4	9.9	10.7	10.2	0.5			
SPM_T_max	18.4	19.7	20.3	17.8	15.8	18.3	18.4	1.6	2%	22%	
SPM_T_nVoxels	11971	6575	13254	9331	11665	6082	9813	2985			
SPM_T_volume (mm³)	17029	9353	18854	13274	16594	8652	13959	4247	21%	116%	

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1048 Supplementary Material

1049 Figure SM 1

Figure collection of high-resolution (0.8 mm) spiral fMRI data. For every subject, 8 figures 1050 are shown, each depicting all 36 slices of the acquisition (top left = most inferior slice, 1051 bottom right = most superior slice). All underlay images are based on the functional time 1052 series after realignment, and the overlaid t-map was computed from the preprocessed 1053 data which included smoothing as well (FWHM 0.8 mm). Order of the figures (1) First 1054 volume of spiral fMRI time series; (2) Time-series magnitude mean of spiral fMRI run; (3) 1055 Bias-field corrected version of (2); (4) Signal-to-Noise Fluctuation Ratio (SFNR) image of 1056 spiral fMRI run (display range 0-30); (5) Standard deviation (SD) image over time of the 1057 1058 same run (display range 0-0.05); (6) Coefficient of Variation (CoV) image of the same run, inverse of (4) (display range 0-0.2); (7) Magnitude-mean spiral fMRI image, overlaid with 1059 edges of anatomical reference (mean multi-echo spin warp); (8) Overlay of differential t-1060 contrast maps (p < 0.001 uncorrected) on transverse slices of mean spiral image (hot 1061 colormap: URLL-ULLR, cool colormap: ULLR-URLL, display range t=3.2-8). 1062

