Multi-echo Acquisition and Thermal Denoising Advances Infant Precision Functional Imaging

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Keywords

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Abstract

The characterization of individual functional brain organization with Precision Functional Mapping has provided important insights in recent years in adults. However, little is known about the ontogeny of inter-individual differences in brain functional organization during human development, but precise characterization of systems organization during periods of high plasticity might be most influential towards discoveries promoting lifelong health. Collecting and analyzing precision fMRI data during early development has unique challenges and emphasizes the importance of novel methods to improve data acquisition, processing, and analysis strategies in infant samples. Here, we investigate the applicability of two such methods from adult MRI research, multi-echo (ME) data acquisition and thermal noise removal with Noise reduction with distribution corrected principal component analysis (NORDIC), in precision fMRI data from three newborn infants. Compared to an adult example subject, T2* relaxation times calculated from ME data in infants were longer and more variable across the brain, pointing towards ME acquisition being a promising tool for optimizing developmental fMRI. The application of thermal denoising via NORDIC increased tSNR and the overall strength of functional connections as well as the split-half reliability of functional connectivity matrices in infant ME data. While our findings related to NORDIC denoising are coherent with the adult literature and ME data acquisition showed high promise, its application in developmental samples needs further investigation. The present work reveals gaps in our understanding of the best techniques for developmental brain imaging and highlights the need for further developmentally-specific methodological advances and optimizations, towards precision functional imaging in infants.

1. Introduction

Brain regions that are functionally connected can be identified by correlations in the blood oxygen level dependent (BOLD) signal, the endogenous contrast used for functional magnetic resonance imaging (fMRI; Biswal et al., 1995; Ogawa et al., 1990). Although common patterns of functional brain organization have been identified via group average studies of functional connectivity among brain regions (e.g. Gordon et al., 2016; Yeo et al., 2011), considerable inter-individual variability exists around these global patterns (Gordon et al., 2017), which is fairly stable within individuals (Gratton et al., 2018; Laumann et al., 2015). Precision functional mapping is a technique that allows for a reliable characterization of these person specific functional brain organizations (i.e., network maps or brain topography, and connection strengths or brain topology) by acquiring abundant data across multiple imaging sessions of the same participant.

Promise of precision imaging during development

The ability to reliably and precisely map personalized systems in individuals has provided an important platform for a whole host of discoveries in recent years in adults. Insights from Precision Functional Mapping (PFM) for example lead to rethinking the classic homunculus (Penfield & Boldrey, 1937) detecting inter-effector regions that interrupt effector-specific areas, forming the somato-cognitive action network (Gordon et al., 2023) and expanded our understanding of experience dependent plasticity (Newbold et al., 2020). Furthermore, recent evidence revealed distinct patterns of the expansion of the salience network in individuals with major depression (Lynch et al., 2023), supporting the idea that PFM can provide important information for designing targeted neuromodulation treatments (Elbau et al., 2023). Functional brain organization in adults is as individual as a fingerprint (Miranda-Dominguez et al., 2014) with areas of high and low probability of network overlap between persons (Hermosillo et al., 2022). Even during childhood and adolescence, personalized network topography is providing insights into the associations of brain development, cognition, age (Cui et al., 2020), and psychopathology (Cui et al., 2022). However, despite all of these growing discoveries, little is known about the ontogeny of these individual differences in brain functional organization during the earliest periods of human development - a time in development when our ability to precisely characterize systems organization in individuals might be most influential towards new discovery, specifically regarding long term health trajectories and the potential for early interventions.

Our ability to collect and analyze precision fMRI data during early development (i.e. children, infants and neonates) is limited for several reasons. For example, PFM at an individual level in adults has historically required upwards of an hour of movement free data for reliable results (Gordon et al., 2017; Laumann et al., 2015). Gathering large amounts of fMRI data in newborns and infants is particularly challenging and requires research teams to adopt specialized strategies (Dubois et al., 2021; Korom et al., 2021). Also, in most cases, infant imaging requires data to be acquired during natural sleep, when spontaneous waking can limit the acquisition of large amounts of good quality, motion free data. There are additional inherent technical challenges of infant imaging like the lack of commercially available head coils optimized for developmental populations, resulting in sub-optimal signal to noise ratio (SNR) when using adult coils. To make matters worse, higher spatial resolutions, relative to standard voxel sizes in adults, are needed to

avoid increases in partial voluming because of the smaller brain sizes (Dubois et al., 2021). As such, it is likely that precision functional mapping in infants needs even larger amounts of data compared to adults. This notion is supported by a recent study (Moore et al., 2023) looking at individual specific functional connectivity networks in newborn infants. Even though infant networks were clearly individual specific and contained all major networks detected in adults, the split-half reliability analysis showed no plateau in stability of network solutions with amounts of data that are known to produce stable solutions in adolescents and adults (Hermosillo et al., 2022; Moore et al., 2023; Sylvester et al., 2022).

Finally, even where large amounts of data could be collected within infants across multiple sessions, PFM in this population is still limited simply by the fast pace at which the brain develops during these early stages of maturation. The rapid growth rate of the infant brain requires collecting multiple datasets in a much shorter time-period compared to a child or an adult sample, where multiple sessions of movement free data can be collected over the course of weeks to months to reliably characterize individual functional brain organization.

These challenges call for improvements in data collection and processing methods

These challenges highlight the difficulties of PFM in infant samples, but also the importance of identifying data acquisition, processing, and analysis strategies that maximize signal and reduce the time in the scanner needed to obtain reliable characterization of functional network topographies and their underlying topology. This paper examines two possible methodological improvements for infant imaging that previously and independently have been shown to increase signal quality and reliability in adult participants: 1) Multi-echo (ME) data acquisition (Lynch et al., 2020) and 2) Noise reduction with distribution corrected principal component analysis (NORDIC; Dowdle et al., 2023; Moeller et al., 2021; Vizioli et al., 2021).

In contrast to traditional BOLD imaging, ME data acquisitions capture images at multiple echo times during a single readout time of the T2* or transverse relaxation signal decay, instead of only one. The T2* weighted fMRI signal reflects the decay in transverse magnetization introduced by the radio frequency (RF) pulse. The more time passes between the RF pulse and capturing an image (echo time), the weaker the signal gets (see Figure 1C for an example). T2* relaxation times vary across age, brain regions and tissue types, due to differences in the underlying neurobiological tissue properties. The optimal echo time to capture an image (i.e. tradeoff between signal to noise and functional contrast) is usually defaulted to the T2* relaxation time of the voxels of interest. Voxels with longer T2*s have higher signal intensities in images from longer echo times compared to voxels with shorter T2*s (Kundu et al., 2017). With ME data acquisition, data from the different acquired echo times can be optimally combined based on the T2* of the underlying tissue (Posse et al., 1999).

The technique of ME data acquisition has been present for some time (e.g. Posse et al., 1999) but has struggled to gain popularity due to the requisite compromises in spatial and temporal resolution as well as the need to use in-plane accelerations to avoid excessively long echo trains during image readout. NORDIC, a recently developed tool for denoising fMRI data and thereby improving data quality could help to overcome some of these challenges and further improve the capabilities and usability of ME data. NORDIC decreases thermal noise in the data by removing zero-mean gaussian noise, improving the SNR without sacrificing spatial precision (Dowdle et al.,

2023; Vizioli et al., 2021). Ultimately however, little is known about the usability of ME fMRI data in pediatric populations.

Translating methods from adults to infants - challenges and opportunities

When trying to leverage methods developed in an adult population for developmental neuroimaging, it is important to consider that infant brains are not just smaller adult brains but instead have specific properties that change with their developmental stage. T2* relaxation, which forms the basis of fMRI, shows a developmental trend, being slower in newborns compared to infants and adults (Rivkin et al., 2004; Williams et al., 2005). This slower T2* decay is related to several factors, including reduction in the amount of free water compared to bound water in brain tissues over development (Engelbrecht et al., 1998; Xydis et al., 2006) as axon myelination increases in both white and gray matter (Baumann & Pham-Dinh, 2001; Dubois et al., 2014; Kostović et al., 2019), an increase in proton density, an abundance of macromolecules, and changes in iron concentration (Goksan et al., 2017). These are important factors to consider for the evaluation of a prospective ME acquisition in newborns as the optimal combination of echoes is dependent on the T2* relaxation time of a given voxel. Given the impact of brain developmental changes on T2* relaxation times ME data acquisitions could be a promising tool for developmental imaging. It opens up the possibility to account for the impact of brain developmental differences on data acquisition, particularly for longitudinal investigations, by using individual optimal echo combinations based on T2* times while still using the same acquisition sequence.

