

Evaluating the effect of denoising submillimeter auditory fMRI data with NORDIC

Lonike K. Faes^{1*}, Agustin Lage-Castellanos^{1,2}, Giancarlo Valente¹, Zidan Yu^{3,4,5}, Martijn A. Cloos^{3,4,6},
Luca Vizioli⁷, Steen Moeller⁷, Essa Yacoub⁷, Federico De Martino^{1,7}

1 Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience,
Maastricht University, 6200 MD, Maastricht, The Netherlands

2 Department of Neuroinformatics, Cuban Neuroscience Center, Havana City 11600, Cuba

3 Center for Advanced Imaging Innovation and Research (CAI2R), Department of Radiology,
New York University School of Medicine, New York, NY, USA

4 Bernard and Irene Schwartz Center for Biomedical Imaging, Department of Radiology, New
York University School of Medicine, New York, NY, USA

5 MRI Research Center, University of Hawaii, United States

6 Australian Institute for Bioengineering and Nanotechnology, University of Queensland, St
Lucia 4066, Australia

7 Center for Magnetic Resonance Research, Department of Radiology, University of
Minnesota, Minneapolis, MN 55455, United States

*Corresponding author, email: l.faes@maastrichtuniversity.nl

21 **Abstract**

22 Functional magnetic resonance imaging (fMRI) has emerged as an essential tool for
23 exploring human brain function. Submillimeter fMRI, in particular, has emerged as a
24 tool to study mesoscopic computations. The inherently low signal-to-noise ratio (SNR)
25 at submillimeter resolutions warrants the use of denoising approaches tailored at
26 reducing thermal noise – the dominant contributing noise component in high resolution
27 fMRI. NORDIC PCA is one of such approaches, and has been benchmarked against
28 other approaches in several applications. Here, we investigate the effects that two
29 versions of NORDIC denoising have on auditory submillimeter data. As investigating
30 auditory functional responses poses unique challenges, we anticipated that the benefit
31 of this technique would be especially pronounced. Our results show that NORDIC
32 denoising improves the detection sensitivity and the reliability of estimates in
33 submillimeter auditory fMRI data. These effects can be explained by the reduction of
34 the noise-induced signal variability. However, we also observed a reduction in the
35 average response amplitude (percent signal), which may suggest that a small amount
36 of signal was also removed. We conclude that, while evaluating the effects of the signal
37 reduction induced by NORDIC may be necessary for each application, using NORDIC
38 in high resolution auditory fMRI studies may be advantageous because of the large
39 reduction in variability of the estimated responses.

40

41 **1 Introduction**

42 In recent years, the use of ultra-high field (UHF) magnetic resonance imaging has
43 rapidly increased for a variety of applications. At UHF, the signal-to-noise ratio (SNR
44 - Vaughan et al., 2001) and the blood-oxygenation-level-dependent (BOLD) contrast

45 (Ogawa et al., 1992), the basis of functional MRI (fMRI), increase (Yacoub et al.,
46 2001). This results in higher sensitivity to fMRI responses compared to more
47 conventional field strengths (e.g. 3T and below). This allows for enormous benefits for
48 the study of human brain function, in particular, the ability to acquire high spatial
49 resolution (below 1 mm isotropic voxels) images. As such, at UHF it is possible to
50 breach into the mesoscale and investigate fundamental computational structures and
51 organizations of cortical functions, such as layers and columns (see e.g. De Martino
52 et al., 2018; Dumoulin et al., 2018; Huber et al., 2015; Kok et al., 2016; Lawrence et
53 al., 2019; Moerel et al., 2021; Olman et al., 2012; Uğurbil, 2018; Yacoub et al., 2008;
54 Zimmermann et al., 2011).

55 The functional contrast to noise ratio (fCNR) in fMRI is dependent on the signal
56 change compared to baseline and both physiological and thermal noise. Submillimeter
57 fMRI at UHF trades the higher SNR for spatial resolution, often times leaving the
58 resulting data in a thermal noise dominated regime (characterized as unstructured,
59 zero-mean Gaussian distributed noise) emanating from electrical sources inherent to
60 MRI hardware (Triantafyllou et al., 2005, 2011). This makes approaches oriented
61 towards reducing thermal noise (i.e. improving the image SNR) of particular interest
62 for neuroscience applications that require mesoscopic level imaging. Importantly,
63 approaches for improving image SNR have to be evaluated against any practical
64 considerations or tradeoffs, for example, their ability to preserve spatial information
65 content at the finest scales (e.g. laminar and columnar cortical responses) (Polimeni
66 et al., 2018) or whether any unwanted biases are introduced (Kay, 2022). Extensive
67 averaging, one of the possible approaches for reducing thermal noise, could in
68 principle help in highlighting small functional changes without altering the signal
69 content. However, this approach – which assumes constant responses to the same

70 stimuli over extended periods of time – is limited by practical implications such as the
71 overall length of scanning sessions and the need for aligning data across multiple
72 imaging sessions. While precision imaging approaches, that collect extensive data in
73 only a few individuals, are becoming increasingly interesting in particular settings (see
74 e.g. Allen et al., 2022; Michon et al., 2022; Poldrack et al., 2017) their application to
75 mesoscopic imaging is far from standard and may not suffice when questions are
76 oriented to generalizing effects at the population level. As an alternative to averaging,
77 spatial smoothing could be used to increase image SNR. However, its application
78 needs careful consideration as it comes with inevitable loss of spatial specificity
79 (Turner & Geyer, 2014), which can be controlled if combined with anatomically
80 informed constraints (e.g. laminar smoothing maintains specificity in the cortical depth
81 direction while smoothing only tangentially) (Huber et al., 2021; Kiebel et al., 2000).
82 Apart from averaging and (image) smoothing (with anatomical constraints),
83 approaches for improving the detectability of effects (i.e. overcoming the limitations of
84 low SNR regimes) have been considered at the analysis stage. Multivariate analyses,
85 for example, have been argued to better leverage the information present in fine
86 grained patterns and in part overcome the lower SNR of high resolution functional
87 images, but may have some limitations in interpretability (Formisano & Kriegeskorte,
88 2012). In univariate analyses, the definition of noise regressors (through e.g. principal
89 component analysis - Kay et al., 2013), has also been considered in order to improve
90 the detectability of effects of interest, but relies on knowledge of the experimental
91 design and assumptions such as the definition of noise pools (i.e. a collection of voxels
92 whose time series is mostly representing noise sources). Denoising based on
93 independent component analysis (ICA) has also been developed in fMRI and
94 evaluated primarily in its ability to remove structured noise components (Pruim et al.,

95 2015) and improving detectability of effects in lower resolution functional data that are
96 mainly challenged by physiological noise (Griffanti et al., 2014; Salimi-Khorshidi et al.,
97 2014). For completeness it is important to note that approaches to remove structured
98 (physiological) noise in fMRI (and thus not tailored to the reduction of thermal noise)
99 include, apart from ICA, the use of multiple echoes to estimate sources of variance
100 (Gonzalez-Castillo et al., 2016; Steel et al., 2022), or measuring physiological data to
101 subsequently remove the noise sources from the data (e.g. RETROICOR - Glover et
102 al., 2000; or RETROKCOR - Hu et al., 1995).

103 A denoising technique tailored to the removal of thermal noise that has recently
104 been introduced is NOise Reduction with DIstribution Corrected Principal Component
105 Analysis (NORDIC PCA - Moeller et al., 2021; Vizioli et al., 2021). NORDIC is a pre-
106 processing approach based on PCA that selectively removes components that are
107 indistinguishable from zero-mean normally distributed noise (see e.g.
108 <https://layerfmri.com/2023/07/10/nordic/#more-3956> for an informal description of the
109 approach). Compared to other PCA denoising techniques (see Veraart et al., 2016),
110 the main difference rests in the approach used to estimate the number of (principal)
111 components that are removed (i.e. the threshold on the eigenvalue spectrum that
112 distinguishes noise components from signal components). NORDIC has been initially
113 extensively evaluated on visual cortical responses elicited by blocked (temporally
114 prolonged ~ 12 seconds) stimulation and has been shown to increase detection
115 sensitivity without affecting the overall signal change and spatial precision of the
116 responses (i.e. without introducing spatial blurring - Vizioli et al., 2021). NORDIC has
117 also been evaluated and compared to other PCA based denoising approaches
118 (dwidenoise - Cordero-Grande et al., 2019; Manzano-Patron et al., 2023; Veraart et
119 al., 2016). Compared to dwidenoise and more conventional smoothing approaches,

120 and in experimental designs ranging from blocked to event related visual stimulation,
121 NORDIC has been shown to better preserve local and global spatial smoothness of
122 the functional data as well as the temporal characteristics of the responses (i.e.
123 temporal smoothing) and it has been shown to not introduce unwanted effects (Dowdle
124 et al., 2023; but see Fernandes et al., 2023 for an evaluation in rodent data). NORDIC
125 has been rapidly picked up by the community and its usability is now being examined
126 across different areas (including visual and motor regions), field strengths (3T and 7T),
127 and acquisition techniques (see e.g. Dowdle et al., 2022; Knudsen et al., 2023;
128 Raimondo et al., 2023). These recent studies consistently show that NORDIC
129 improves detectability of the effects. However, while NORDIC has been shown to
130 improve (statistical) signal detection, generalizing these results to other cortical
131 regions and to designs that are particularly SNR limited (e.g. auditory cortical
132 responses elicited by slow event-related designs) still requires careful evaluation of its
133 benefits as opposed to any potential unwanted bias.

134 Here we focus on the application of NORDIC to submillimeter functional MRI
135 data collected to investigate auditory cortical responses elicited by a slow event-
136 related design. The auditory cortex is located next to large air cavities, with parts of it
137 like primary cortical regions lying further away from the receive coils compared to other
138 sensory regions (e.g. visual and somatosensory regions). These and other factors
139 (e.g. the need for large field of views to image bilateral auditory cortical areas) make
140 imaging auditory cortical regions sensitive to geometric distortions and signal dropouts
141 due to large B_0 inhomogeneities (Moerel et al., 2021) and not only for BOLD type
142 acquisitions (Faes et al., 2023). Furthermore, the percent signal change elicited in
143 auditory regions is lower than in visual cortex (De Martino et al., 2015). However,
144 despite these challenges, there have been several high resolution auditory studies that

145 look at cortical depth dependent responses (see e.g. Ahveninen et al., 2016; De
146 Martino et al., 2015; Gau et al., 2020; Moerel et al., 2018). As such, given that auditory
147 submillimeter studies are especially restricted by low SNR, they would greatly benefit
148 from thermal noise reduction. However, the efficacy of PCA-based denoising methods
149 also depends on the relative contribution of signal and noise. Therefore, submillimeter
150 auditory fMRI may present a challenge for NORDIC. Collectively, these considerations
151 warrant the need to explore the effect of NORDIC denoising on submillimeter fMRI
152 data collected in the auditory cortex. We center our evaluation on the improvements
153 in tSNR by considering changes to both the mean percent signal change and its
154 variability.

155

156 **2 Methods**

157

158 2.1 NORDIC

159 NORDIC is a denoising approach that operates on either complex-valued or
160 magnitude-only fMRI time series. As the use of parallel imaging results in a spatially
161 varying amplification of the thermal noise according to the g-factor (Pruessmann et al.,
162 1999), if necessary, the NORDIC algorithm first normalizes the functional data by the
163 g-factor, resulting in the thermal noise being uniformly distributed across space (to
164 fulfill the assumption of PCA denoising that noise is identically distributed across
165 voxels). NORDIC uses a locally low rank approach to perform a patch-wise PCA
166 across space and time. An estimate of the noise level is obtained from an appended
167 acquisition without a radiofrequency excitation (e.g. a noise scan) or an estimate of
168 the g-factor noise (Ma et al., 2020). In each patch, the noise threshold defines the
169 principal components that are removed from the eigenspectrum as they are
170 considered to be indistinguishable from zero-mean Gaussian distributed noise. The

171 noise threshold is chosen with Monte-Carlo simulations for a Casorati matrix with zero-
172 mean normally distributed sampling and, depending on the settings, considering an
173 ideal or realistic noise distribution. After the removal of noisy principal components,
174 the patches are recombined and the g-factor is re-applied to reconstruct the fMRI
175 images. Assuming signal redundancy within the patch (i.e. enough voxels carrying the
176 same information), NORDIC aims at removing thermal noise from the time series while
177 preserving the fine-grained temporal and spatial structure of the signal that is assumed
178 to be carried by the preserved principal components. For more details on NORDIC we
179 refer to the original publications (Moeller et al., 2021; Vizioli et al., 2021).

180 Currently, there are two implementations of NORDIC available
181 (https://github.com/SteenMoeller/NORDIC_Raw). We focus on the use of
182 (NIFTI_NORDIC - version 04-22-2021) which takes nifti formatted data of both
183 magnitude and phase images as input.

184

185 2.2 MR imaging acquisition

186 Data was collected with a 7T Siemens Magnetom System with a single channel
187 transmit and 32-channel receive NOVA head coil (Siemens Medical Systems,
188 Erlangen). Whole-brain anatomical T1-weighted images were collected using a
189 Magnetisation Prepared 2 Rapid Acquisition Gradient Echo (MP2RAGE) sequence at
190 a resolution of 0.75 mm isotropic (192 slices, TR = 4300 ms, TE = 2.27 ms) (Marques
191 et al., 2010).