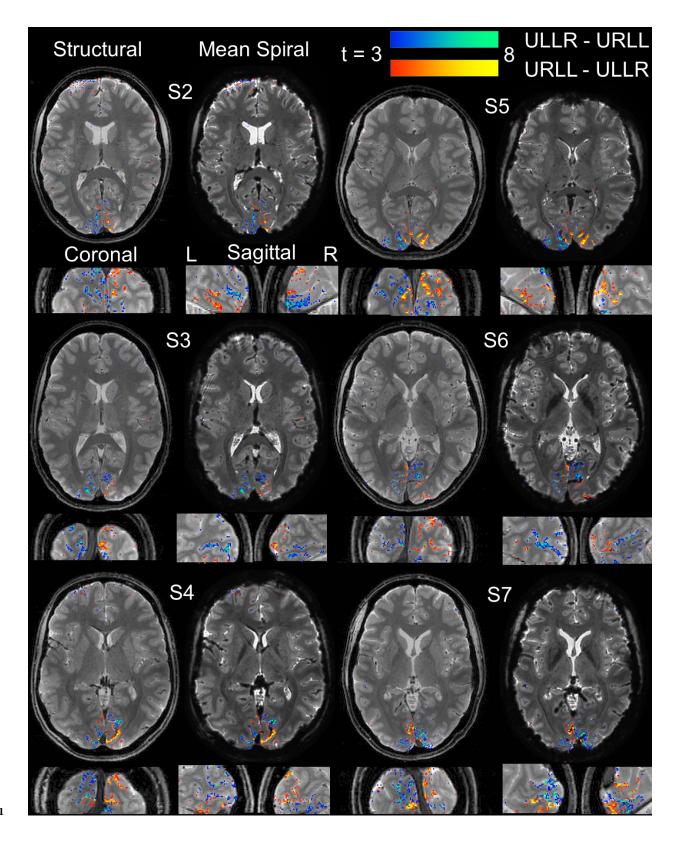
Advances in Spiral fMRI

1064 Figure SM 2

1065 Figure collection of spiral in/out fMRI data (1.5 mm resolution). For every subject, 24=3x8 figures are shown, i.e., 8 per set of spiral-in, spiral-out, and combined in/out images. Each 1066 figure depicts all 36 slices of the acquisition (top left = most inferior slice, bottom right = 1067 1068 most superior slice). All underlay images are based on the functional time series after realignment, and the overlaid t-map was computed from the preprocessed data which 1069 1070 included smoothing as well (FWHM 0.8 mm). Order of the figures: (1) First volume of spiral fMRI time series; (2) Time-series magnitude mean of spiral fMRI run; (3) Bias-field 1071 corrected version of (2); (4) Signal-to-Noise Fluctuation Ratio (SFNR) image of spiral 1072 fMRI run (display range o-30); (5) Standard deviation (SD) image over time of the same 1073 run (display range o-0.05); (6) Coefficient of Variation (CoV) image of the same run, 1074 inverse of (4) (display range o-o.2); (7) Magnitude-mean spiral fMRI image, overlaid with 1075 1076 edges of anatomical reference (mean multi-echo spin warp); (8) Overlay of differential t-1077 contrast maps (p < 0.001 uncorrected) on transverse slices of mean spiral image (hot colormap: URLL-ULLR, cool colormap: ULLR-URLL, display range t=3.2-8). 1078

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1080 Figure SM 3



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Mean spiral images and activation maps over subjects (S2-S7) for high-resolution spiral-1082 out fMRI, based on unsmoothed data (See Fig. 7 for same visualization using smoothed 1083 data). For each subject, the following 4 sections are displayed, with the mean ME image 1084 as anatomical underlay: transverse, coronal and sagittal slice (for left (L) and right (R) 1085 hemisphere), each chosen for the maximum number of activated voxels (over both 1086 1087 differential statistical t-contrasts, p < 0.001 uncorrected). To assess raw spiral data quality, 1088 the corresponding mean functional image is displayed side-by-side to the anatomical transverse slice as an alternative underlay. 1089

1090

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Advances in Spiral fMRI

1093 Figure SM 4

Impact of readout duration and spatial smoothing on activation maps in high-resolution 1094 spiral-out fMRI data. The animated slideshow toggles between t-maps of the differential 1095 contrast (+/- ULLR-URLL), overlaid on the structural image (mean ME) in a single subject 1096 (S₂): (1) T-map based on smoothed data (FWHM 0.8 mm), thresholded at t > 3.2, 1097 (p < 0.001 uncorrected), as presented throughout the other figures, (2) T-map based on 1098 unsmoothed data, same thresholding (t > 3.2), and (3) T-map based on unsmoothed data, 1099 with more liberal thresholding (t > 2.4, p < 0.01 uncorrected). (4-6) as (1-3), but with 1100 spiral-out fMRI k-space data retrospectively cropped to 1 mm resolution before image 1101 reconstruction. 1102

(1-3) illustrate that moderate spatial smoothing elevates overall CNR (higher t-values) and
increases the spatial extent of existing activation clusters in the unsmoothed data. The
activation clusters of the smoothed data resemble those in the unsmoothed data at lower
thresholds, but without the single-voxel false-positives. This suggests that the averaging
of thermal noise via smoothing delivers an implicit cluster size correction.

(4-6) illustrate that cropping the spiral readout to 1 mm resolution yields similar
activation maps to using the full 0.8 mm readout, both before and after smoothing. This
indicates that the assessment of spatial specificity is SNR-limited for the short functional
runs (5.5 min) investigated here.