We however first need to gain a better understanding of ME data acquisition and optimal echo times in infants compared to adults, where ME fMRI has recently been shown to provide advantages over single-echo (SE) acquisitions (Lynch et al., 2020), rather than trying to make a direct comparison with a standard SE fMRI sequence, potentially using a suboptimal echo time for the target population. The application of NORDIC denoising on the other hand, with its targeting of thermal noise, should be useful independent of the age of the target sample and outcomes can be directly compared within the same ME data without NORDIC denoising.

Methods under investigation in the present study

In the present study, we investigated the T2* relaxation times and optimal echo combinations of newborn ME fMRI data and the impact of NORDIC thermal noise removal on these datasets. For testing the usability and benefit of these methodological approaches in an infant sample, we utilized precision imaging data with ME data acquisition from three different newborns across multiple days. We additionally compared our ME infant data to adult data acquired with the same sequence to highlight age specific differences. We use NORDIC denoising on all newborn datasets to look at differences in data quality with and without thermal noise removal. Data quality was operationalized through temporal SNR (tSNR), strength of functional connections, and split-half reliability of brain functional connectivity within individuals. This investigation provides insights into the applicability of these methods to infant neuroimaging with the goal of improving signal quality to facilitate precision functional imaging.

2. Methods

2.1 Sample

This sample consists of three healthy neonates enrolled at Washington University in St. Louis, ages 28 days (43 weeks postmenstrual age (wPMA); PB004), 12 days (41 wPMA; PB005) and 13 days (41 wPMA; PB001). And one adult for reference also enrolled at Washington University in St. Louis. For all neonates, data was acquired over four to five days within one week. This study was approved by the Human Studies Committees at Washington University and written informed consent was obtained from all parents of neonatal participants. Anatomical and resting state data in neonates was acquired during natural sleep.

2.2 Data acquisition

rs-fMRI data for all neonatal subjects was acquired with the CMRR multiband (MB)-ME sequence (Feinberg et al., 2010; Moeller et al., 2010) with 5 echoes (14ms, 38ms, 63ms, 88ms, 113ms; TR = 1.761s, 2mm resolution, MB factor = 6, IPAT = 2, flip angle = 68°). A total of 72 minutes of rs-fMRI data were acquired from PB004 (split into 9 runs), 117 minutes from PB005 (13 runs), and 142 minutes from PB001 (21 runs). This sequence was also used for the adult participant included as a reference. Additionally, spin echo fieldmaps were acquired in both AP and PA direction (SE, single-band, 3 frames per run, TR = 8.0s, TE = 66 ms, flip angle = 90°) for all participants.

For anatomical references, a T1 weighted scan (infants: TR = 2.4s, TE = 2.2ms, resolution = 0.8 x 0.8 x 0.8 mm, flip angle = 8°); and a T2 weighted scan (infant: TR = 4.5s, TE = 563ms, resolution = 0.8 x 0.8 x 0.8 mm, flip angle = 120°); was acquired for all participants. Adult anatomical references were taken from a previously acquired (now publicly available) dataset (T1w: TR = 2.4s, TE = 3.7ms, resolution = 0.8 x 0.8 x 0.8 mm, flip angle = 8°; T2w: TR = 3.2s, TE = 479ms, resolution = 0.8 x 0.8 x 0.8 mm, flip angle = 120°) (Gordon et al., 2017). We additionally acquired some single-echo rs-fMRI data for PB004 and PB005 with a more standard fMRI acquisition protocol (TR 1.51s, TE = 37ms, 2mm resolution, MB factor = 4, flip angle = 52°; 77 min and 8 runs for PB004 and 123 min and 13 runs for PB005).

Neonatal imaging was performed using a Siemens 3-T Prisma scanner and a 32 channel head coil. Adult functional imaging was performed using a Siemens 3-T Prisma scanner and a 64 channel head coil.

2.3 Data processing

For analyses in which NORDIC was applied to a dataset, this step was performed before the regular preprocessing, using the phase and the magnitude images of the scan data in addition to noise frames acquired at the end of a functional run, when available (PB004, PB005, adult). For the one participant where noise scans were not acquired (PB001), we used the theoretical thermal noise level (equal to 1/sqrt(2)) (Moeller et al., 2021; Vizioli et al., 2021). We utilized NORDIC implemented in Matlab R2019a (Vizioli et al., 2021). In the case of ME data acquisition, NORDIC denoising was performed for each echo individually.

Neonatal images were preprocessed with the infant-abcd-hcp-pipeline (Sturgeon et al 2023), an infant specific modification of the HCP pipeline (Feczko et al., 2021; Glasser et al., 2013). Segmentations of anatomical images were created using BIBSnet, a deep learning tool specifically trained for infant MRI image segmentation. (Hendrickson et al., 2023). During preprocessing, these precomputed segmentations were utilized by the infant-abcd-hcp-pipeline, anatomical images were registered to the MNI infant atlas and functional data was projected onto the atlas space surfaces. Spin echo fieldmaps were leveraged for susceptibility distortion correction using FSL topup (Andersson et al., 2003). Functional data was additionally denoised and motion censored using framewise displacement (FD). Runs with less than 30% of remaining data at an FD of 0.3mm were excluded. After censoring frames with high motion (above FD 0.3mm) during data preprocessing, PB004 retained 57 minutes of low motion data (out of 77), PB005 79 minutes (out of 117) and PB001 112 minutes (out of 142) with one entire run excluded. From the additional SE data PB004 retained 72 minutes (out of 77) and PB005 85 minutes (out of 123).

As the infant-abcd-hcp-pipeline is not constructed for ME data, data from all five echoes were optimally combined using Tedana (DuPre et al., 2021; Kundu et al., 2012, 2013; The tedana Community et al., 2022) before running the pipeline. For the optimal combination we used the T2* based echo weighting implemented in Tedana ($w_{TE} = TE * \frac{-TE}{e^{T2*}}$; (Posse et al., 1999)). In addition, motion regressors were calculated from the first echo and applied to all individual echoes before combining them.

Adult imaging data were processed using fMRIprep 23.1.3 (Esteban et al., 2019), with an additional patch to modify the mapping of subcortical voxels to grayordinate indices to match the HCP 91k grayordinates space. Susceptibility distortion correction of BOLD time series was done within fMRIPrep, using an FSL topup-based method to estimate fieldmaps from “PEPolar” acquisitions (acquisitions with opposite phase encoding direction) (Andersson et al., 2003); these fieldmaps were then used to correct distortion of the BOLD time series data. Additional options enabled for fMRIPrep processing were “--project-goodvoxels”, to exclude voxels with locally high coefficient of variation from volume-to-surface projection of the BOLD time series, and “--cifti-output 91k” to enable output of BOLD time series and morphometric data (surface curvature, sulcal depth, and cortical thickness maps) in the HCP grayordinates space (Glasser et al., 2013).

2.4 Data analysis

We investigated optimal echo times (T2*) as outputted by Tedana as well as the weights of each echo used for the T2* based optimal echo combination for each greyordinate.

We calculated temporal signal to noise ratio (tSNR), defined as mean intensity over the timeseries divided by the time series standard deviation, in the data with and without NORDIC applied as well as the strength of functional connections using a parcel-to-parcel connectivity matrix (parcels defined after Gordon et al., (2016). For T2* and tSNR estimates averages across runs with >90% low motion data were used.

Reliability was assessed by the vertex-by-vertex correlation of dense functional connectivity matrices within subject similar to Lynch et al., (2020). Dense connectivity matrices were constructed using a smoothing Kernel of 2.5mm. To account for natural variations in data quality

during one session and across multiple days, the order of runs was randomly permuted 100 times and an average curve calculated.

For investigating the impact on necessary time in the scanner for a reliable determination of person-specific functional brain organization, we used data from PB001 who had the largest amounts of data in our sample and calculated reliability curves. Reliability curves were constructed using split halves of the data, comparing various consecutive amounts of data to the held-out half, used as ground truth. As an addition, we explored varying smoothing Kernels as well as the parcellated time series to investigate the effect of smoothing on reliability.

3. Results

Infants show longer T2 relaxation times which affect optimal combination in ME*

The five echo ME data acquisition protocol used in this study allowed us to model the T2 decay curve across five different time points. T2* relaxation times estimated from these curves were longer and more variable in all infants compared to an example adult subject (Figure 1). The mean T2* relaxation time across cortical voxels for the adult was 50.12ms (SD = 13.67ms, 5th and 95th percentile = [24.24ms, 67,93ms]) which is consistent with the adult literature (Fera et al., 2004; Wansapura et al., 1999). Whereas PB004 showed a mean of 93.84ms (SD = 27.04ms, 5th and 95th percentile = [37.23ms, 130.22ms]), PB005 77.10ms (SD = 28.94, 5th and 95th percentile = [28.91ms, 121.27ms]) and PB001 81.51ms (SD = 27.84, 5th and 95th percentile = [31.91ms, 124.10ms]). Prior application of NORDIC denoising to the data did not impact the estimate of T2* (Suppl Fig 1).