192 Functional data were acquired with 2D gradient-echo (GE) echo planar imaging
193 (EPI) along with simultaneous multi-slice (SMS)/(MB) multiband (Moeller et al., 2010;
194 Setsompop et al., 2012) (0.8 mm isotropic, 42 slices, TR = 1600 ms, TE = 26.4 ms,
195 MB factor 2, iPAT factor 3, 6/8 Partial Fourier, bandwidth 1190 Hz, field of view: 170 x

196 170 mm, matrix size: 212 x 212, phase encoding = anterior to posterior; coil
197 combination = SENSE1).

198

199 **2.3 Participants**

200 Ten healthy participants took part in this fMRI study (aged between 23 and 69 years
201 old, 5 females). Participants had no history of neurological disease or hearing
202 disorders. Eight participants were scanned at the Center for Magnetic Resonance
203 Research in Minneapolis (CMRR) and two were scanned at New York University
204 (NYU) using the identical imaging protocol except for slight differences in TR (TR_{CMRR}
205 = 1600 ms, TR_{NYU} = 1650 ms). The local IRB at the individual institutions approved
206 the experiment. All participants signed informed consent forms before commencing
207 the study.

208

209 **2.4 Experimental design**

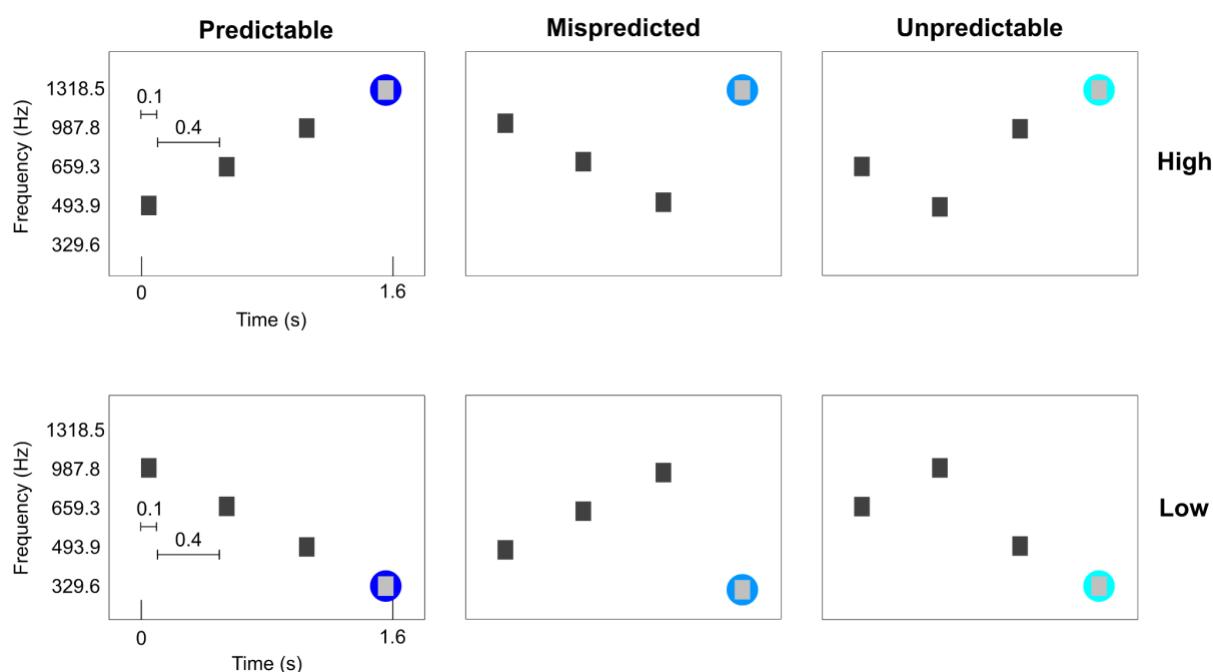
210 Participants passively listened to tone sequences. Conditions were designed to
211 investigate predictive processing in the auditory cortex (based on sequences used in
212 Berlot et al., 2018), but we will disregard the neuroscientific purpose of the
213 experimental paradigm and focus on the effect of denoising instead.

214 Six conditions were presented. All conditions consisted of sequences of four
215 tones. The four tones were presented for 100 ms each with a 400 ms gap between
216 tones (total tone sequence length was 1.6 seconds). The conditions were designed
217 such that the first 3 tones were 'contextual' tones ordered in either a descending,
218 ascending or scrambled fashion. The frequencies used for these contextual tones
219 were always the same three (493.9, 659.3 and 987.8 Hz), albeit presented in a
220 different order. The fourth tone was selected such that three conditions ended in a

221 high frequency (1318.5 Hz) and three conditions ended in a low frequency (329.6 Hz).
222 This resulted in two predictable sequences (PredH and PredL), two mispredicted
223 sequences (MispredH and MispredL), and two unpredictable sequences (UnpredH
224 and UnpredL) as displayed in Figure 1. The auditory stimuli were presented
225 concomitantly with the scanner noise (i.e. no silent gap for sound presentation was
226 used).

227 Per run, each of the predictable sequences were presented 10 times, the
228 mispredicted sequences and the unpredictable sequences were each presented 4
229 times in a randomized order (for a total of 36 trials in one run). Tone sequences were
230 presented in a slow event-related design with an average inter-trial interval of 6 TR's
231 (ranging between 5 and 7 TR's). For each participant, we collected 6 to 8 runs that
232 lasted approximately 6 minutes each (including noise scans at the end of each run).
233 Magnitude and phase Dicom images were exported from the scanner.

234



235
236 **Figure 1. Experimental conditions.** The first three tones are contextual eliciting a strong or weak
237 prediction. The three contextual tones are presented at the same frequencies, albeit in different orders.
238 The fourth tone can either be a high or low target frequency. The fourth tone can either consecutively
239 follow the ascending or descending order (PredH and PredL), or the contextual tones could be deviant

240 (MispredH and MispredL) or the contextual tones could be scrambled (UnpredH and UnpredL). The two
241 predictable sequences were presented ten times per run, whereas the other four conditions were
242 presented four times per run.

243

244 **2.5. Data preprocessing**

245 ***2.5.1 NORDIC preprocessing***

246 Dicom files were converted to NIfTI format (separately for magnitude and phase
247 images - MRICron, version 1.0.2). The magnitude and phase NIfTI files were used as
248 the input to NIFTI_NORDIC. We used two different settings for NORDIC denoising: 1)
249 using default settings for fMRI data (PCA kernel size of 11:1, temporal phase = 1,
250 phase filter width = 10, the noise scan is used for empirical noise estimation) and 2)
251 the same as the default except for the use of the noise scan in the estimation of the
252 noise threshold. In the NIFTI_NORDIC implementation, not using the noise scan
253 results in using a noise threshold based on the g-factor estimation (in the
254 implementation, a threshold of $1/\sqrt{2}$), which is generally more conservative (i.e.
255 resulting in the removal of less principal components) than the estimated threshold
256 when using the noise scan, reflecting the empirical observation that the approach for
257 g-factor estimation underestimates the value by up to 10%. This resulted in three
258 datasets (per run), the first, which will be referred to as the '*Original*', represents the
259 fMRI data without NORDIC denoising. The second, which we will refer to as '*NORDIC*
260 *default*' (NORdef), represents the fMRI time series resulting from the processing with
261 default NORDIC settings. The third, we will refer to as '*NORDIC No Noise*' (NORnn),
262 represents the fMRI time series resulting from the use of NORDIC without separate
263 noise scans for the estimation of the noise threshold.

264

265

266

267 *2.5.2 Pre-processing*

268 The anatomical and functional data were analyzed using a BrainVoyager software
269 package (BV - version 21.4, Brain Innovation, Maastricht, The Netherlands) and
270 custom Matlab scripts (The MATHWORKS Inc., Natick, MA, USA). After the initial
271 NORDIC denoising step, functional processing was performed identically across
272 datasets. The noise acquisitions were removed from each time series. Pre-processing
273 of the functional data included slice scan time correction using sinc interpolation and
274 motion correction along three dimensions using intrasession alignment to the run
275 closest in time to the collection of opposite phase encoding images (run 1 in most
276 participants, run 4 in two participants). In addition, temporal filtering was applied to
277 remove low frequencies (high-pass filtering with 7 cycles per run) and high frequencies
278 (temporal gaussian smoothing with a full width half maximum kernel of 2 data points).
279 Reversed phase polarity acquisitions were used to correct for geometric distortions
280 using Topup (FSL version 6.0.4). In one participant we experienced issues collecting
281 opposed phase polarity images and therefore no distortion correction was performed
282 in this participant.

283 The anatomical data were upsampled to 0.4 mm isotropic, corrected for
284 inhomogeneities and transformed to ACPC space. A segmentation was created using
285 the deep neural network in BV to determine the initial white matter (WM) and gray
286 matter (GM) boundary and GM/cerebral spinal fluid (CSF) border. The segmentation
287 of the temporal lobe was manually corrected in ITK snap (Yushkevich et al., 2006).
288 With this corrected segmentation, we created mid-GM surface meshes in BV.
289 Additionally, we estimate the cortical thickness of the high-resolution segmentation.

290

291

292 *2.5.3 ROI definition*

293 Five bilateral regions of interest (ROIs) were drawn on the individual mid-GM meshes
294 based on macro-anatomical landmarks (as described in Kim et al., 2000), covering the
295 temporal lobe including Heschl's Gyrus (HG), Planum Polare (PP), Planum Temporale
296 (PT), anterior superior temporal gyrus (aSTG) and posterior superior temporal gyrus
297 (pSTG). These ROIs were projected back onto the anatomy in volume space
298 (extending 3 mm inwards and outwards from the mid-GM surface). These masks were
299 first intersected with the GM definition and then dilated (six steps) in order to obtain
300 the final masks that include GM as well as the WM and the CSF surrounding it. The
301 union of all the masks (temporal lobe mask) was used to run the statistical analysis
302 (General Linear Model, see below), while results were inspected separately per ROI
303 in some analyses.

304

305 **2.6. Analyses**

306 *2.6.1. General Linear Model*

307 All statistical analyses were performed with custom Matlab scripts. Time series were
308 first normalized to percent signal change (PSC). For our first-level analysis, we fitted
309 a general linear model (GLM) with single trials per condition as predictors (36 trials
310 and one constant per run). Predictors were convolved with a standard two-gamma
311 hemodynamic response function (HRF) that peaked at 5 seconds after the onset of
312 the stimuli. In order to evaluate the effects that NORDIC has on the reliability of the
313 responses, we obtained response estimates (beta weights) and computed statistical
314 activation maps by considering the variability across single trials (i.e. beta time series)
315 for all predictors combined (sounds versus no sounds) and for each condition
316 separately. In other words, we here estimate the variance of the response considering

317 the variability across trials and not the variance of the residuals of the GLM fit. This
318 helped us in evaluating measures of reliability of the response estimates.

319 After the GLM, in each individual's anatomical ROI (considering all voxels in the
320 ROI) we evaluated: 1) the change in beta (PSC) per condition before and after
321 NORDIC processing; 2) the change in single trial t-statistics (mean divided by variance
322 across trials); 3) the spatial replicability of the mean betas (PSC); and 4) the spatial
323 replicability of the t-statistics. For all individual subject data, all analyses were
324 performed by randomly sampling half of the runs (i.e. repeated split half with 50
325 repetitions - Valente et al., 2021). The spatial replicability of the betas and t-statistics
326 was computed by correlating the variable of interest (PSC or t-statistics) across the
327 two random splits of the data. Finally, across all ROIs we investigated changes in beta
328 values (before and after NORDIC) in relation to the tSNR. Note that we compute tSNR
329 (defined as the mean divided by the standard deviation of the time series) on the
330 original data after pre-processing ($tSNR_{pr}$). This choice inflates the tSNR we report
331 compared to the more conventional choice to calculate tSNR on the un-preprocessed
332 data (in analyses not shown we confirmed that the results we report here are not
333 dependent on the choice of pre-processing applied to the time series).

334 At the group level, interactions were tested with repeated measures ANOVA
335 (where processing strategy is the repeated measure). Main effects were tested for
336 significance using permutation testing by permuting, for each test, individual subject
337 data across processing strategies (all possible permutations [2^{10}]) and corrected for
338 multiple comparisons using Bonferroni.

339

340 *2.6.2. Correlation and cross-validation analyses*

341 To evaluate the spatial similarity of beta estimates across processing strategies we
342 computed the correlation of the estimated beta maps. In particular, we considered: 1)
343 the correlation of each NORDIC processed run (NORdef and NORnn) to the
344 corresponding original run (separately for each of the six conditions); 2) the run-to-run
345 correlation within each processing strategy (i.e. within Original, NORdef and NORnn
346 data) and 3) using leave-one-run-out, the correlation of each run (i.e. run 3) to the
347 average of all other runs (all runs except run 3). Importantly for this last analysis the
348 reference model (i.e. the averaged map coming from all runs except one) was always
349 kept to be the one extracted from the original time series.