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1113 Table SM 5

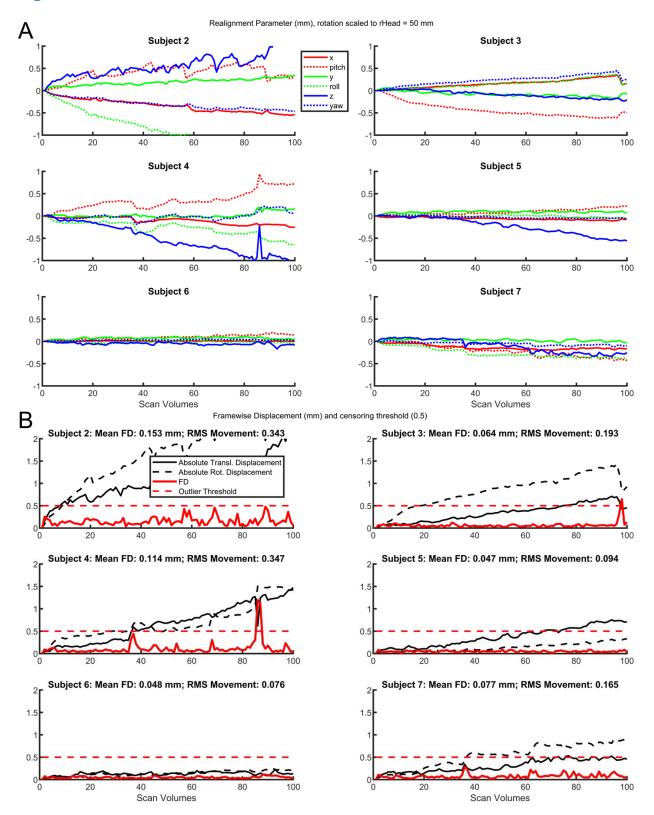
Comparison of acquisition efficiency in published 2D spiral fMRI studies. Nominal acquisition efficiency, computed as resolved voxels per unit time (i.e., matrix size per volume TR) is compared for several publications referenced in this manuscript. The combination of single-shot sequences with long readouts and parallel imaging, as utilized in this study, achieves the highest acquisition efficiency.

	resoluti [mmj				matrix size		inter- leave s	TR / interlea f	volum e TR	acquisition efficiency
Publication	ху	z	ху	z	ху	z		[s]	[s]	[1000 voxels/s]
(Glover and Lai,		5.	22							
1998)	2.4	0	0	30	90	6	1	1	1.0	49
	-	5.	24	12		2				
(Weiger et al., 2002)	3	0	0	0	80	4	1	2.5	2.5	61
(Ress et al., 2007)	0.7	0. 9	10 0	10	14 1	1 1	2	1	2	109
(IC35 Ct al., 2007)	0.7	0.	10	10	16	Т	Z	T	2	109
	0.6	9	0	7	0	8	3	0.7	2	102
(Preston et al., 2009; Wolosin et al., 2012;										
Zeithamova et al.,		3.	22		12	2				
2016)	1.7	0	0	66	9	2	4	1.0	4	92
$(\mathbf{U} + 1 + 1)$		1.	17		14				-	
(Katyal et al., 2010)	1.2	2	0	10	2	8	3	1.0	3	54
(Chang and Glover,	1 7	4.	22	00	12	2	1	2 5	2 5	4 5 7
2011)	1.7	0 2.	0 25	96	8 25	4 1	1	2.5	2.5	157
(Jung et al., 2013)	1	2. 0	23 6	30	25	5	4	1.0	4	246
	-	1.	24	50	16	2		1.0	·	210
	1.5	5	0	36	0	4	2	1.5	3	205
		0.			12					
(Kim and Ress, 2017)	0.7	9	90	7	8	8	3	1.0	3	44
(Saviani at al acre)	1 0	1.	17	10	14		2	0.0	2.4	C7
(Savjani et al., 2018)	1.2	2 1.	0 19	10	2 16	8 1	3	0.8	2.4	67
(Singh et al., 2018)	1.2	1. 2	2	14	0	2	3	1.0	3	102
This study	_	0.	23		28	3	_	-	-	
This study	0.8	9	0	32	8	6	1	3.3	3.3	902

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1121 Figure SM 6



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Motion parameters for all subjects during high-resolution (0.8 mm) spiral-out fMRI runs. 1123 Displayed are (A) the 3 translational and 3 rotational realignment parameter traces over 1124 volumes obtained by rigid-body registration, as well as (B) corresponding framewise 1125 displacement (FD) curves (Power et al., 2012). Mean FD was well below 0.2 mm for every 1126 subject (max. 0.15 mm, mean FD and standard deviation over subjects 0.09±0.04 mm), 1127 which is often considered a very rigorous criterion for censoring of motion-contaminated 1128 data (Power et al., 2015). Individual FDs of larger than 0.5 mm occurred in only 3 volumes 1129 of 2 subjects (red dashed line threshold). 1130

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