		T2*	**e1**	**e2**	**e3**	**e4**	**e5**
adult	mean	50.12	0.167	0.246	0.235	0.197	0.155
	SD	13.67	0.096	0.028	0.030	0.042	0.044
	5th pct	24.24	0.111	0.210	0.194	0.097	0.045
	95th pct	67.93	0.334	0.308	0.243	0.232	0.206
PB004	mean	93.84	0.101	0.194	0.232	0.240	0.233
	SD	27.04	0.047	0.035	0.008	0.031	0.049
	5th pct	37.23	0.074	0.167	0.224	0.170	0.113
	95th pct	130.22	0.198	0.281	0.242	0.259	0.274
PB005	mean	77.10	0.124	0.214	0.233	0.224	0.204
	SD	28.94	0.063	0.044	0.011	0.041	0.061
	5th pct	28.91	0.076	0.170	0.218	0.129	0.070
	95th pct	121.27	0.269	0.314	0.243	0.257	0.269
PB001	mean	81.51	0.114	0.207	0.234	0.230	0.214
	SD	27.84	0.054	0.039	0.009	0.035	0.055
	5th pct	31.91	0.075	0.169	0.224	0.146	0.086
	95th pct	124.06	0.239	0.302	0.243	0.258	0.271

Table 1: T2 times in ms and normalized weights for each echo for the example adult and the three newborns. Highlighted: echo weightings above 20%*

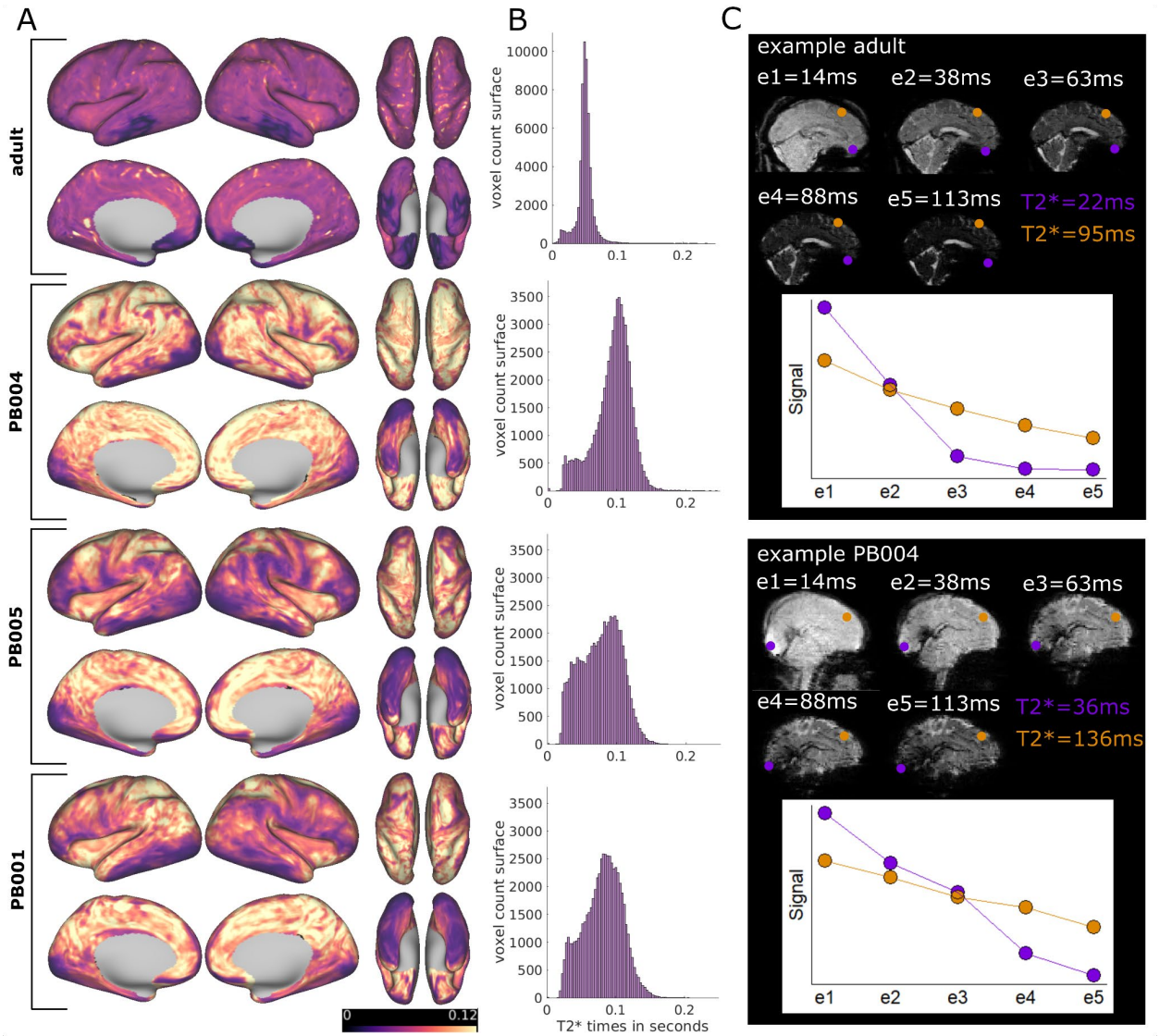

Figure 1: A: T2 values (in seconds) for all three precision babies and one adult recorded with the same ME protocol (average of runs with >90% low motion) B: distribution of T2* times from the cortical surface. C: Example for T2 decay curve for the example adult and PB004 at two voxels with short and long T2* over five echoes.*

The difference in T2* relaxation times between infants and the adult (Figure 1) altered echo weighting as visualized in Figure 2, such that the optimal weighting of echo times to combine data differed between the two age groups (Table 1). The mean normalized weighting per echo in the adult was highest for the second and third echo while for the infants, the third to fifth echo was weighted heaviest. In all subjects weighting of the first echo was highest in limited areas which is likely related to signal dropout in these areas (Figure 2).

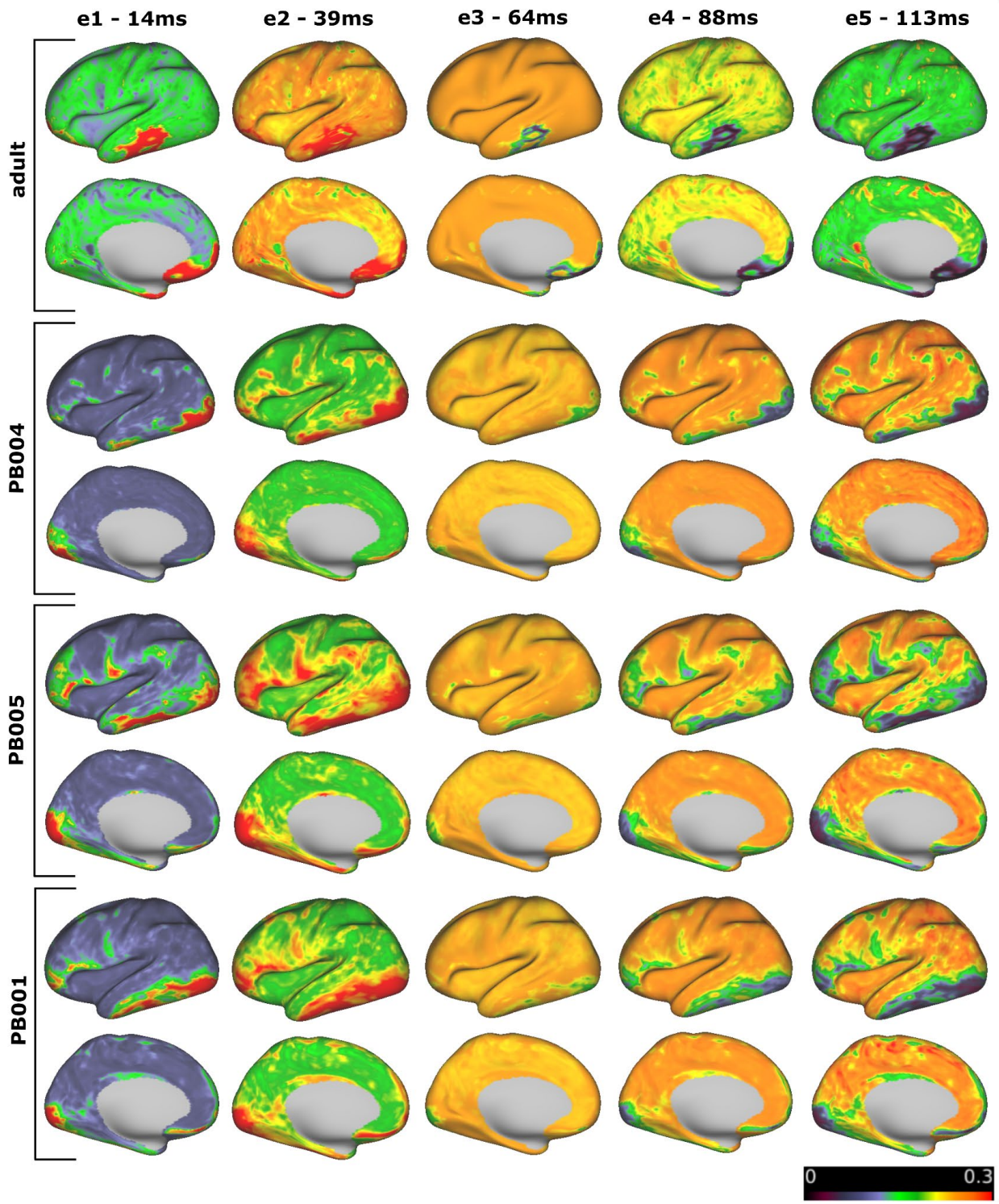

Figure 2: Echo weighting distribution across the cortex for all five echoes for the example adult and the newborns resulting from the T2 maps*