350 At the group level, interactions (e.g. processing strategy and condition in the
351 first analysis) were tested with repeated measures ANOVA (where processing strategy
352 is the repeated measure). To do this, data were Fisher z-transformed prior to the
353 ANOVA. Main effects were tested for significance using permutation testing by
354 permuting, for each test, individual subject data across processing strategies (all
355 possible permutations [2^{10}]) and corrected for multiple comparisons using Bonferroni.

356

357 *2.6.3 Tonotopic maps*

358 From the two predictable conditions we create tonotopic maps (as best frequency
359 maps, see Formisano et al., 2003; Heynckes et al., 2023 for an example where the
360 procedure is applied with only two frequencies, as is the case here). Tonotopic maps
361 were computed in volume space and interpolated to the mid cortical surface.

362

363 2.6.4 Variance Partitioning

364 We reasoned that the total variance from the original (magnitude) time series (per
365 voxel) could be partitioned as follows:

366
$$Y_{ori} = \alpha Y_{AN} + b + \varepsilon_{AN}$$

367 Where Y_{ori} and Y_{AN} are the original time series and the time series after NORDIC
368 preprocessing respectively (Y_{AN} can then come from either NORdef or NORnn). The
369 values for the scaling factor and intercept were estimated with ordinary least squares
370 (OLS), thus obtaining an estimate of the scaling and intercept ($\hat{\alpha}$ and \hat{b}). The estimated
371 scaling and intercept are then used to compute (per voxel) estimated residuals $\hat{\varepsilon}_{AN}$.
372 These residuals can be interpreted as the portion of the original time series that is
373 orthogonal to the NORDIC time series. We refer to this as the residuals of the original
374 time series after NORDIC (residuals after NORDIC in short). This decomposition
375 guarantees that the total sum of squares of the original data (representing the
376 variability in the data with respect to their mean) can be expressed as the sum of
377 squares of the data after NORDIC (weighted by $\hat{\alpha}$) and the sum of squares of portion
378 of the original data that is orthogonal to the data processed with NORDIC (i.e. the
379 residuals after NORDIC $\hat{\varepsilon}_{AN}$). That is:

380
$$SSY_{ori} = \hat{\alpha}^2 SSY_{AN} + SSY_{\hat{\varepsilon}_{AN}}$$

381 To quantify the variance associated with the experimental design in the original data,
382 as well as the data after NORDIC processing and the residuals after NORDIC ($\hat{\varepsilon}_{AN}$),
383 we regressed Y_{ori} , Y_{AN} , and $\hat{\varepsilon}_{AN}$ against our design matrix (X). This second regression
384 allowed us to partition the variance that, in each of the three signals of interest (Y_{ori} ,
385 Y_{AN} , and $\hat{\varepsilon}_{AN}$), is related to the design (SSY_{ori}^X , SSY_{AN}^X , $SSY_{\hat{\varepsilon}_{AN}}^X$), along with an error
386 term for each.

387 We present the results by calculating the ratio of the sum of squares. First,
388 within each processing strategy (Original, NORdef and NORnn), we compared the
389 variance explained by the design to the total variance of each respective time series.
390 Second, for the NORDIC processed data (NORdef and NORnn) we compared the
391 variance associated with the design, in their respective residuals after NORDIC
392 ($\hat{\epsilon}_{AN_NORdef}$ $\hat{\epsilon}_{AN_NORnn}$), to the total sum of squares of the original time series. This last
393 analysis allowed us to reveal the portion of the variance associated with the design
394 that is not present in the NORDIC processed data and is thus removed by NORDIC.

395

396 *2.6.5 Laminar analysis*

397 We explored the effect of NORDIC denoising on the cortical depth dependent
398 estimates. Beta maps were computed across 11 cortical depths and sampled on the
399 mid-GM surface in BV. These maps were subsequently intersected with a mask of
400 HG. The single trial betas were averaged across vertices and subsequently across
401 trials. The variability was computed across trials.

402

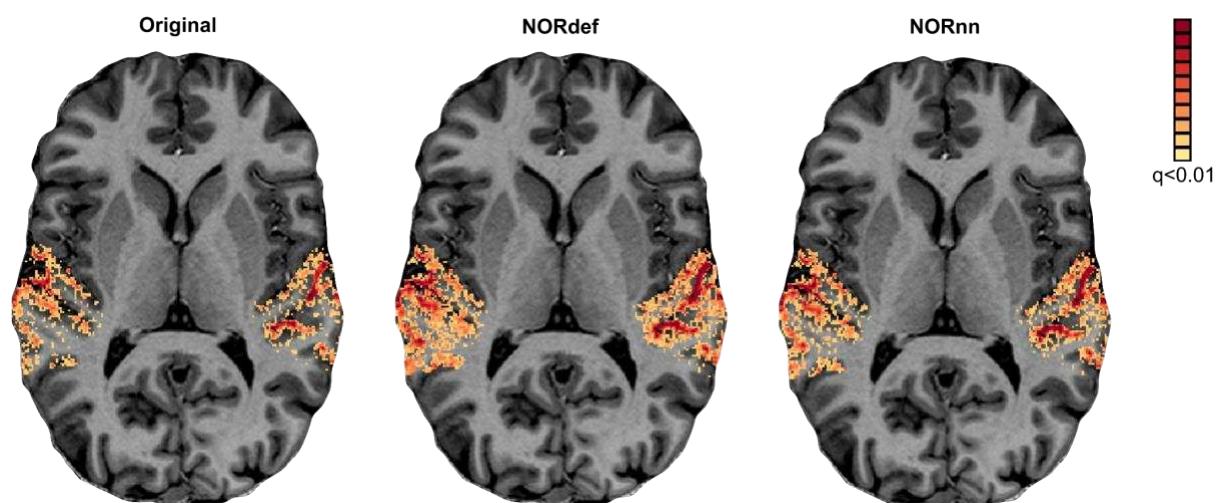
403 **3 Results**

404 3.1 Activation and spatial patterns

405 We assessed the effect of NORDIC on detection sensitivity by evaluating the overall
406 activation (sounds > no sounds) elicited by single trials in our experimental design.
407 Statistical maps were computed by considering the mean and variability (t statistic)
408 across (single) trials (not the GLM residuals) and corrected for multiple comparisons
409 using false discovery rate of $qFDR < 0.01$. This is a more stringent threshold than the
410 customary $qFDR < 0.05$ because it allows better appreciation of the differences
411 between processing strategies in each individual. Figure 2 presents the results in one

412 exemplary volunteer (all other volunteers showed similar results - data not shown) on
413 a representative transversal anatomical slice, highlighting the statistical advantage in
414 detection sensitivity conferred by denoising. At the same statistical threshold both
415 NORdef and NORnn resulted in more activation. In this volunteer, for example, 34%
416 of voxels in our temporal lobe mask were significantly active at the qFDR threshold,
417 whereas NORdef and NORnn resulted in 51% and 44% of voxels active, respectively.
418 NORDIC denoising results in overall higher t-statistics, the 90th percentile across
419 voxels for each of three datasets was 10.38, 13.42, and 12.38, respectively. These
420 results are in line with previous applications of NORDIC (Dowdle et al., 2022, 2023;
421 Knudsen et al., 2023; Raimondo et al., 2023; Vizioli et al., 2021) and similar to these
422 previous reports, activation maps do not appear spatially distorted (i.e. blurred) when
423 comparing NORDIC processed data to the original.

424



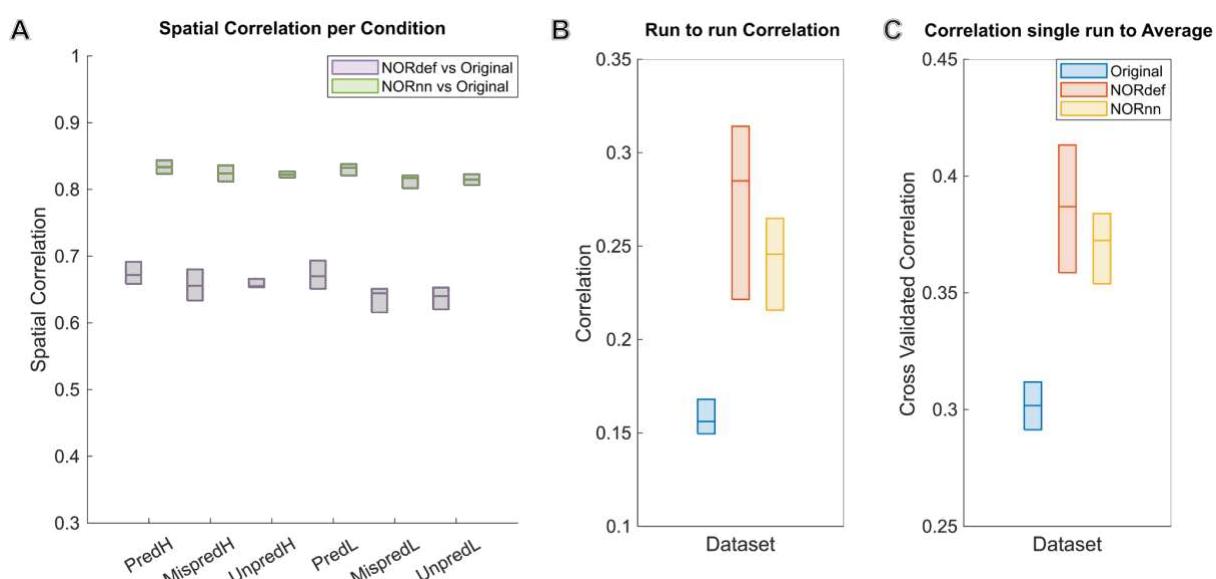
425

426 **Figure 2. Single subject overall response to sounds (qFDR<0.01).** From left to right we show the t-
427 maps resulting from a GLM with single trials as predictors of the Original, NORdef and NORnn data on
428 a transversal slice.
429

430 To evaluate some of these effects further, we analyzed the spatial patterns of
431 activation (separately per condition). Figure 3A shows the similarity (correlation) of
432 beta maps averaged across trials of NORdef and NORnn to the beta maps obtained

433 from the original data (median and interquartile range across runs). NORnn resulted
434 in a higher correlation to the original data compared to NORdef but the correlation
435 values were similar across conditions. That is, the similarity was not influenced by the
436 different amount of repetitions of specific conditions (e.g. the mispredicted and
437 unpredictable conditions). In what follows, we present results of the predictable
438 condition(s) only. Figure 3B shows the run-to-run reproducibility of the spatial patterns
439 of activation within each processing strategy for PredH. NORdef and NORnn resulted
440 in more reproducible spatial patterns compared to the original dataset. These first two
441 analyses show that NORdef and NORnn effectively reduce thermal noise and improve
442 reliability of the estimates (Figure 3B), while NORnn preserves more similarity to the
443 original data. In the absence of a ground truth, we reasoned that the spatial pattern
444 elicited by averaging multiple runs of the original data would be a reasonable choice
445 to compare the results of single runs in their ability to approximate results obtained
446 with higher SNR. To this end, we computed the average of the spatial pattern of
447 activation elicited by PredH in the original data in all but one run. This reference pattern
448 was correlated to the left out run in the original data and to the same run after NORDIC
449 processing. We repeated this analysis each time leaving a different run out. The results
450 (Figure 3C) show that after NORDIC, activation patterns in individual runs are more
451 similar to the reference.

452

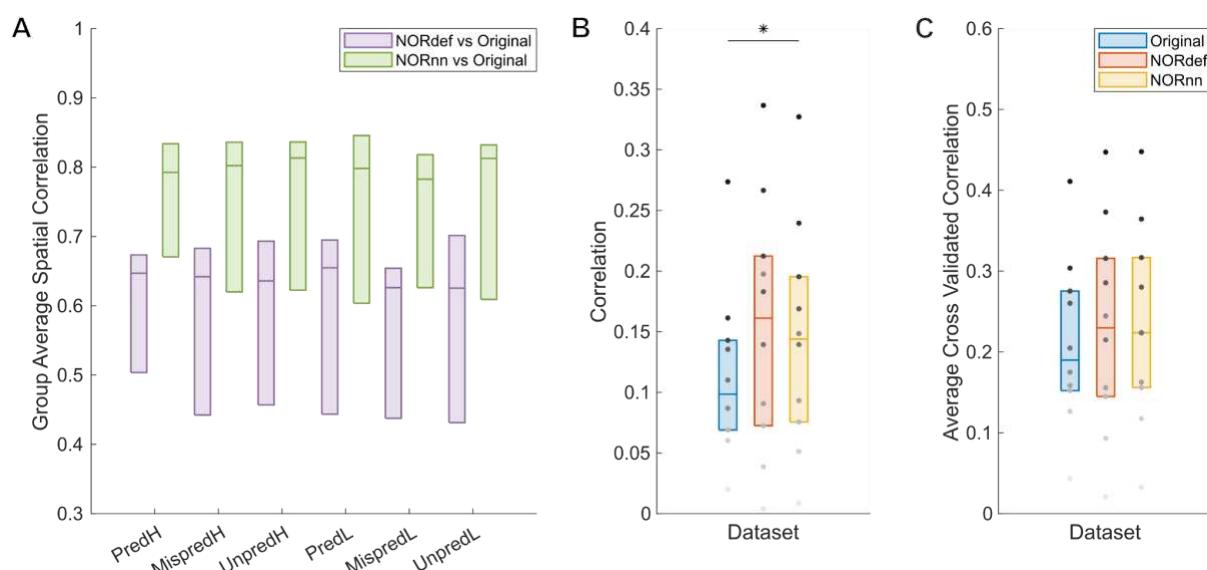


453 **Figure 3. Single participant correlation analyses.** Box charts display the median and interquartile
454 ranges. A) Spatial correlations of beta maps for each condition. There is no difference in correlations
455 between conditions. The correlation values between NORnn and the Original dataset are higher,
456 indicating that noise removal in NORnn is more conservative than in the NORdef dataset. B) Run-to-
457 run pairwise correlations computed per dataset for the PredH condition. Beta estimates across runs
458 become more similar in both denoised datasets, albeit the estimates are more stable in the denoised
459 data. C) Cross-validated correlation of one run to the average of n-1 runs of the Original data for the
460 PredH condition. Both denoised datasets are more similar to the average of the Original dataset.
461

462 Figure 3 reports the result in a representative volunteer, while the group results
463 (median and interquartile range across all our volunteers) is presented in Figure 4
464 (considering the variability across the mean estimates of every subject). The group
465 results support the trend seen in the single-subject analysis, except in two individuals
466 that showed very little improvement in either run-to-run variability or correlation to the
467 reference pattern obtained in the original data (light gray dots in Figure 4B and C).
468 Correlation coefficients were compared with a two-way repeated measures ANOVA
469 (with condition and processing strategy as factors). There was no interaction between
470 condition and processing strategy. Permutation testing showed a main effect of
471 method, ($p < 0.001$) indicating that at the group level NORnn results in a larger similarity
472 of the spatial patterns to the original data. This is in line NORnn being more
473 conservative, that is, resembling more the original data (due to a lower noise threshold

474 and the removal of less noise components). The stability of run-to-run estimates
475 (Figure 4B) was significantly higher for the NORnn compared to the Original data
476 ($p=0.041$), whereas there was no evidence of a difference between NORdef and the
477 Original data ($p=0.064$). At the group level, the correlation of a single run to the
478 average of our reference was not significant in either NORdef compared to the Original
479 data ($p=0.258$) or NORnn compared to the Original data ($p=0.053$).

480



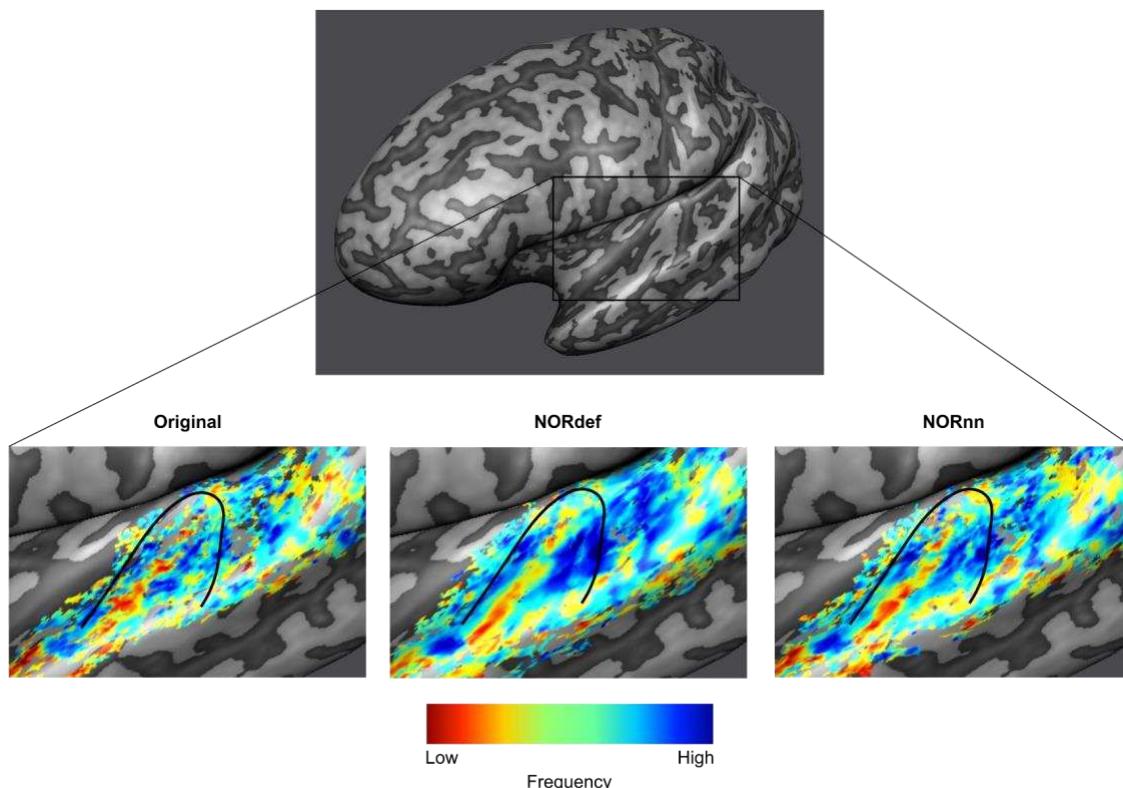
481
482

483 **Figure 4. Group Figure of the same analysis as Figure 3.** A) Across conditions, correlations between
484 NORDIC denoised datasets and the Original data are indistinguishable indicating that number of
485 repetitions do not affect the effect of NORDIC denoising. B) In general, stability of beta estimates
486 increases with the use of NORDIC denoising. Gray dots indicate different participants. C) Average cross
487 validated correlation values of single runs to the average of the Original data, for both predictable
488 conditions. * indicates $p<0.05$, ** indicates $p<0.01$.
489

490 Our design also allows the derivation of tonotopic maps, albeit from only two
491 frequencies, by computing best frequency maps on the predictable high and
492 predictable low conditions. Figure 5 shows, for a single left hemisphere, tonotopic
493 maps projected on the mid-GM surface intersected with their respective t-map. As
494 expected (Moerel et al., 2014), a low frequency preferring region is visible along
495 Heschl's gyrus (HG) surrounded by two high frequency preferring areas. This gradient
496 is visible in the Original data and becomes more discernible in the NORnn and NORdef

497 tonotopic maps, respectively. The fact that some regions are more clearly preferring
498 one of the two frequencies (i.e. blue regions anterior to HG) highlights the fact that
499 after NORDIC the frequency preference is more spatially homogeneous and less
500 corrupted by noise.

501



502
503 **Figure 5. Tonotopic maps.** Frequency preference maps are computed for each dataset and for one
504 example participant we display these maps on an inflated mid-GM surface. Denoising does not seem
505 to alter the frequency preference as the high-low high gradient is visible in all three datasets. The maps
506 computed from the denoised datasets are less noisy.
507

508 The previous applications of NORDIC (Dowdle et al., 2023; Vizioli et al., 2021)
509 have shown that detection sensitivity with NORDIC comes due to a reduction in
510 variance without any change to the percent signal response. While this effect would
511 explain our results at the level of the whole temporal lobe (reported in Figures 3 and
512 4), we investigated changes in percent signal as well as its variability across trials also
513 in separate anatomically defined ROIs. In the temporal lobe, across all ROIs, NORDIC
514 denoising resulted in reduced percent signal change (Figure 6A). This reduction was

515 more pronounced in the NORdef compared to NORnn. Changes in PSC though come
516 with a larger change in variability of the response when using NORDIC. This is clear
517 when considering t-values within each of the ROIs (Figure 6B). The increase in t-
518 values is most apparent in the NORdef time series. These changes induced by
519 NORDIC processing are visible in ROIs that are activated by our design (i.e. the
520 pattern is less visible in the aSTG that has little activation in our experiment). The
521 change in betas induced by NORDIC is most evident in voxels whose overall signal
522 level is low (see Figure 7). The bias introduced by NORDIC in the single ROIs does
523 not come with detrimental effects to the reliability of the estimates in each ROI
524 compared to the analysis at the level of the whole temporal lobe. When analyzing the
525 reliability of spatial patterns in the individual ROIs (Figure 6C and D for PSC and t-
526 value, respectively) the results are in line with the previously reported pattern at the
527 level of the whole temporal cortex (Figures 3 and 4), that is NORDIC processing is
528 associated with a general improvement in reliability.

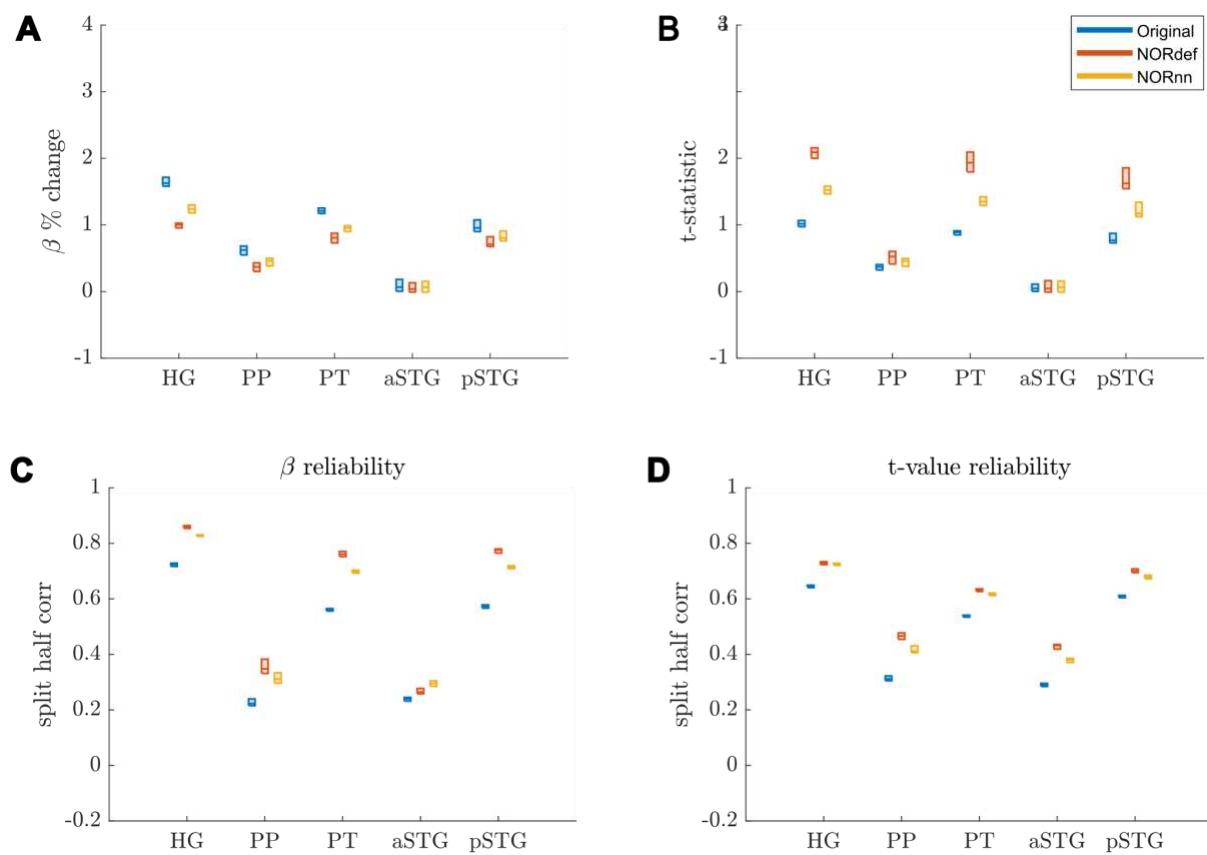
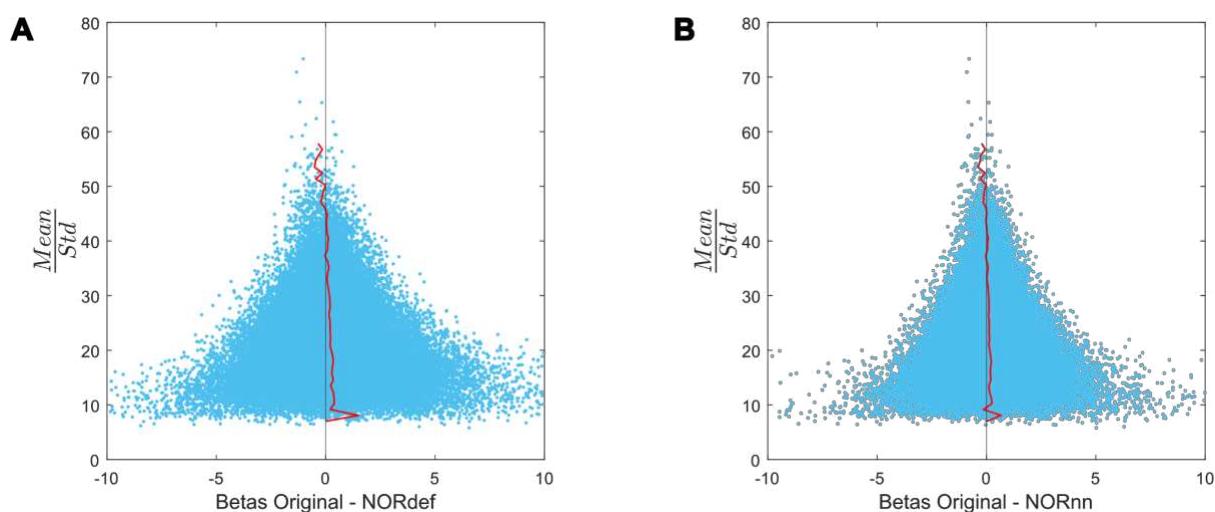


Figure 6. Responses in gray matter confined to regions of interest. A) Beta values calculated in percent signal change. In each ROI where there is signal present in the Original dataset, we observed a reduction in beta values after denoising. This reduction was lower in NORnn. B) T-statistics are increased after denoising, which was most pronounced in the NORdef dataset. C) Split half correlations were calculated to estimate the stability of beta responses. This revealed that beta values are more stably estimated after denoising. D) T-values are more reliably estimated in NORDIC.