NORDIC improves tSNR and increases connectivity strength and split half reliability

To evaluate the impact of NORDIC denoising on infant ME data, we investigated changes in tSNR, split-half reliability and strength of functional connections. We calculated the average tSNR from runs with greater than 90% of low motion data (5 runs for PB004, 3 runs for PB005 and 12 runs for PB001). We saw an overall improvement in tSNR with NORDIC (Figure 3A). Across the whole brain, NORDIC denoising increased tSNR by 33.8% (without NORDIC: M = 95.40, SD = 38.33; with NORDIC: M = 127.66, SD = 48.90) in PB004; by 19% in PB005 (without NORDIC: M = 69.66, SD = 26.90; with NORDIC: M = 82.43, SD = 29.85) and by 54% in PB001 (without NORDIC: M = 94.21, SD = 39.33; with NORDIC: M = 145.84, SD = 53.62). See also Suppl Figure 2A and Suppl Figure 3A. Similar benefits are also afforded single echo data (Suppl Figure 4A and Suppl Figure 5A).

We furthermore investigated the impact of NORDIC denoising on the absolute strength of functional connections between brain areas (Figure 3B; Suppl Figure 2B; Suppl Figure 3B). For this comparison, we looked at parcellated connectivity matrices using 55 minutes of low motion data for each condition for PB004. The average (absolute) connectivity strengths per condition were: M = 0.123 (SD = 0.394), ranging from -0.392 to 1.280 without NORDIC and M = 0.136 (SD = 0.397), ranging from -0.556 to 1.437 with NORDIC (all fisher z-transformed values, range excludes the matrix diagonal). PB005 and PB001 showed a similar pattern (using 75 minutes and 110 minutes of low motion data per condition). The average (absolute) connectivity strength per condition were: M = 0.127/0.119 (SD = 0.396/0.394), ranging from -0.420/-0.353 to 1.426/1.38 without NORDIC and M = 0.138/0.149 (SD = 0.398/0.399), ranging from -0.467/-0.453 to 1.489/1.356 with NORDIC (fisher z-transformed values, range excludes the matrix diagonal). The increase of connectivity strength with NORDIC was M = 0.028 (SD = 0.025) for PB004, M = 0.024 (SD = 0.022) for PB005 and M = 0.047 (SD = 0.044) for PB001 (min = -0.148/-0.167/-0.222, max = 0.297/0.288/0.457).

In addition to these two metrics, we investigated the impact of NORDIC on the split-half reliability of functional connectivity matrices. Calculating the vertex-by-vertex correlation to estimate split-half reliability of these matrices we saw that correlation values differ across the cortex with highest values in sensorimotor areas (Figure 3C; Suppl Figure 2C; Suppl Figure 3C). The overall (averaged over the cortical surface) split-half reliability was higher for data where NORDIC was applied PB004: M = 0.20, SD = 0.02 without NORDIC and M = 0.24, SD = 0.02 with NORDIC (25 min in each half). Similarly for PB005: M = 0.39, SD = 0.01 without NORDIC and M = 0.43, SD = 0.02 with NORDIC (35 min in each half) and PB001: M = 0.4, SD = 0.01 without NORDIC and M = 0.47, SD = 0.02 with NORDIC (50 min in each half).

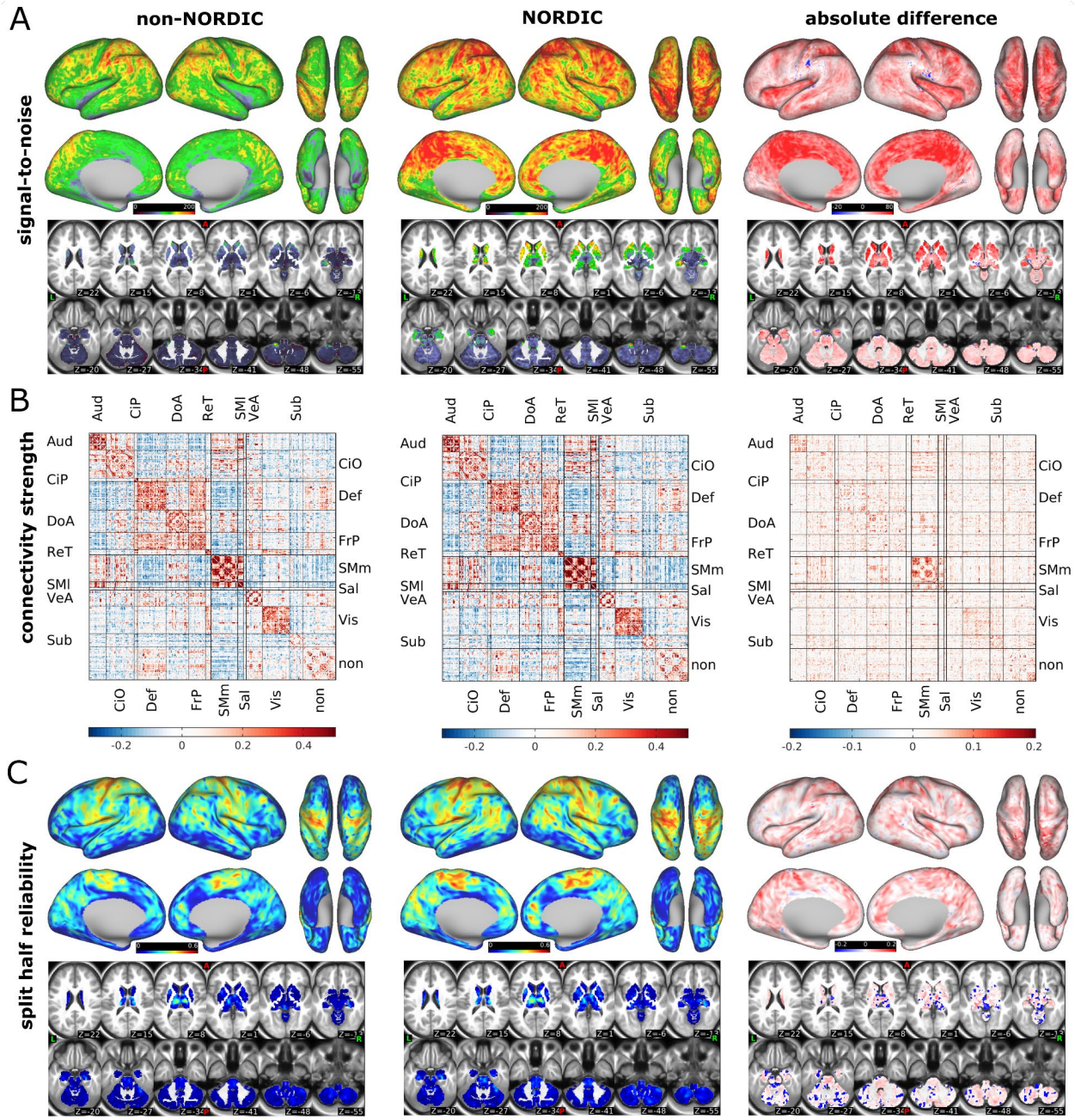

Figure 3: A) tSNR values for cortical and subcortical structures with and without NORDIC within infant participant PB004 (average of runs with >90% low motion). B) Parcellated connectivity matrix (PB004; 55 min of data) showing connectivity strength with and without NORDIC and their absolute difference. C) Map of vertex-wise split half reliability (25 min per half) for PB004 using a smoothing Kernel of 2.5 for the dense connectivity matrices.

Large amounts of data are needed to reach plateau in signal reliability

A key feature of PFM in adults has been the acquisition of large amounts of resting-state data that may not be feasible in developmental populations. To gain insights into the amount of data necessary to stably determine individual functional connectivity patterns with ME data and ME

plus NORDIC in infants, we investigated the reliability of functional network topology as a function of available data. Stability in this case is characterized by a plateau in the reliability curve created from correlations of connectivity matrices from varying amounts of data with those from the held out half.

With the amounts of data available for the precision imaging subjects in this study (highest amount for PB001) no plateau in signal reliability could be reached. None of the curves depicted in Figure 4 reached a plateau in correlation values. This indicates that the available split-half data (50 minutes for PB001) is not sufficient to stably characterize individual network topology. Considering this, absolute values should be considered with caution as the held out half can as a consequence not be treated as 'ground truth'. Furthermore, absolute reliability values depend on the amount of spatial smoothing used when calculating the connectivity matrices as visualized in Figure 4A. In our example the highest reliability was reached when using a parcellated time series, which was expected as this averages data from neighbor grayordinates, which results in a drastic reduction in spatial precision. In all cases, reliability is higher for data which underwent NORDIC denoising (Figure 4B).

As spatial smoothing is an efficient data denoising method, the application of NORDIC shows the greatest benefits for reliability when using little spatial smoothing (Figure 4B). For PB001, we see an improvement of 43.8% when using no spatial smoothing (from 0.16 to 0.23) and of 6.3% when using parcellated data (from 0.63 to 0.67). The boost in signal reliability with the application of NORDIC was similar to the boost with using a smoothing Kernel of 1.5, however, without the loss in spatial precision (Figure 4C & D).

4. Discussion

This study focused on potential methodological avenues to improve quality and reliability of infant fMRI data to facilitate precision functional imaging in this age group. The two methods evaluated were ME data acquisitions and NORDIC thermal denoising. ME acquisition was evaluated for its applicability in newborn infants. T2* values calculated from ME data were longer and more variable in infants compared to an adult example subject. This led to a differential optimal echo combination, with heavier weighting of later echoes for the infant datasets. The application of NORDIC increased tSNR and the overall strength of functional connections. Application of NORDIC also increased split-half reliability of functional connectivity matrices. However, even for the participant with the largest amounts of data available (50 minutes in each half), we did not see a plateau in reliability curves, characteristic of similar work in adults with the same acquisition methods. These results thus emphasize potential gains but also the need for further methodological advancements to facilitate precision functional mapping in infants.

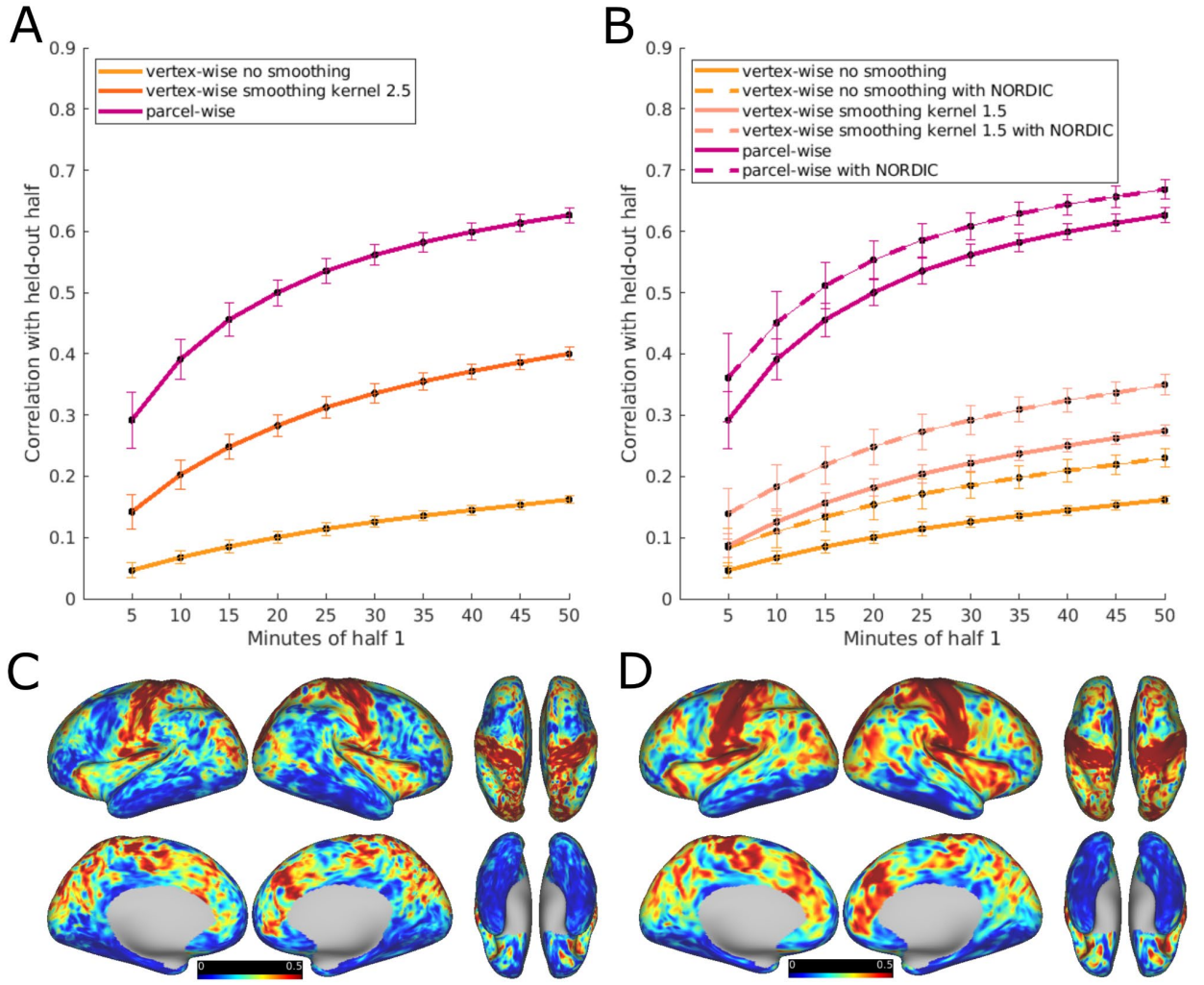

Figure 4: A) Reliability curves for PB001 derived from average over cortical data. Curves are plotted by smoothing Kernel/parcel B) Curves with and without NORDIC C) Reliability (at 50 min) for no-smoothing with NORDIC is similarly high as D) a smoothing kernel of 1.5 without NORDIC however it preserves spatial precision.

Infant PFM is feasible but requires developmentally-specific consideration

The datasets used to investigate the impact of methodological advances in the present study show that extended fMRI data acquisitions are feasible in newborn infants. Particularly, collecting data over consecutive days to minimize brain developmental changes within the data acquisition period is possible. This mitigates one major constraint for precision imaging in infants as the brain develops rapidly in early infancy (e.g. Kostović et al., 2019) and sessions for data collection need to be spaced as closely together as possible in order to concatenate data without introducing variability caused by developmental changes in the brain. Even though the overall process itself was feasible, we saw that motion is a considerable challenge for this age group and can vary a lot between individuals as can be seen by the difference in the amount of retained data between the subjects (PB004: 74%, PB005: 68%, PB001: 79%).

ME data acquisition in newborns has several advantages

The evaluation of ME data acquisitions in newborn infants confirmed the findings of previous studies that showed overall longer T2* relaxation times in newborns compared to adults (Rivkin et al., 2004; Williams et al., 2005). It should be noted that T2* times vary with magnetic field strength (Peters et al., 2007) and many past infant studies used a 1.5T magnet (e.g. (Leppert et al., 2009; Rivkin et al., 2004)). In addition to overall longer T2* relaxation times, our evaluation shows that newborn brains have a larger variability of T2* compared to adults, which may be in part due to the combination of longer T2* times for developing tissues and short T2*s in areas impacted by high magnetic susceptibility effects (e.g. air – tissue interfaces). This result highlights the challenge in finding an optimal echo time for data acquisition within a given developmental age group (e.g. newborns) and supports the idea that ME fMRI could be a useful tool for imaging during brain development. Developmental studies (particularly longitudinal studies) could possibly benefit from using ME as it allows to use T2* based optimal echo weighting to dynamically adapt to developmental changes.

Further investigations into the use of ME acquisitions in infants should also be done using a task fMRI design, similar to (Goksan et al., 2017), who acquired data with five different SE protocols in infants using noxious stimuli at the heel, looking for the maximal task contrast to identify an optimal echo time. Using a task design with a ME acquisition in infants could help determine which range of echo times are particularly helpful to optimally characterize task activation and which ones potentially introduce more noise. Our results which show a large variability in T2* relaxation times in the newborn brain suggest that it is unlikely that one will find a single optimal echo time for infant fMRI. In any case, the number and timing of echoes in a ME fMRI protocol for developmental studies can still, however, be further optimized. It will be important to consider the balance between the number of echoes, the spatial and temporal resolutions, and the acceleration factors, which are all interdependent with respect to the overall functional contrast to noise ratio.