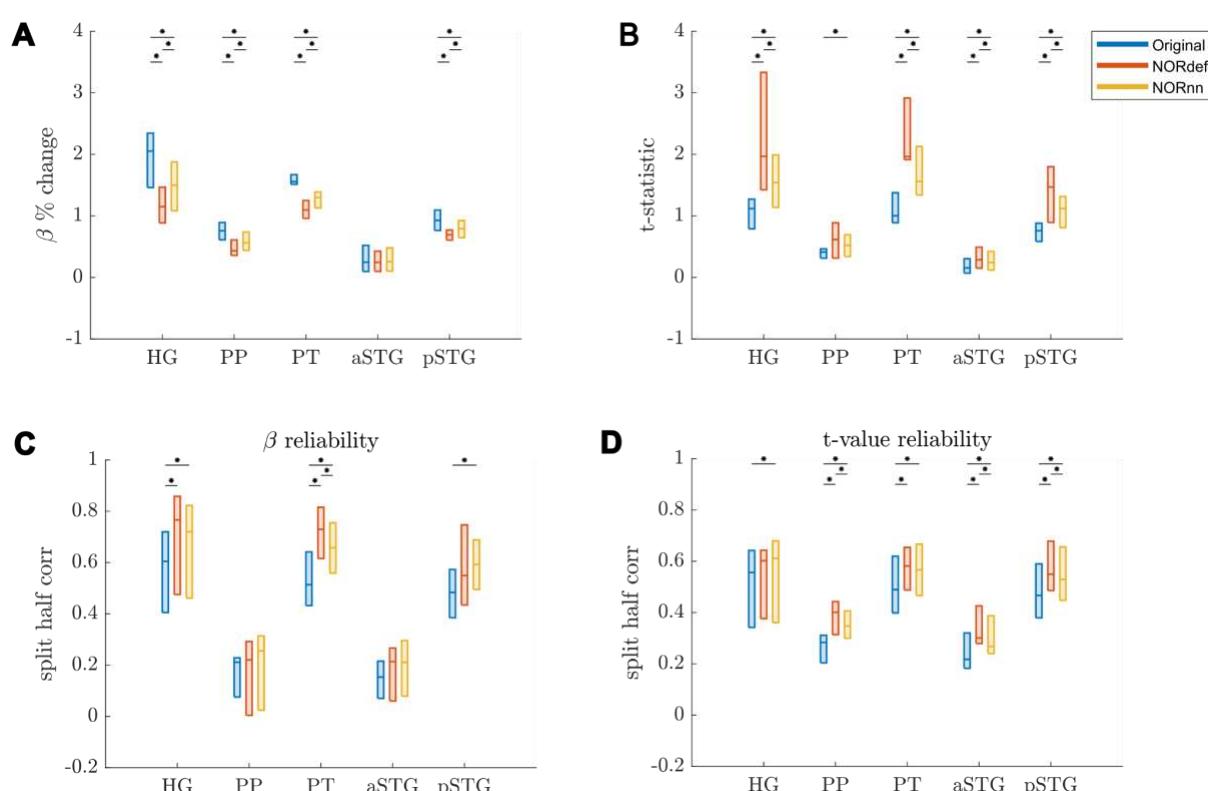
529
530
531
532
533
534
535
536

537

Figure 7. Beta difference in relation to tSNR for one representative subject. A) Betas before and after NORDIC are displayed as a function of mean/standard deviation ($tSNR_{pr}$). For low $tSNR_{pr}$ values, the betas change in both directions. However, at high $tSNR_{pr}$, the betas remain relatively similar after NORDIC. The red line indicates the mean beta difference per bin. The black line indicates a beta difference of zero. B) Same as A but for the beta difference between Original minus NORnn betas.

544 At the group level (Figure 8), a similar result becomes apparent. These results indicate
545 that, in our data, there is evidence for a bias-variance tradeoff associated with the
546 application of NORDIC. Repeated measures ANOVAs showed a significant interaction
547 between processing strategy and ROI for each of the subfigures of Figure 8 (all p-
548 values were smaller than 0.001). Per ROI we subsequently tested all three
549 comparisons using permutation testing and corrected for multiple comparisons. The
550 resulting p-values can be found in Table 1 in the Supplementary Materials.

551



552

553 **Figure 8. Group Figure of beta- and t-value estimates.** A) Average reduction of beta values across
554 participants. B) At the group level, the increase in t-values remains. C) On average, denoising results
555 in a better estimate of beta values calculated with split half correlations in ROIs where there is more
556 signal in the data. D) t-value reliability is generally higher after NORDIC than in the Original data.
557 * indicates $p < 0.05$.

558

559

560 3.2 Variance Explained

561 To investigate the nature of the bias introduced by NORDIC further, we quantified the
562 variance explained by the design both in the time series as well as in the portions of

563 the original time series that are not present in either the NORdef or NORnn time series.

564 When computing the variance explained by the design compared to the total variance

565 of the signal (in each respective method dataset – Total SS), denoising resulted in an

566 increasingly higher portion of variance explained by the experimental design (Figure

567 9A). This is in line with the increased statistical detection sensitivity afforded by

568 NORDIC denoising (with or without the noise scan - Figure 2). Interestingly though,

569 after NORDIC, information related to the experimental design was present in the part

570 of the signal that was removed by the denoising procedure. In relation to the total

571 original variance (Total SS Original), the variance explained by the design in the

572 residuals after NORDIC was higher for NORdef compared to NORnn, which is in line

573 with the higher number of principal components that are removed when using NORdef

574 compared to NORnn. Similar patterns of variance explained in the data or the residuals

575 after NORDIC were visible across all individual subjects (Figure 10). Permutations

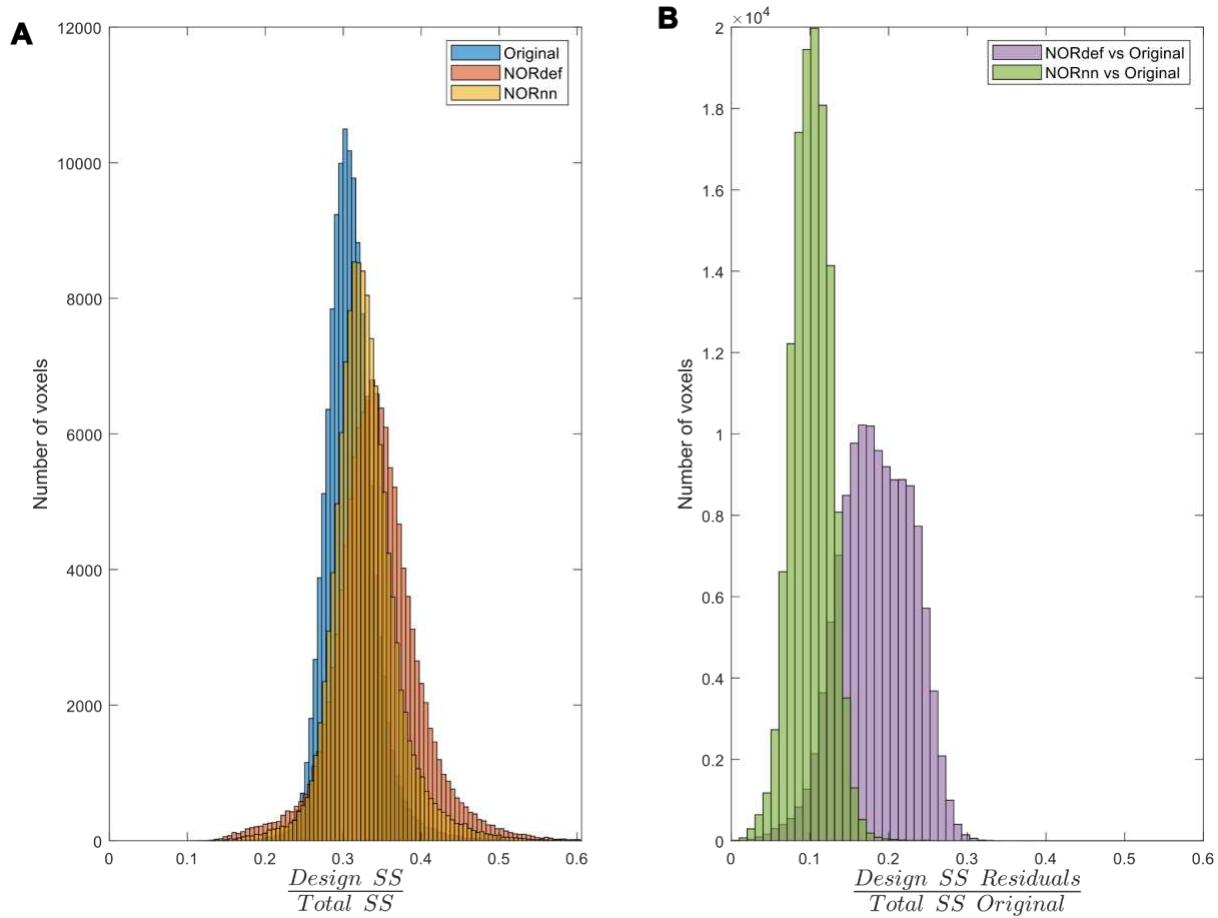
576 indicated that the effects described were significant against and alpha level of 0.05,

577 corrected for multiple comparisons, both for the increase in variance explained by the

578 design in the time series (before and after NORDIC) and for the increase in variance

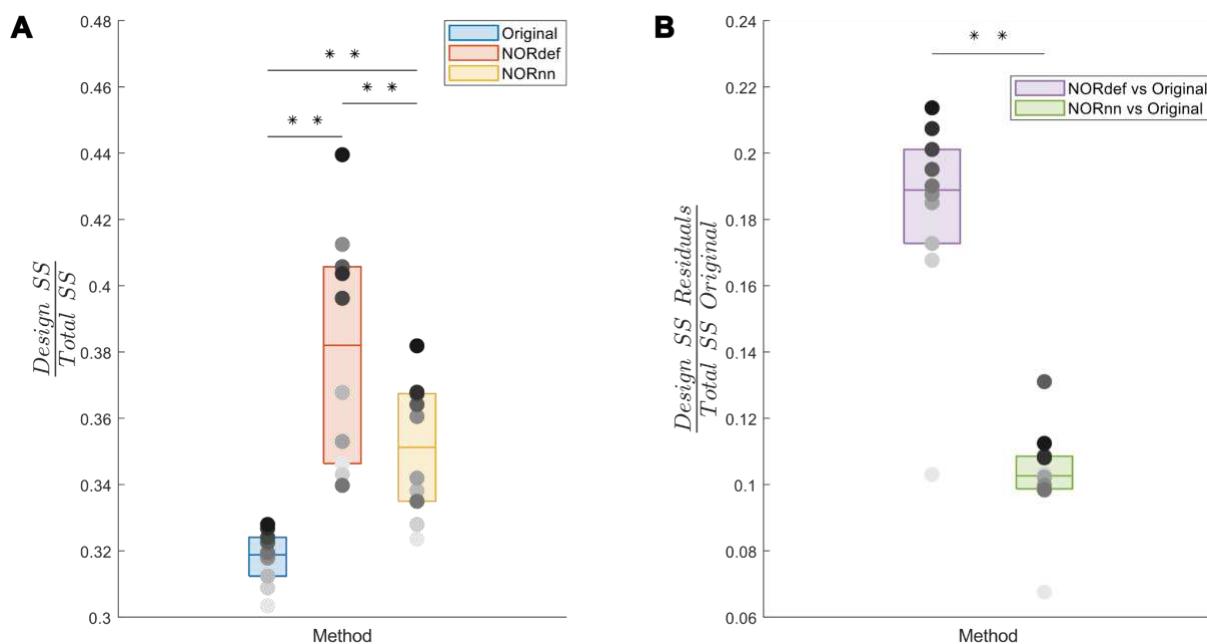
579 explained by the design in the residuals after NORDIC ($p < 0.001$).

580



581
582
583
584
585
586
587
588
589

Figure 9. Variance partitioning. A) The amount of variance explained by our design in the data increases consecutively with the use of NORnn and NORdef respectively for one exemplary participant. B) Denoising results in the removal of part of the signal. A proportion of the variance in the residuals after NORDIC can be explained by our stimulation design.