NORDIC thermal noise reduction improves data quality

Our results showed an overall benefit in data quality when using NORDIC denoising in the infant brain. We saw an increase in tSNR as well as in the strength of functional connections and split half reliability with NORDIC. We also saw an increase in the magnitude of reliability curves, though benefits decreased with the amount of smoothing in the data. As smoothing is commonly used to reduce noise in the data, the decrease in the difference between NORDIC and non-NORDIC with larger amounts of smoothing is expected. Comparing those two methods as a means to increase reliability, the application of NORDIC preferred over smoothing in order to retain spatial precision in the data (Dowdle et al., 2023; Vizioli et al., 2021), which is already compromised compared to the adult, because of the smaller infant brain.

The present results suggest that NORDIC could be a valuable addition to future studies, especially since it does not come with any significant cost, as it only requires saving the phase and magnitude data from the scanner. The acquisition of additional noise frames at the end of the scan (as done in PB004 and PB005) results in more significant noise removal when used in the NORDIC denoising process, however, the default parameters (as used for PB001), which did not have a separate noise scan, still resulted in SNR benefits after NORDIC preprocessing.

Investigation of reliability shows limitations infant precision functional mapping is currently facing

The investigation on data reliability within this study showed that it is difficult to reach a very stable estimate of brain functional connectivity for a newborn infant. Even for PB001 who had unusually high amounts of low motion data for an infant (112 min) split half reliability did not reach a stable point, speaking towards the need for more than 1h of low motion data for reliable functional precision imaging in infants. The lack of a plateau in the curves we constructed indicates that the available data was not sufficient to act as suitable 'ground truth' held out data. Therefore the relative differences in values between conditions given comparable amounts of data may be a more useful metric, compared to absolute reliability values. The quantification of reliability in this study followed the example of (Lynch et al., 2020) who performed vertex-wise correlations between dense connectivity matrices. It has to be noted that reliability curves based on the correlation of entire vectorized parcellated matrices as presented in previous literature (Gordon et al., 2017; Laumann et al., 2015) yield higher values overall.

Given this constraint, reliability values were rather low and not uniformly distributed across the cortex. Curious differences that can be noted between newborns and adults (compare to Lynch et al., 2020) are that somatomotor areas showed the highest reliability values in infants and the lowest in adults and that the cerebellum which is the most reliable subcortical structure in adults has very low values in infants.

Both the removal of thermal noise with NORDIC and spatial smoothing increase reliability. Irrespective of the relative gains with NORDIC and smoothing, and in addition to the lack of a plateau, the reliability curves showed shallower slopes than what has previously been shown in adults (see Lynch et al., 2020). This is in line with findings by Moore et al., (2023) and Sylvester et al., (2022) who suggested that larger amounts of data are needed for precision imaging in infants compared to adolescents or adults. The need for longer acquisition times in infants may be explained by the general factors challenging infant imaging, such as increased motion, smaller head size relative to voxel size, distance to the coil, or the lack of fully optimized infant specific processing pipelines (Dubois et al., 2021; Korom et al., 2021). It may, however, be in part related to more biological factors like the variability in potential behavioral states in newborns during scanning (quiet sleep, active sleep, wakefulness) compared to adults who are usually awake, fixating at a crosshair. Another source of variance could be smaller brain developmental changes across the recording days. Given the reliability limitations in infant precision functional imaging, working on the level of infant specific parcels (Wang et al., 2023) or individual networks (Moore et al., 2023), using alternative methods to increase overall SNR, such as higher magnetic fields (Annink et al., 2020) or infant specific coils (Hughes et al., 2017; Keil et al., 2011; Lopez Rios et al., 2018), may be extremely beneficial.

Limitations and outlook

One major advantage of ME fMRI is the possibility of using use multi-echo independent component analysis (MEICA) for T2* based denoising (Kundu et al., 2012, 2013; Lynch et al., 2020). This is a feature we were not able to use for the present study as thresholds commonly used for MEICA are not applicable for our infant data. This is likely due to the developmental differences in T2* and will need further investigation. Given the promise of ME acquisitions for

developmental neuroimaging, the development of an infant specific MEICA version could be valuable for the field. Furthermore, the present investigation and findings are limited as they only explored one ME fMRI protocol. More thorough investigations using different ME protocols within infant subjects, and potentially even within longitudinal recordings, will help exploit the advantages and disadvantages of a given combination of echoes. A longitudinal approach could help characterize the precise evolution of T2* relaxation times, informing the optimization of age specific protocols. Furthermore, in the present study, we did not elaborate on the role of well trained MR operators in making the data more reliable by obtaining optimal positioning of the infant in the coil and minimizing motion during data acquisition, which are critical to this developmental period. Development of comprehensive training materials and guidelines will help mitigate some of the challenges even before the availability of adequate data processing and analysis methods. As mentioned, the limitations of the present work highlight the need for more infant specific methods developments, in particular on the avenue towards precision functional mapping during early development.

5. Conclusions

The present work shows that some methodological advances from the adult literature (like NORDIC denoising) can be translated well to infant precision functional imaging cohorts. ME data acquisitions show high promise but are more complicated in their translation and need further investigation. There are still gaps in our understanding of the best techniques for developmental brain imaging, motivating further infant specific methodological advances as we work towards broadly applicable and robust precision functional imaging in infants.

6. Data and Code Availability

Data can be made available upon request, given a formal data sharing agreement is set up by the institutions involved.
Code is available from the following repository: https://github.com/DCAN-Labs/code_infant_me_nordic_paper

7. Author Contributions

Julia Moser: Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing - Original Draft; Sanju Koirala: Formal analysis, Writing - Original Draft; Thomas Madison: Formal analysis, Methodology, Software, Writing - Review & Editing; Alyssa Labonte: Conceptualization, Data Curation, Writing - Review & Editing; Cristian Morales-Carrasco: Methodology, Software; Eric Feczko: Methodology, Software; Lucille A. Moore: Methodology; Weli Ahmed: Formal analysis; Michael J. Myers: Data Curation; Essa Yacoub: Methodology, Writing - Review & Editing; Brenden Trevo-Clemmens: Writing - Review & Editing; Bart Larsen: Writing - Review & Editing; Timothy O. Laumann: Methodology; Steven M. Nelson: Writing - Review & Editing; Luca Vizioli: Methodology, Writing - Review & Editing; Chad M. Sylvester: Conceptualization, Writing - Review & Editing, Supervision; Damien A. Fair: Conceptualization, Writing - Review & Editing, Supervision.

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9. Declaration of Competing Interests

Damien A. Fair is a patent holder on the Framewise Integrated Real-Time Motion Monitoring (FIRMM) software. He is also a co-founder of Turing Medical Inc that licenses this software. The nature of this financial interest and the design of the study have been reviewed by two committees at the University of Minnesota. They have put in place a plan to help ensure that this research study is not affected by the financial interest. The other authors declare no competing interests.

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References

Andersson, J. L. R., Skare, S., & Ashburner, J. (2003). How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *NeuroImage*, *20*(2), 870–888.

Annink, K. V., van der Aa, N. E., Dudink, J., Alderliesten, T., Groenendaal, F., Lequin, M., Jansen, F. E., Rhebergen, K. S., Luijten, P., Hendrikse, J., Hoogduin, H. J. M., Huijing, E. R., Versteeg, E., Visser, F., Raaijmakers, A. J. E., Wiegers, E. C., Klomp, D. W. J., Wijnen, J. P., & Benders, M. J. N. L. (2020). Introduction of Ultra-High-Field MR Imaging in Infants: Preparations and Feasibility. *AJNR. American Journal of Neuroradiology*, *41*(8), 1532–1537.

Baumann, N., & Pham-Dinh, D. (2001). Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiological Reviews*, *81*(2), 871–927.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the

motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *34*(4), 537–541.

Cui, Z., Li, H., Xia, C. H., Larsen, B., Adebimpe, A., Baum, G. L., Cieslak, M., Gur, R. E., Gur, R. C., Moore, T. M., Oathes, D. J., Alexander-Bloch, A. F., Raznahan, A., Roalf, D. R., Shinohara, R. T., Wolf, D. H., Davatzikos, C., Bassett, D. S., Fair, D. A., … Satterthwaite, T. D. (2020). Individual Variation in Functional Topography of Association Networks in Youth. *Neuron*, *106*(2), 340–353.e8.

Cui, Z., Pines, A. R., Larsen, B., Sydnor, V. J., Li, H., Adebimpe, A., Alexander-Bloch, A. F., Bassett, D. S., Bertolero, M., Calkins, M. E., Davatzikos, C., Fair, D. A., Gur, R. C., Gur, R. E., Moore, T. M., Shanmugan, S., Shinohara, R. T., Vogel, J. W., Xia, C. H., … Satterthwaite, T. D. (2022). Linking Individual Differences in Personalized Functional Network Topography to Psychopathology in Youth. *Biological Psychiatry*, *92*(12), 973–983.

Dowdle, L. T., Vizioli, L., Moeller, S., Akçakaya, M., Olman, C., Ghose, G., Yacoub, E., & Uğurbil, K. (2023). Evaluating increases in sensitivity from NORDIC for diverse fMRI acquisition strategies. *NeuroImage*, *270*, 119949.

Dubois, J., Alison, M., Counsell, S. J., Hertz-Pannier, L., Hüppi, P. S., & Benders, M. J. N. L. (2021). MRI of the Neonatal Brain: A Review of Methodological Challenges and Neuroscientific Advances. *Journal of Magnetic Resonance Imaging: JMRI*, *53*(5), 1318–1343.

Dubois, J., Dehaene-Lambertz, G., Kulikova, S., Poupon, C., Hüppi, P. S., & Hertz-Pannier, L. (2014). The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. *Neuroscience*, *276*, 48–71.

DuPre, E., Salo, T., Ahmed, Z., Bandettini, P., Bottenhorn, K., Caballero-Gaudes, C., Dowdle, L., Gonzalez-Castillo, J., Heunis, S., Kundu, P., Laird, A., Markello, R., Markiewicz, C., Moia, S., Staden, I., Teves, J., Uruñuela, E., Vaziri-Pashkam, M., Whitaker, K., &

Handwerker, D. (2021). TE-dependent analysis of multi-echo fMRI with tedana. *Journal of Open Source Software*, *6*(66), 3669.

Elbau, I. G., Lynch, C. J., Downar, J., Vila-Rodriguez, F., Power, J. D., Solomonov, N., Daskalakis, Z. J., Blumberger, D. M., & Liston, C. (2023). Functional Connectivity Mapping for rTMS Target Selection in Depression. *The American Journal of Psychiatry*, *180*(3), 230–240.

Engelbrecht, V., Rassek, M., Preiss, S., Wald, C., & Mödder, U. (1998). Age-dependent changes in magnetization transfer contrast of white matter in the pediatric brain. *AJNR. American Journal of Neuroradiology*, *19*(10), 1923–1929.

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., Snyder, M., Oya, H., Ghosh, S. S., Wright, J., Durnez, J., Poldrack, R. A., & Gorgolewski, K. J. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature Methods*, *16*(1), 111–116.

Feczko, E., Conan, G., Marek, S., Tervo-Clemmens, B., Cordova, M., Doyle, O., Earl, E., Perrone, A., Sturgeon, D., Klein, R., Harman, G., Kilamovich, D., Hermosillo, R., Miranda-Dominguez, O., Adebimpe, A., Bertolero, M., Cieslak, M., Covitz, S., Hendrickson, T., … Fair, D. A. (2021). Adolescent Brain Cognitive Development (ABCD) Community MRI Collection and Utilities. In *bioRxiv* (p. 2021.07.09.451638). https://doi.org/10.1101/2021.07.09.451638

Feinberg, D. A., Moeller, S., Smith, S. M., Auerbach, E., Ramanna, S., Gunther, M., Glasser, M. F., Miller, K. L., Ugurbil, K., & Yacoub, E. (2010). Multiplexed echo planar imaging for sub-second whole brain FMRI and fast diffusion imaging. *PloS One*, *5*(12), e15710.

Fera, F., Yongbi, M. N., van Gelderen, P., Frank, J. A., Mattay, V. S., & Duyn, J. H. (2004). EPI-BOLD fMRI of human motor cortex at 1.5 T and 3.0 T: sensitivity dependence on echo time and acquisition bandwidth. *Journal of Magnetic Resonance Imaging: JMRI*, *19*(1), 19–26.

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L.,

Xu, J., Jbabdi, S., Webster, M., Polimeni, J. R., Van Essen, D. C., Jenkinson, M., & WU-Minn HCP Consortium. (2013). The minimal preprocessing pipelines for the Human Connectome Project. *NeuroImage*, *80*, 105–124.

Goksan, S., Hartley, C., Hurley, S. A., Winkler, A. M., Duff, E. P., Jenkinson, M., Rogers, R., Clare, S., & Slater, R. (2017). Optimal echo time for functional MRI of the infant brain identified in response to noxious stimulation. *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *78*(2), 625–631.

Gordon, E. M., Chauvin, R. J., Van, A. N., Rajesh, A., Nielsen, A., Newbold, D. J., Lynch, C. J., Seider, N. A., Krimmel, S. R., Scheidter, K. M., Monk, J., Miller, R. L., Metoki, A., Montez, D. F., Zheng, A., Elbau, I., Madison, T., Nishino, T., Myers, M. J., … Dosenbach, N. U. F. (2023). A somato-cognitive action network alternates with effector regions in motor cortex. *Nature*, *617*(7960), 351–359.

Gordon, E. M., Laumann, T. O., Adeyemo, B., Huckins, J. F., Kelley, W. M., & Petersen, S. E. (2016). Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. *Cerebral Cortex* , *26*(1), 288–303.

Gordon, E. M., Laumann, T. O., Gilmore, A. W., Newbold, D. J., Greene, D. J., Berg, J. J., Ortega, M., Hoyt-Drazen, C., Gratton, C., Sun, H., Hampton, J. M., Coalson, R. S., Nguyen, A. L., McDermott, K. B., Shimony, J. S., Snyder, A. Z., Schlaggar, B. L., Petersen, S. E., Nelson, S. M., & Dosenbach, N. U. F. (2017). Precision Functional Mapping of Individual Human Brains. *Neuron*, *95*(4), 791–807.e7.

Gratton, C., Laumann, T. O., Nielsen, A. N., Greene, D. J., Gordon, E. M., Gilmore, A. W., Nelson, S. M., Coalson, R. S., Snyder, A. Z., Schlaggar, B. L., Dosenbach, N. U. F., & Petersen, S. E. (2018). Functional Brain Networks Are Dominated by Stable Group and Individual Factors, Not Cognitive or Daily Variation. *Neuron*, *98*(2), 439–452.e5.

Hendrickson, T. J., Reiners, P., Moore, L. A., Perrone, A. J., Alexopoulos, D., Lee, E. G.,

Styner, M., Kardan, O., Chamberlain, T. A., Mummaneni, A., Caldas, H. A., Bower, B., Stoyell, S., Martin, T., Sung, S., Fair, E., Uriarte-Lopez, J., Rueter, A. R., Rosenberg, M. D., … Feczko, E. (2023). BIBSNet: A Deep Learning Baby Image Brain Segmentation Network for MRI Scans. In *bioRxiv* (p. 2023.03.22.533696). https://doi.org/10.1101/2023.03.22.533696

Hermosillo, R. J. M., Moore, L. A., Fezcko, E., Dworetsky, A., Pines, A., Conan, G., Mooney, M. A., Randolph, A., Adeyemo, B., Earl, E., Perrone, A., Carrasco, C. M., Uriarte-Lopez, J., Snider, K., Doyle, O., Cordova, M., Nagel, B. J., Feldstein Ewing, S. W., Satterthwaite, T., … Fair, D. A. (2022). A Precision Functional Atlas of Network Probabilities and Individual-Specific Network Topography. In *bioRxiv* (p. 2022.01.12.475422). https://doi.org/10.1101/2022.01.12.475422

Hughes, E. J., Winchman, T., Padormo, F., Teixeira, R., Wurie, J., Sharma, M., Fox, M., Hutter, J., Cordero-Grande, L., Price, A. N., Allsop, J., Bueno-Conde, J., Tusor, N., Arichi, T., Edwards, A. D., Rutherford, M. A., Counsell, S. J., & Hajnal, J. V. (2017). A dedicated neonatal brain imaging system. *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *78*(2), 794–804.

Keil, B., Alagappan, V., Mareyam, A., McNab, J. A., Fujimoto, K., Tountcheva, V., Triantafyllou, C., Dilks, D. D., Kanwisher, N., Lin, W., Grant, P. E., & Wald, L. L. (2011). Size-optimized 32-channel brain arrays for 3 T pediatric imaging. *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *66*(6), 1777–1787.

Korom, M., Camacho, M. C., Filippi, C. A., Licandro, R., Moore, L. A., Dufford, A., Zöllei, L., Graham, A. M., Spann, M., Howell, B., FIT'NG, Shultz, S., & Scheinost, D. (2021). Dear reviewers: Responses to common reviewer critiques about infant neuroimaging studies. *Developmental Cognitive Neuroscience*, *53*, 101055.