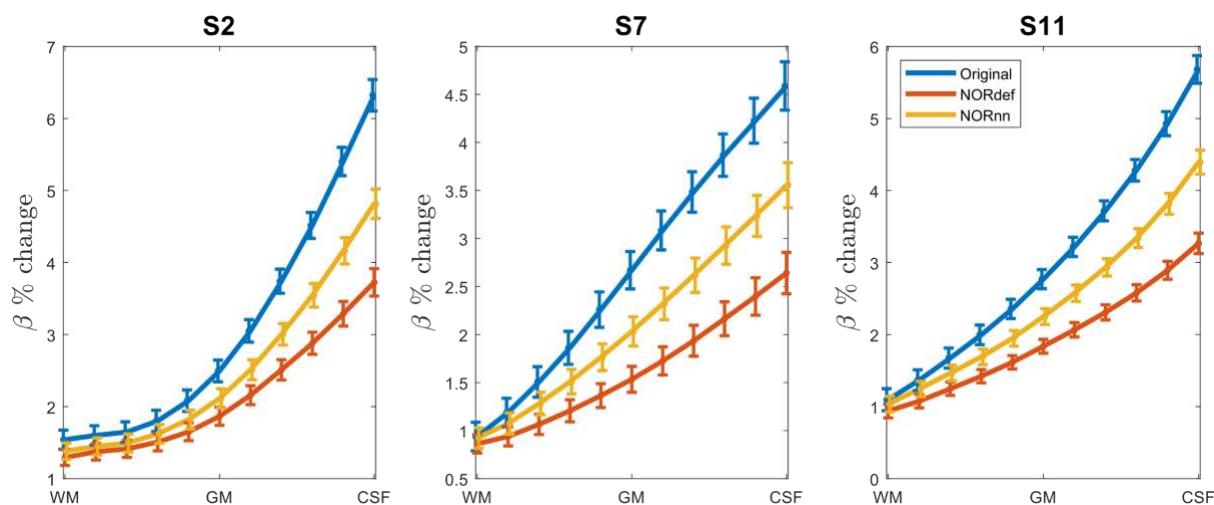


590

591 **Figure 10. Group analysis of the variance explained by the stimulation design.** A) Box charts show
592 the interquartile percentile range of variance explained by the design in the data across participants.
593 After NORDIC denoising, an increased proportion of the variance is explained by the experimental
594 design. NORnn shows an increase in explained variance compared to the original data, but a slightly
595 lower increase than NORdef. B) The proportion of variance explained by the design that is removed
596 from the Original data after NORDIC. NORdef removed a larger proportion of the signal compared to
597 NORnn. * indicates $p < 0.05$, ** indicates $p < 0.01$.
598

599 **3.3 Laminar data**

600 Submillimeter data collected with experimental designs presented here are often used
601 to investigate task-related cortical depth dependent changes in functional activity. In
602 preparation for such future studies, we set out to determine the effect NORDIC has on
603 the laminar profiles. We considered the depth dependent changes (11 equivolume
604 cortical depths) associated with the PredH condition. While in all participants, we could
605 observe the expected increase towards the surface in our GE-BOLD data (Heinzel et
606 al., 2016; Menon et al., 1995; Turner, 2002), NORDIC denoising is associated with a
607 clear reduction in percent signal in superficial cortical depths (see Figure 11 for three
608 representative subjects).



610 **Figure 11. Effect of NORDIC across depth.** For three participants we plot the laminar response
611 profiles for the PredH condition. In all plots we can easily identify the draining vein effect. However, we
612 see a gradual decrease in slope for NORnn and NORdef, indicating that NORDIC denoising has a
613 differential effect across depths.
614

615 4 Discussion

616 Functional MRI is an indispensable tool for the investigation of human brain function.
617 However, fMRI data is inherently limited by physiological and thermal noise
618 (Triantafyllou et al., 2005, 2011). For this reason, in the fMRI community, the
619 development of methods for removing unwanted sources of variance in the data has
620 been a longstanding goal. Denoising techniques in fMRI can be broadly distinguished
621 in those that tackle the removal of structured (physiological) noise and those that
622 instead aim to reduce thermal noise. A technique that has been introduced to deal with
623 thermal noise in particular is NORDIC PCA. NORDIC denoising has been vetted in
624 various brain areas, voxel sizes, experimental designs and field strengths (for
625 examples see Dowdle et al., 2022, 2023; Knudsen et al., 2023; Raimondo et al., 2023;
626 Vizioli et al., 2021). While in fMRI several approaches have been introduced to improve
627 (statistical) detection power of the signals of interest, it is important to note that any
628 denoising approach may affect the temporal or spatial precision of the underlying fMRI
629 signal as well as their bias-variance tradeoff (Kay, 2022). Ideally, denoising techniques
630 should not spatially or temporally blur the data, while also minimizing any bias
631 introduced. In its initial applications to fMRI, NORDIC denoising has been shown to
632 preserve spatial and temporal information as well as not introducing unwanted biases
633 in the data. These applications have focused primarily on visual and motor cortical
634 areas at different magnetic field strengths (3T and 7T) and using different experimental
635 designs as well as contrast mechanisms (Dowdle et al., 2022, 2023; Knudsen et al.,
636 2023; Raimondo et al., 2023).

637 Investigating fMRI responses in temporal cortical areas with high spatial
638 resolution (at UHF) is particularly challenging. The location of (primary) cortical areas
639 in particular calls for large field-of-view acquisitions (in either transversally or coronally

640 applied slices to ensure bilateral coverage), which requires high in-plane acceleration
641 to reduce distortions in the resulting EPI images. In addition, when using a single
642 transmit coil, as is the case in most applications, inhomogeneities in the radio
643 frequency transmit field result in suboptimal flip angles (Moerel et al., 2021). While ad-
644 hoc solutions can be found (e.g. by limiting the coverage to single hemispheres), high
645 spatial resolution investigations of temporal cortical areas result in lower temporal SNR
646 compared to e.g. visual or motor cortical regions. For these reasons, we evaluated the
647 consequences associated with the use of NORDIC denoising in temporal cortical
648 areas and extend this to a larger number of subjects. We compared two processing
649 strategies to the original data (i.e. no NORDIC denoising), one dataset using the
650 default settings for fMRI NORDIC (i.e. using magnitude and phase images and a noise
651 threshold estimated using noise scans) and one dataset with a more conservative
652 noise threshold obtained from g-factor estimation.

653 Our results indicate that NORDIC processing results in increased reliability of
654 the response estimates, increased reliability of the spatial patterns and increase
655 similarity of single run patterns to an ideal model formed by averaging multiple runs.
656 However, our results suggest that, in auditory cortical regions, NORDIC denoising is
657 associated with a non-negligible difference in the percent signal changes, compared
658 to the original data, elicited by our slow event-related design (Figures 6 and 8). These
659 effects are reminiscent of regularization approaches in regression as it results in lower
660 estimated regression coefficients (i.e. betas) while reducing their variance. The
661 variance reduction is proportionally larger with respect to the introduced bias, as
662 evidenced by the increased t-statistics (Figures 6 and 8) and underlies the increased
663 statistical detection sensitivity following NORDIC processing compared to the original
664 data (Figure 2 - and in agreement with previous studies Dowdle et al., 2023; Vizioli et

665 al., 2021). Importantly, the reduced variance in the NORDIC processed data results in
666 increased spatial consistency (especially when evaluated in a repeated split half
667 analysis). All our analyses performed at the level of beta estimates in different temporal
668 cortical regions showed a gradual improvement (e.g. in t-statistics) from NORnn to
669 NORdef (and an associated larger bias in NORdef compared to NORnn), in line with
670 our assumption that NORnn is the more conservative approach. Interestingly, even
671 within a dataset, the deviations from the original data introduced by NORDIC are not
672 uniform, it is associated with the amount of signal present in the data. That is, voxels
673 with more signal (as measured by the mean of the time series divided by the standard
674 deviation of the time series [tSNR]) show the lowest change in estimated percent
675 signal (Figure 7).

676 At the group level, the lower variance associated with the estimated responses
677 also resulted in a higher run-to-run correlation (with significant effects at the group
678 level observed for NORnn, see Figures 3 and 4). It is interesting to note that when
679 considering the run-to-run variability or the correlation to a multi-run reference,
680 NORDIC seems to improve data in most, but not all of our participants. For participants
681 in which the original data exhibit the lowest reliability the improvements are not
682 noticeable (see single participants points in Figure 4). We can only speculate about
683 the reason for the lack of improvement. These two participants displayed the most
684 movement across their scanning session, which may have resulted in the noise in the
685 data being mainly physiological of origin. This could be a reason why NORDIC
686 denoising did not result in a large improvement for these two participants.

687 The difference between the original data and NORDIC processed data is
688 suggestive of the fact that some signal (associated with the experimental design) has
689 been removed by the approach. We confirmed this by analyzing the portion of the

690 signal from the magnitude images that is removed by NORDIC (computed as the
691 portion of the original data time series orthogonal to either the NORdef or NORnn time
692 series). While the design explained larger portions of variance in the data after
693 NORDIC processing, the design also explained larger portions of variance in the
694 residuals after NORDIC (Figures 9 and 10). This indicates, that perhaps not
695 surprisingly, NORDIC can remove portions of the signal that in a given sample (i.e. a
696 functional run) are indistinguishable from the noise. These results are in agreement
697 with the results indicating larger changes in beta estimates after NORDIC (compared
698 to the original data) in voxels with lower tSNR (putatively voxels in which the signal
699 and the noise are more confounded - Figure 7).

700 As a preliminary analysis, we investigated the difference in laminar profiles
701 between NORDIC and the original data (Figure 11). The larger changes in estimated
702 percent signal were noticeable on superficial cortical layers (and more so for NORdef
703 compared to NORnn). This interesting effect may relate to the changes in signal and
704 noise contributions across depths in GE-fMRI. Further research is necessary to
705 explore the causes of these changes induced by NORDIC in the layer dependent
706 signals and the consequences they may have on neuroscientific conclusions drawn
707 by investigating differential responses across layers, or when more elaborate modeling
708 techniques are used (Markuerkiaga et al., 2016; Uludag & Havlicek, 2021; van Mourik
709 et al., 2019).

710 It is important to note that we here defined the bias introduced by NORDIC as
711 the reduction in percent signal changes that is visible when analyzing the time series
712 after NORDIC compared to the original data (Figures 6 and 8). While NORDIC acts
713 on complex data (to ensure a Gaussian distribution of the noise) the percent signal
714 estimates are computed on the magnitude data. The noise distribution in magnitude

715 only data is not Gaussian but Rician (see e.g. Manzano-Patron et al., 2023) and can
716 result in a biased estimate of the effects. That is, it is possible that the reduced percent
717 signal change we observe after NORDIC is stemming from a larger bias in the
718 estimates obtained from the original data induced by the elevated noise floor. While
719 this explanation offers an alternative interpretation of the reduced percent signal
720 changes obtained after NORDIC, it is not clear how it can explain the effects we report
721 on the portion of the variance explained by the design in the residuals of the time series
722 after NORDIC (Figure 9 and Figure 10). This is because any amplitude difference
723 between the original and the NORDIC time series is accounted for in the way we
724 estimate the residuals after NORDIC (i.e. these residuals are not a simple subtraction
725 of the data before and after NORDIC).

726 Our results have some implications for the use of NORDIC in neuroscientific
727 investigations as well as for future methodological developments of this denoising
728 technique. First, as NORDIC can (in low SNR regimes as ours) remove portions of the
729 signal, it follows that its application on a run-to-run basis may not combine its benefits
730 to the more general practice of averaging. That is, while averaging will preserve all
731 signal portions in the single run data (and with enough runs may render small effects
732 detectable), NORDIC may remove some of these effects in the single runs and make
733 them undetectable even after extensive averaging. Second, any biases introduced by
734 NORDIC is likely related to signal components that, in a given sample (i.e. a run) are
735 indistinguishable from noise. This consideration highlights the need to further
736 investigate the interaction between the experimental design and any bias introduced
737 by NORDIC processing. That is, in our data the effect may have been exacerbated by
738 the slow event-related stimulus presentation that may confound the response (i.e. the
739 signal) more with the noise in low SNR regimes. While in visual areas event-related

740 designs do not result in a detectable bias after NORDIC (Dowdle et al., 2023), this
741 may relate to the higher SNR of visual areas compared to temporal regions. Finally, it
742 is tempting to speculate that several approaches could be undertaken to abate the
743 bias. Here, we showed that a more conservative threshold for the identification of noisy
744 eigenvalues results in a lower bias (NORnn). Further investigations are warranted in
745 evaluating the effect that other settings (e.g. the patch size) have on the bias. More
746 sophisticated approaches could be considered to, for example, select principal
747 components for removal only if their relationship with the experimental design is
748 negligible akin to the selection of interesting components when performing
749 independent component analysis for task fMRI (De Martino et al., 2007; McKeown et
750 al., 1998; Moritz et al., 2005; Schmithorst & Brown, 2004). Such an approach would
751 not generalize to resting state fMRI but could help for task based functional studies.