Kostović, I., Sedmak, G., & Judaš, M. (2019). Neural histology and neurogenesis of the human fetal and infant brain. *NeuroImage*, *188*, 743–773.

Kundu, P., Brenowitz, N. D., Voon, V., Worbe, Y., Vértes, P. E., Inati, S. J., Saad, Z. S., Bandettini, P. A., & Bullmore, E. T. (2013). Integrated strategy for improving functional connectivity mapping using multiecho fMRI. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(40), 16187–16192.

Kundu, P., Inati, S. J., Evans, J. W., Luh, W.-M., & Bandettini, P. A. (2012). Differentiating BOLD and non-BOLD signals in fMRI time series using multi-echo EPI. *NeuroImage*, *60*(3), 1759–1770.

Kundu, P., Voon, V., Balchandani, P., Lombardo, M. V., Poser, B. A., & Bandettini, P. A. (2017). Multi-echo fMRI: A review of applications in fMRI denoising and analysis of BOLD signals. *NeuroImage*, *154*, 59–80.

Laumann, T. O., Gordon, E. M., Adeyemo, B., Snyder, A. Z., Joo, S. J., Chen, M.-Y., Gilmore, A. W., McDermott, K. B., Nelson, S. M., Dosenbach, N. U. F., Schlaggar, B. L., Mumford, J. A., Poldrack, R. A., & Petersen, S. E. (2015). Functional System and Areal Organization of a Highly Sampled Individual Human Brain. *Neuron*, *87*(3), 657–670.

Leppert, I. R., Almli, C. R., McKinstry, R. C., Mulkern, R. V., Pierpaoli, C., Rivkin, M. J., Pike, G. B., & Brain Development Cooperative Group. (2009). T(2) relaxometry of normal pediatric brain development. *Journal of Magnetic Resonance Imaging: JMRI*, *29*(2), 258–267.

Lopez Rios, N., Foias, A., Lodygensky, G., Dehaes, M., & Cohen-Adad, J. (2018). Size-adaptable 13-channel receive array for brain MRI in human neonates at 3 T. *NMR in Biomedicine*, *31*(8), e3944.

Lynch, C. J., Elbau, I., Ng, T., Ayaz, A., Zhu, S., Manfredi, N., Johnson, M., Wolk, D., Power, J. D., Gordon, E. M., Kay, K., Aloysi, A., Moia, S., Caballero-Gaudes, C., Victoria, L. W., Solomonov, N., Goldwaser, E., Zebley, B., Grosenick, L., … Liston, C. (2023). Expansion of a frontostriatal salience network in individuals with depression. In *bioRxiv* (p.

2023.08.09.551651). https://doi.org/10.1101/2023.08.09.551651

Lynch, C. J., Power, J. D., Scult, M. A., Dubin, M., Gunning, F. M., & Liston, C. (2020). Rapid Precision Functional Mapping of Individuals Using Multi-Echo fMRI. *Cell Reports*, *33*(12), 108540.

Miranda-Dominguez, O., Mills, B. D., Carpenter, S. D., Grant, K. A., Kroenke, C. D., Nigg, J. T., & Fair, D. A. (2014). Connectotyping: model based fingerprinting of the functional connectome. *PloS One*, *9*(11), e111048.

Moeller, S., Pisharady, P. K., Ramanna, S., Lenglet, C., Wu, X., Dowdle, L., Yacoub, E., Uğurbil, K., & Akçakaya, M. (2021). NOise reduction with DIstribution Corrected (NORDIC) PCA in dMRI with complex-valued parameter-free locally low-rank processing. *NeuroImage*, *226*, 117539.

Moeller, S., Yacoub, E., Olman, C. A., Auerbach, E., Strupp, J., Harel, N., & Uğurbil, K. (2010). Multiband multislice GE-EPI at 7 tesla, with 16-fold acceleration using partial parallel imaging with application to high spatial and temporal whole-brain fMRI. *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *63*(5), 1144–1153.

Moore, L. A., Hermosillo, R. J. M., Feczko, E., Moser, J., Koirala, S., Allen, M. C., Buss, C., Conan, G., Juliano, A. C., Marr, M., Miranda-Dominguez, O., Mooney, M., Myers, M., Rasmussen, J., Rogers, C., Smyser, C., Snider, K., Sylvester, C., Thomas, E., … Graham, A. M. (2023). *Towards Personalized Precision Functional Mapping in Infancy*. https://doi.org/10.2139/ssrn.4428815

Newbold, D. J., Laumann, T. O., Hoyt, C. R., Hampton, J. M., Montez, D. F., Raut, R. V., Ortega, M., Mitra, A., Nielsen, A. N., Miller, D. B., Adeyemo, B., Nguyen, A. L., Scheidter, K. M., Tanenbaum, A. B., Van, A. N., Marek, S., Schlaggar, B. L., Carter, A. R., Greene, D. J., … Dosenbach, N. U. F. (2020). Plasticity and Spontaneous Activity Pulses in Disused Human Brain Circuits. *Neuron*, *107*(3), 580–589.e6.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*, *87*(24), 9868–9872.

Penfield, W., & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain: A Journal of Neurology*, *60*(4), 389–443.

Peters, A. M., Brookes, M. J., Hoogenraad, F. G., Gowland, P. A., Francis, S. T., Morris, P. G., & Bowtell, R. (2007). T2* measurements in human brain at 1.5, 3 and 7 T. *Magnetic Resonance Imaging*, *25*(6), 748–753.

Posse, S., Wiese, S., Gembris, D., Mathiak, K., Kessler, C., Grosse-Ruyken, M. L., Elghahwagi, B., Richards, T., Dager, S. R., & Kiselev, V. G. (1999). Enhancement of BOLD-contrast sensitivity by single-shot multi-echo functional MR imaging. *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *42*(1), 87–97.

Rivkin, M. J., Wolraich, D., Als, H., McAnulty, G., Butler, S., Conneman, N., Fischer, C., Vajapeyam, S., Robertson, R. L., & Mulkern, R. V. (2004). Prolonged T*2 values in newborn versus adult brain: Implications for fMRI studies of newborns. *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *51*(6), 1287–1291.

Sylvester, C. M., Kaplan, S., Myers, M. J., Gordon, E. M., Schwarzlose, R. F., Alexopoulos, D., Nielsen, A. N., Kenley, J. K., Meyer, D., Yu, Q., Graham, A. M., Fair, D. A., Warner, B. B., Barch, D. M., Rogers, C. E., Luby, J. L., Petersen, S. E., & Smyser, C. D. (2022). Network-specific selectivity of functional connections in the neonatal brain. *Cerebral Cortex* . https://doi.org/10.1093/cercor/bhac202

The tedana Community, Ahmed, Z., Bandettini, P. A., Bottenhorn, K. L., Caballero-Gaudes, C., Dowdle, L. T., DuPre, E., Gonzalez-Castillo, J., Handwerker, D., Heunis, S., Kundu, P.,

Laird, A. R., Markello, R., Markiewicz, C. J., Maullin-Sapey, T., Moia, S., Salo, T., Staden, I., Teves, J., … Whitaker, K. (2022). *ME-ICA/tedana: 0.0.12*. https://doi.org/10.5281/zenodo.6461353

Vizioli, L., Moeller, S., Dowdle, L., Akçakaya, M., De Martino, F., Yacoub, E., & Uğurbil, K. (2021). Lowering the thermal noise barrier in functional brain mapping with magnetic resonance imaging. *Nature Communications*, *12*(1), 5181.

Wang, F., Zhang, H., Wu, Z., Hu, D., Zhou, Z., Girault, J. B., Wang, L., Lin, W., & Li, G. (2023). Fine-grained functional parcellation maps of the infant cerebral cortex. *eLife*, *12*. https://doi.org/10.7554/eLife.75401

Wansapura, J. P., Holland, S. K., Dunn, R. S., & Ball, W. S., Jr. (1999). NMR relaxation times in the human brain at 3.0 tesla. *Journal of Magnetic Resonance Imaging: JMRI*, *9*(4), 531–538.

Williams, L.-A., Gelman, N., Picot, P. A., Lee, D. S., Ewing, J. R., Han, V. K., & Thompson, R. T. (2005). Neonatal brain: regional variability of in vivo MR imaging relaxation rates at 3.0 T--initial experience. *Radiology*, *235*(2), 595–603.

Xydis, V., Astrakas, L., Zikou, A., Pantou, K., Andronikou, S., & Argyropoulou, M. I. (2006). Magnetization transfer ratio in the brain of preterm subjects: age-related changes during the first 2 years of life. *European Radiology*, *16*(1), 215–220.

Yeo, B. T. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165.