752 Independent of the biases we describe here, NORDIC processing remains an
753 important tool for fMRI investigations especially when SNR is limited (i.e. when thermal
754 noise is dominant), such as laminar studies or functional MRI studies using less
755 sensitive contrast mechanisms (e.g. spin-echo BOLD or non-BOLD contrast
756 mechanisms such as cerebral blood flow-based vascular space occupancy or blood
757 flow based contrast mechanisms such as arterial spin labeling). NORDIC can then be
758 used as a complement to techniques that target physiological noise components to
759 improve the usability of these different SNR starved acquisition approaches. Similarly,
760 NORDIC could be very beneficial in patient studies that cannot rely on long scan times
761 (i.e. extensive averaging) because of practical constraints. In general, though, while
762 any given processing or reconstruction step likely introduces some bias, and while it
763 may be acceptable in some circumstances, it is reasonable to advise NORDIC users
764 to evaluate the amount of bias introduced in their data (by e.g. plotting percent signal

765 estimates before and after NORDIC) apart from focusing only on the increased
766 (statistical) detectability of the effects.

767 In conclusion, NORDIC can be added to the family of preprocessing techniques
768 that can be utilized to improve the detection sensitivity and reliability of the responses
769 estimated from the fMRI signal. The improvements NORDIC affords warrant its use in
770 SNR challenged settings. Following previous reports, also in our data these positive
771 effects were significant. The signal changes we report here, on the other hand, suggest
772 that some care is required when using NORDIC – new applications may have to further
773 characterize the effect of NORDIC to better evaluate the generalizability of its effects.

774

775 **Data and Code Availability**

776 Analyses codes (after preprocessing) are available on Github
777 https://github.com/lonikefaes/auditory_nordic. The anonymized raw data of this study
778 is available and can be downloaded from [doi:10.18112/openneuro.ds004928.v1.0.0](https://doi.org/10.18112/openneuro.ds004928.v1.0.0).
779 (The dataset will be made publicly available upon acceptance).

780

781 **Author Contributions**

782 **Lonike K. Faes:** Conceptualization, Formal Analysis, Methodology, Visualization,
783 Writing – Original Draft, Writing – Review & Editing **Agustin Lage-Castellanos:**
784 Conceptualization, Formal Analysis, Methodology, Visualization, Writing – Review &
785 Editing **Giancarlo Valente:** Methodology, Writing – Review & Editing **Zidan Yu:**
786 Investigation, Resources **Martijn A. Cloos:** Investigation, Resources, Writing –
787 Review & Editing **Luca Vizioli:** Investigation, Resources, Writing – Review & Editing
788 **Steen Moeller:** Writing – Review & Editing **Essa Yacoub:** Conceptualization, Funding
789 Acquisition, Writing – Review & Editing **Federico De Martino:** Conceptualization,

790 Funding Acquisition, Methodology, Supervision, Writing – Original Draft, Writing –
791 Review & Editing.

792

793 **Funding**

794 The research was supported by the National Institute of Health (RF1MH116978-01
795 and P41EB027061). Additionally, this research was supported by the European
796 Research Council (ERC) under the European Union’s Horizon 2020 research and
797 innovation program (grant agreement No. 101001270) awarded to FDM.

798

799 **Declaration of Competing Interests**

800 The authors declare no conflict of interest.

801

802 **Acknowledgements**

803 We would like to thank Logan Dowdle for the useful discussions. Moreover, we would
804 like to thank Renzo Huber and Lasse Knudsen for the helpful discussions and
805 comments on the first draft of this manuscript.

806

807 **References**

808 Ahveninen, J., Chang, W.-T., Huang, S., Keil, B., Kopco, N., Rossi, S., Bonmassar, G.,
809 Witzel, T., & Polimeni, J. R. (2016). Intracortical depth analyses of frequency-
810 sensitive regions of human auditory cortex using 7T fMRI. *NeuroImage*, 143, 116–
811 127. <https://doi.org/10.1016/j.neuroimage.2016.09.010>
812 Allen, E. J., St-Yves, G., Wu, Y., Breedlove, J. L., Prince, J. S., Dowdle, L. T., Nau, M.,
813 Caron, B., Pestilli, F., Charest, I., Hutchinson, J. B., Naselaris, T., & Kay, K. (2022). A
814 massive 7T fMRI dataset to bridge cognitive neuroscience and artificial intelligence.

815 *Nature Neuroscience*, 25(1), 116–126. <https://doi.org/10.1038/s41593-021-00962-x>

816 Cordero-Grande, L., Christiaens, D., Hutter, J., Price, A. N., & Hajnal, J. V. (2019). Complex
817 diffusion-weighted image estimation via matrix recovery under general noise models.

818 *NeuroImage*, 200, 391–404. <https://doi.org/10.1016/j.neuroimage.2019.06.039>

819 De Martino, F., Gentile, F., Esposito, F., Balsi, M., Di Salle, F., Goebel, R., & Formisano, E.
820 (2007). Classification of fMRI independent components using IC-fingerprints and
821 support vector machine classifiers. *NeuroImage*, 34(1), 177–194.
822 <https://doi.org/10.1016/j.neuroimage.2006.08.041>

823 De Martino, F., Moerel, M., Ugurbil, K., Goebel, R., Yacoub, E., & Formisano, E. (2015).
824 Frequency preference and attention effects across cortical depths in the human
825 primary auditory cortex. *Proceedings of the National Academy of Sciences*, 112(52),
826 16036–16041. <https://doi.org/10.1073/pnas.1507552112>

827 De Martino, F., Yacoub, E., Kemper, V., Moerel, M., Uludağ, K., De Weerd, P., Ugurbil, K.,
828 Goebel, R., & Formisano, E. (2018). The impact of ultra-high field MRI on cognitive
829 and computational neuroimaging. *NeuroImage*, 168, 366–382.
830 <https://doi.org/10.1016/j.neuroimage.2017.03.060>

831 Dowdle, L., Ghose, G., Moeller, S., Ugurbil, K., Yacoub, E., & Vizioli, L. (2022). *Task
832 Demands Differentiate Regional Depth-Dependent Activity Profiles Within the Ventral
833 Visual Pathway* [Preprint]. Neuroscience. <https://doi.org/10.1101/2022.12.03.518973>

834 Dowdle, L., Vizioli, L., Moeller, S., Akçakaya, M., Olman, C., Ghose, G., Yacoub, E., &
835 Uğurbil, K. (2023). Evaluating Increases in Sensitivity from NORDIC for Diverse fMRI
836 Acquisition Strategies. *NeuroImage*, 119949.
837 <https://doi.org/10.1016/j.neuroimage.2023.119949>

838 Dumoulin, S. O., Fracasso, A., van der Zwaag, W., Siero, J. C. W., & Petridou, N. (2018).
839 *Ultra-high field MRI_ Advancing systems neuroscience towards mesoscopic human
840 brain function*.

841 Faes, L. K., De Martino, F., & Huber, L. (2023). *Cerebral blood volume sensitive layer-fMRI
842 in the human auditory cortex at 7T: Challenges and capabilities*.

843 Fernandes, F. F., Olesen, J. L., Jespersen, S. N., & Shemesh, N. (2023). MP-PCA denoising
844 of fMRI time-series data can lead to artificial activation “spreading.” *NeuroImage*,
845 273, 120118. <https://doi.org/10.1016/j.neuroimage.2023.120118>

846 Formisano, E., Kim, D.-S., Di Salle, F., van de Moortele, P.-F., Ugurbil, K., & Goebel, R.
847 (2003). Mirror-Symmetric Tonotopic Maps in Human Primary Auditory Cortex.
848 *Neuron*, 40(4), 859–869. [https://doi.org/10.1016/S0896-6273\(03\)00669-X](https://doi.org/10.1016/S0896-6273(03)00669-X)

849 Formisano, E., & Kriegeskorte, N. (2012). Seeing patterns through the hemodynamic veil—
850 The future of pattern-information fMRI. *NeuroImage*, 62(2), 1249–1256.
851 <https://doi.org/10.1016/j.neuroimage.2012.02.078>

852 Gau, R., Bazin, P.-L., Trampel, R., Turner, R., & Noppeney, U. (2020). Resolving
853 multisensory and attentional influences across cortical depth in sensory cortices.
854 *eLife*, 9, e46856. <https://doi.org/10.7554/eLife.46856>

855 Glover, G. H., Li, T.-Q., & Ress, D. (2000). Image-based method for retrospective correction
856 of physiological motion effects in fMRI: RETROICOR. *Magnetic Resonance in
857 Medicine*, 44(1), 162–167. [https://doi.org/10.1002/1522-2594\(200007\)44:1<162::AID-MRM23>3.0.CO;2-E](https://doi.org/10.1002/1522-2594(200007)44:1<162::AID-MRM23>3.0.CO;2-E)

859 Gonzalez-Castillo, J., Panwar, P., Buchanan, L. C., Caballero-Gaudes, C., Handwerker, D.
860 A., Jangraw, D. C., Zachariou, V., Inati, S., Roopchansingh, V., Derbyshire, J. A., &
861 Bandettini, P. A. (2016). Evaluation of multi-echo ICA denoising for task based fMRI
862 studies: Block designs, rapid event-related designs, and cardiac-gated fMRI.
863 *NeuroImage*, 141, 452–468. <https://doi.org/10.1016/j.neuroimage.2016.07.049>

864 Griffanti, L., Salimi-Khorshidi, G., Beckmann, C. F., Auerbach, E. J., Douaud, G., Sexton, C.
865 E., Zsoldos, E., Ebmeier, K. P., Filippini, N., Mackay, C. E., Moeller, S., Xu, J.,
866 Yacoub, E., Baselli, G., Ugurbil, K., Miller, K. L., & Smith, S. M. (2014). ICA-based
867 artefact removal and accelerated fMRI acquisition for improved resting state network
868 imaging. *NeuroImage*, 95, 232–247.
869 <https://doi.org/10.1016/j.neuroimage.2014.03.034>

870 Heinze, J., Koopmans, P. J., den Ouden, H. E. M., Raman, S., & Stephan, K. E. (2016). A

871 hemodynamic model for layered BOLD signals. *NeuroImage*, 125, 556–570.

872 <https://doi.org/10.1016/j.neuroimage.2015.10.025>

873 Heynckes, M., Lage-Castellanos, A., De Weerd, P., Formisano, E., & De Martino, F. (2023).

874 Layer-specific correlates of detected and undetected auditory targets during

875 attention. *Current Research in Neurobiology*, 4, 100075.

876 <https://doi.org/10.1016/j.crneur.2023.100075>

877 Hu, X., Le, T. H., Parrish, T., & Erhard, P. (1995). *Retrospective estimation and correction of*

878 *physiological fluctuation in functional MRI*. <https://doi.org/10.1002/mrm.1910340211>

879 Huber, L., Goense, J., Kennerley, A. J., Trampel, R., Guidi, M., Reimer, E., Ivanov, D., Neef,

880 N., Gauthier, C. J., Turner, R., & Möller, H. E. (2015). Cortical lamina-dependent

881 blood volume changes in human brain at 7 T. *NeuroImage*, 107, 23–33.

882 <https://doi.org/10.1016/j.neuroimage.2014.11.046>

883 Huber, L., Poser, B. A., Bandettini, P. A., Arora, K., Wagstyl, K., Cho, S., Goense, J.,

884 Nothnagel, N., Morgan, A. T., van den Hurk, J., Müller, A. K., Reynolds, R. C., Glen,

885 D. R., Goebel, R., & Gulban, O. F. (2021). LayNii: A software suite for layer-fMRI.

886 *NeuroImage*, 237, 118091. <https://doi.org/10.1016/j.neuroimage.2021.118091>

887 Kay, K. N. (2022). The risk of bias in denoising methods: Examples from neuroimaging.

888 *PLOS ONE*, 17(7), e0270895. <https://doi.org/10.1371/journal.pone.0270895>

889 Kay, K. N., Rokem, A., Winawer, J., Dougherty, R. F., & Wandell, B. A. (2013). GLMdenoise:

890 A fast, automated technique for denoising task-based fMRI data. *Frontiers in*

891 *Neuroscience*, 7. <https://doi.org/10.3389/fnins.2013.00247>

892 Kiebel, S. J., Goebel, R., & Friston, K. J. (2000). Anatomically Informed Basis Functions.

893 *NeuroImage*, 11(6), 656–667. <https://doi.org/10.1006/nimg.1999.0542>

894 Knudsen, L., Bailey, C. J., Blicher, J. U., Yang, Y., Zhang, P., & Lund, T. E. (2023). Improved

895 sensitivity and microvascular weighting of 3T laminar fMRI with GE-BOLD using

896 NORDIC and phase regression. *NeuroImage*, 271, 120011.

897 <https://doi.org/10.1016/j.neuroimage.2023.120011>

898 Kok, P., Bains, L. J., van Mourik, T., Norris, D. G., & de Lange, F. P. (2016). Selective

899 Activation of the Deep Layers of the Human Primary Visual Cortex by Top-Down
900 Feedback. *Current Biology*, 26(3), 371–376.
901 <https://doi.org/10.1016/j.cub.2015.12.038>

902 Lawrence, S. J., Norris, D. G., & de Lange, F. P. (2019). Dissociable laminar profiles of
903 concurrent bottom-up and top-down modulation in the human visual cortex. *eLife*, 8,
904 e44422. <https://doi.org/10.7554/eLife.44422>

905 Ma, X., Uğurbil, K., & Wu, X. (2020). Denoise magnitude diffusion magnetic resonance
906 images via variance-stabilizing transformation and optimal singular-value
907 manipulation. *NeuroImage*, 215, 116852.
908 <https://doi.org/10.1016/j.neuroimage.2020.116852>

909 Manzano-Patron, J.-P., Moeller, S., Andersson, J. L. R., Yacoub, E., & Sotiropoulos, S. N.
910 (2023). *Denoising Diffusion MRI: Considerations and implications for analysis*
911 [Preprint]. Neuroscience. <https://doi.org/10.1101/2023.07.24.550348>

912 Markuerkiaga, I., Barth, M., & Norris, D. G. (2016). A cortical vascular model for examining
913 the specificity of the laminar BOLD signal. *NeuroImage*, 132, 491–498.
914 <https://doi.org/10.1016/j.neuroimage.2016.02.073>

915 Marques, J. P., Kober, T., Krueger, G., van der Zwaag, W., Van de Moortele, P.-F., &
916 Gruetter, R. (2010). MP2RAGE, a self bias-field corrected sequence for improved
917 segmentation and T1-mapping at high field. *NeuroImage*, 49(2), 1271–1281.
918 <https://doi.org/10.1016/j.neuroimage.2009.10.002>

919 McKeown, M. J., Makeig, S., Brown, G. G., Jung, T.-P., Kindermann, S. S., Bell, A. J., &
920 Sejnowski, T. J. (1998). Analysis of fMRI data by blind separation into independent
921 spatial components. *Human Brain Mapping*, 6(3), 160–188.
922 [https://doi.org/10.1002/\(SICI\)1097-0193\(1998\)6:3<160::AID-HBM5>3.0.CO;2-1](https://doi.org/10.1002/(SICI)1097-0193(1998)6:3<160::AID-HBM5>3.0.CO;2-1)

923 Menon, R. S., Ogawa, S., Hu, X., Strupp, J. P., Anderson, P., & Ugurbil, K. (1995). BOLD
924 based functional MRI at 4 Tesla includes a capillary bed contribution: Echo-planar
925 imaging correlates with previous optical imaging using intrinsic signals. *Magn. Reson.*
926 *Med.*, 33, 453–459. <https://doi.org/10.1002/mrm.1910330323>

927 Michon, K. J., Khammash, D., Simmonite, M., Hamlin, A. M., & Polk, T. A. (2022). Person-
928 specific and precision neuroimaging: Current methods and future directions.
929 *NeuroImage*, 263, 119589. <https://doi.org/10.1016/j.neuroimage.2022.119589>

930 Moeller, S., Pisharady, P. K., Ramanna, S., Lenglet, C., Wu, X., Dowdle, L., Yacoub, E.,
931 Uğurbil, K., & Akçakaya, M. (2021). NOise reduction with DIstribution Corrected
932 (NORDIC) PCA in dMRI with complex-valued parameter-free locally low-rank
933 processing. *NeuroImage*, 226, 117539.
934 <https://doi.org/10.1016/j.neuroimage.2020.117539>

935 Moeller, S., Yacoub, E., Olman, C. A., Auerbach, E., Strupp, J., Harel, N., & Uğurbil, K.
936 (2010). Multiband multislice GE-EPI at 7 tesla, with 16-fold acceleration using partial
937 parallel imaging with application to high spatial and temporal whole-brain fMRI.
938 *Magnetic Resonance in Medicine*, 63(5), 1144–1153.
939 <https://doi.org/10.1002/mrm.22361>

940 Moerel, M., De Martino, F., & Formisano, E. (2014). An anatomical and functional
941 topography of human auditory cortical areas. *Frontiers in Neuroscience*, 8.
942 <https://doi.org/10.3389/fnins.2014.00225>

943 Moerel, M., De Martino, F., Kemper, V. G., Schmitter, S., Vu, A. T., Uğurbil, K., Formisano,
944 E., & Yacoub, E. (2018). Sensitivity and specificity considerations for fMRI encoding,
945 decoding, and mapping of auditory cortex at ultra-high field. *NeuroImage*, 164, 18–
946 31. <https://doi.org/10.1016/j.neuroimage.2017.03.063>

947 Moerel, M., Yacoub, E., Gulban, O. F., Lage-Castellanos, A., & De Martino, F. (2021). Using
948 high spatial resolution fMRI to understand representation in the auditory network.
949 *Progress in Neurobiology*, 207, 101887.
950 <https://doi.org/10.1016/j.pneurobio.2020.101887>

951 Moritz, C. H., Carew, J. D., McMillan, A. B., & Meyerand, M. E. (2005). Independent
952 component analysis applied to self-paced functional MR imaging paradigms.
953 *NeuroImage*, 25(1), 181–192. <https://doi.org/10.1016/j.neuroimage.2004.11.009>

954 Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., & Ugurbil, K.

955 (1992). Intrinsic signal changes accompanying sensory stimulation: Functional brain
956 mapping with magnetic resonance imaging. *Proceedings of the National Academy of*
957 *Sciences*, 89(13), 5951–5955. <https://doi.org/10.1073/pnas.89.13.5951>

958 Olman, C. A., Harel, N., Feinberg, D. A., He, S., Zhang, P., Ugurbil, K., & Yacoub, E. (2012).
959 Layer-Specific fMRI Reflects Different Neuronal Computations at Different Depths in
960 Human V1. *PLoS ONE*, 7(3), e32536. <https://doi.org/10.1371/journal.pone.0032536>

961 Poldrack, R. A., Baker, C. I., Durnez, J., Gorgolewski, K. J., Matthews, P. M., Munafò, M. R.,
962 Nichols, T. E., Poline, J.-B., Vul, E., & Yarkoni, T. (2017). Scanning the horizon:
963 Towards transparent and reproducible neuroimaging research. *Nature Reviews*
964 *Neuroscience*, 18(2), 115–126. <https://doi.org/10.1038/nrn.2016.167>

965 Polimeni, J. R., Renvall, V., Zaretskaya, N., & Fischl, B. (2018). Analysis strategies for high-
966 resolution UHF-fMRI data. *NeuroImage*, 168, 296–320.
967 <https://doi.org/10.1016/j.neuroimage.2017.04.053>

968 Pruessmann, K. P., Weiger, M., Scheidegger, M. B., & Boesiger, P. (1999). SENSE:
969 Sensitivity encoding for fast MRI. *Magnetic Resonance in Medicine*, 42(5), 952–962.
970 [https://doi.org/10.1002/\(SICI\)1522-2594\(199911\)42:5<952::AID-MRM16>3.0.CO;2-S](https://doi.org/10.1002/(SICI)1522-2594(199911)42:5<952::AID-MRM16>3.0.CO;2-S)

971 Pruim, R. H. R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J. K., & Beckmann, C. F.
972 (2015). ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from
973 fMRI data. *NeuroImage*, 112, 267–277.
974 <https://doi.org/10.1016/j.neuroimage.2015.02.064>

975 Raimondo, L., Priovoulos, N., Passarinho, C., Heij, J., Knapen, T., Dumoulin, S. O., Siero, J.
976 C. W., & van der Zwaag, W. (2023). Robust high spatio-temporal line-scanning fMRI
977 in humans at 7T using multi-echo readouts, denoising and prospective motion
978 correction. *Journal of Neuroscience Methods*, 384, 109746.
979 <https://doi.org/10.1016/j.jneumeth.2022.109746>

980 Salimi-Khorshidi, G., Douaud, G., Beckmann, C. F., Glasser, M. F., Griffanti, L., & Smith, S.
981 M. (2014). Automatic denoising of functional MRI data: Combining independent
982 component analysis and hierarchical fusion of classifiers. *NeuroImage*, 90, 449–468.

983 <https://doi.org/10.1016/j.neuroimage.2013.11.046>

984 Schmithorst, V. J., & Brown, R. D. (2004). Empirical validation of the triple-code model of
985 numerical processing for complex math operations using functional MRI and group
986 Independent Component Analysis of the mental addition and subtraction of fractions.
987 *NeuroImage*, 22(3), 1414–1420. <https://doi.org/10.1016/j.neuroimage.2004.03.021>

988 Setsompop, K., Cohen-Adad, J., Gagoski, B. A., Raji, T., Yendiki, A., Keil, B., Wedeen, V. J.,
989 & Wald, L. L. (2012). Improving diffusion MRI using simultaneous multi-slice echo
990 planar imaging. *NeuroImage*, 63(1), 569–580.
991 <https://doi.org/10.1016/j.neuroimage.2012.06.033>

992 Steel, A., Garcia, B. D., Silson, E. H., & Robertson, C. E. (2022). Evaluating the efficacy of
993 multi-echo ICA denoising on model-based fMRI. *NeuroImage*, 264, 119723.
994 <https://doi.org/10.1016/j.neuroimage.2022.119723>

995 Triantafyllou, C., Hoge, R. D., Krueger, G., Wiggins, C. J., Potthast, A., Wiggins, G. C., &
996 Wald, L. L. (2005). Comparison of physiological noise at 1.5 T, 3 T and 7 T and
997 optimization of fMRI acquisition parameters. *NeuroImage*, 26(1), 243–250.
998 <https://doi.org/10.1016/j.neuroimage.2005.01.007>

999 Triantafyllou, C., Polimeni, J. R., & Wald, L. L. (2011). Physiological noise and signal-to-
1000 noise ratio in fMRI with multi-channel array coils. *NeuroImage*, 55(2), 597–606.
1001 <https://doi.org/10.1016/j.neuroimage.2010.11.084>

1002 Turner, R. (2002). How Much Cortex Can a Vein Drain? Downstream Dilution of Activation-
1003 Related Cerebral Blood Oxygenation Changes. *NeuroImage*, 16(4), 1062–1067.
1004 <https://doi.org/10.1006/nimg.2002.1082>

1005 Turner, R., & Geyer, S. (2014). Comparing Like with Like: The Power of Knowing Where You
1006 Are. *Brain Connectivity*, 4(7), 547–557. <https://doi.org/10.1089/brain.2014.0261>

1007 Uğurbil, K. (2018). *Imaging at ultrahigh magnetic fields_ History, challenges, and solutions*.

1008 Uludag, K., & Havlicek, M. (2021). Determining laminar neuronal activity from BOLD fMRI
1009 using a generative model. *Progress in Neurobiology*, 207, 102055.
1010 <https://doi.org/10.1016/j.pneurobio.2021.102055>

1011 Valente, G., Castellanos, A. L., Hausfeld, L., De Martino, F., & Formisano, E. (2021). Cross-
1012 validation and permutations in MVPA: Validity of permutation strategies and power of
1013 cross-validation schemes. *NeuroImage*, 238, 118145.
1014 <https://doi.org/10.1016/j.neuroimage.2021.118145>

1015 van Mourik, T., van der Eerden, J. P. J. M., Bazin, P.-L., & Norris, D. G. (2019). Laminar
1016 signal extraction over extended cortical areas by means of a spatial GLM. *PLOS
1017 ONE*, 14(3), e0212493. <https://doi.org/10.1371/journal.pone.0212493>

1018 Vaughan, J. T., Garwood, M., Collins, C. M., Liu, W., DelaBarre, L., Adriany, G., Andersen,
1019 P., Merkle, H., Goebel, R., Smith, M. B., & Ugurbil, K. (2001). 7T vs. 4T: RF power,
1020 homogeneity, and signal-to-noise comparison in head images. *Magnetic Resonance
1021 in Medicine*, 46(1), 24–30. <https://doi.org/10.1002/mrm.1156>

1022 Veraart, J., Novikov, D. S., Christiaens, D., Ades-aron, B., Sijbers, J., & Fieremans, E.
1023 (2016). Denoising of diffusion MRI using random matrix theory. *NeuroImage*, 142,
1024 394–406. <https://doi.org/10.1016/j.neuroimage.2016.08.016>

1025 Vizioli, L., Moeller, S., Dowdle, L., Akçakaya, M., De Martino, F., Yacoub, E., & Uğurbil, K.
1026 (2021). Lowering the thermal noise barrier in functional brain mapping with magnetic
1027 resonance imaging. *Nature Communications*, 12(1), 5181.
1028 <https://doi.org/10.1038/s41467-021-25431-8>

1029 Yacoub, E., Harel, N., & Uğurbil, K. (2008). High-field fMRI unveils orientation columns in
1030 humans. *Proceedings of the National Academy of Sciences*, 105(30), 10607–10612.
1031 <https://doi.org/10.1073/pnas.0804110105>

1032 Yacoub, E., Shmuel, A., Pfeuffer, J., Van De Moortele, P.-F., Adriany, G., Andersen, P.,
1033 Vaughan, J. T., Merkle, H., Ugurbil, K., & Hu, X. (2001). Imaging brain function in
1034 humans at 7 Tesla. *Magnetic Resonance in Medicine*, 45(4), 588–594.
1035 <https://doi.org/10.1002/mrm.1080>

1036 Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., & Gerig, G.
1037 (2006). User-guided 3D active contour segmentation of anatomical structures:
1038 Significantly improved efficiency and reliability. *NeuroImage*, 31(3), 1116–1128.

1039 https://doi.org/10.1016/j.neuroimage.2006.01.015

1040 Zimmermann, J., Goebel, R., De Martino, F., van de Moortele, P.-F., Feinberg, D., Adriany,
1041 G., Chaimow, D., Shmuel, A., Uğurbil, K., & Yacoub, E. (2011). Mapping the
1042 Organization of Axis of Motion Selective Features in Human Area MT Using High-
1043 Field fMRI. *PLoS ONE*, 6(12), e28716. <https://doi.org/10.1371/journal.pone.0028716>

1044