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Neurobiology, not artifacts: Challenges and guidelines for imaging the high risk infant

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ABSTRACT

The search for the brain-basis of atypical development in human infants is challenging because the process of imaging and the generation of the MR signal itself relies on assumptions that reflect biophysical properties of the brain tissue. These assumptions are not inviolate, have been questioned by recent empirical evidence from high risk infant-sibling studies, and to date remain largely underexamined at the between-group level. In particular, I consider recent work showing that infants at High vs. Low familial risk (HR vs. LR, respectively) for developing Autism Spectrum Disorders (ASD) have atypical patterns of head movements during an MR scan that are functionally important—they are linked to future learning trajectories in toddlerhood. Addressing head movement issues in neuroimaging analyses in *infant* research as well as understanding the causes of these movements from a developmental perspective requires acknowledging the complexity of this endeavor. For example, head movement signatures in infants can interact with experimental task conditions (such as listening to language compared to sleeping), autism risk, and age. How can new knowledge about newborns' individual, subject-specific behavioral differences which may impact MR signal acquisition and statistical inference ignite critical thinking for the field of infant brain imaging across the spectrum of typical and atypical development? Early behavioral differences between HR and LR infant cohorts that are often examples of "artifactual" confounds in MR work provide insight into nascent neurobiological differences, including biophysical tissue properties and hemodynamic response variability, in these and related populations at risk for atypical development. Are these neurobiological drivers of atypical development? This work identifies important knowledge gaps and suggests guidelines at the leading edge of baby imaging science to transform our understanding of atypical brain development in humans. The precise study of the neurobiological underpinnings of atypical development in humans calls for approaches including quantitative MRI (qMRI) pulse sequences, multi-modal imaging (including DTI, MRS, as well as MEG), and infant-specific HRF shapes when modeling BOLD signal.

1. Introduction

While the biological basis of Autism Spectrum Disorders (ASD) remains elusive (Lange, 2012), most researchers agree that extreme phenotypic heterogeneity is an intrinsic feature of individuals receiving diagnoses. It is surprising, then that potential neurobiologically driven individual differences are not evaluated or considered for their potential impact on Magnetic Resonance (MR) signal acquisition and statistical inference in imaging studies of infants at high familial risk (HR) for autism. This presents a fundamental challenge when obtaining an *in-vivo* and non-invasive estimate of brain structure and function in early life.

Neurobiology is the "branch of the life sciences that deals with the anatomy, physiology, and pathology of the nervous system" (https://www.merriam-webster.com/dictionary/neurobiology). Because neurobiologically driven differences could produce artifactual confounds as well as contribute towards "true" signals measured during a neuroimaging scan, distinguishing between "noise" and "signal" in Magnetic Resonance Imaging (MRI) research is challenging.

My thesis is that early behavioral differences between HR and low risk (LR) infant cohorts that are often examples of "artifactual" confounds in MRI work (such as head movements) actually provide insight into important nascent neurobiological differences in these populations and that these atypical neurobiological drivers constitute a cause for subsequent atypical development; thus, our collective aim as researchers is to

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discover an effective way to study these differences, either by adopting existing tools and neuroscientific methods, or by imagining new approaches. I focus on some challenges related to obtaining reliable functional and structural MR data in HR infants (HR status is defined by virtue of having an older sibling diagnosed with ASD) and highlight opportunities to rethink our current approach in those with atypical development as these challenges can offer us insights for the study of atypical neurobiology in infant cohorts. Acknowledging the role of potential neurobiological differences can inform analytic approaches in *in-vivo* imaging modalities in preverbal infants across the spectrum of risk for atypical development, including prematurely born infants.

2. Head movements

2.1. The problem

Head movements during an MRI scan present a challenge for imaging research, and this challenge is particularly multifaceted when considering imaging of infants at risk for atypical development. The challenge is both technical (e.g., head movements disturb homogeneity of the magnetic field and cause geometric distortions, affecting the quality of acquired functional and anatomical MRI data) as well as conceptual (e.g., head movements even in typical infants are not a trait; they interact with experimental conditions and autism risk; see below).

Movements during a functional MRI or resting-state functional MRI (fMRI and rs-fMRI, respectively) scan can contribute to "the geometric distortions and intensity of EPI data" (Speck et al., 2006) (EPI: Echo-Planar Imaging). To give an example relevant for the head movement issue, it is important to know that the slices that comprise a volume are acquired at slightly different times. If a participant moves while the k-space is being acquired, then some slices will be in a different degree of excitation, causing distortions in EPI data (http://imaging.mrc-cbu.cam.ac.uk/imaging/CommonArtefacts) (see Supplemental Figure 1 in (Denisova and Zhao, 2017) for an example from a 1-2 mo-old HR infant, showing geometry-related striping artifacts in the Blood Oxygenation-Level Dependent (BOLD) data, relative to a LR infant during a sleep rs-fMRI scan). That is, not only movements occurring between volume acquisitions (inter-volume) present a problem; those movements occurring while a volume is being acquired (i.e., intra-volume) are especially troublesome. Another example is related to shimming, a process whereby additional coils fine-tune the homogeneity of the main magnetic field precisely for each participant's head, in order to reduce signal variations due to inhomogeneities (the scans acquired during this procedure are referred to as "dummy" scans and are normally discarded). For data acquired without prospective motion correction (PMC), the shimming occurs at only one time, at the beginning of each run, but movements occurring throughout a given run will impact the field's homogeneity and affect signal quality of EPI data. For a review of the complex and interacting mechanisms that corrupt MRI data, see (Zaitsev et al., 2015) and (Zaitsev et al., 2017); I return to this point below, as well as in section 5.1.

2.2. Head movement issues specific to children and development

Recent work from several laboratories serves as the basis for the theory that important neurobiological differences exist between HR and LR infants, and can be detectable soon after birth. HR infants as young as 2 months present with atypical eye-looking at baseline (Jones and Klin, 2013). Further, we have recently shown in a sample of 56 infants that relative to LR infants, HR infants move more and in a different way during a resting-state sleep fMRI, showing higher noise-to-signal levels and reduced symmetry (Denisova and Zhao, 2017). Surprisingly, these characteristics of head movements have functional value, predicting future learning trajectories: HR infants with the "worst" or most noisy movements during sleep as 1-2 mo-olds had the flattest, least rapidly rising trajectory on their Mullen Early Learning Composite (ELC) scores.

More remarkably, we detected that LR, but not HR, infants' head movements significantly differed as a function of context (experimental condition). Specifically, 1-2 mo-old LR infants showed significantly noisier movements (increased noise-to-signal levels and a less symmetric (more exponential) shape of the distribution) while native language was presented to them, and more symmetric movements while sleeping, while 1-2 mo-old HR infants' head movements were more similar during the two conditions (Fig. 1). The finding of an interaction between autism status and task reveals sensitivity to evolutionarily important input in the LR cohort, and a relative lack thereof in the HR cohort. At least in early life, head movements can help infer the level of neurobiological atypicalities (here, suggestive of differences in higher-level cognitive functioning when comparing performance across the 2 conditions; see section 4.4).

Previous researchers have considered head movements during an MR scan as a representation of a neurobiologically meaningful signal (e.g., (Zeng et al., 2014)). However, addressing head movement issues in neuroimaging analyses in *infant* research as well as understanding the causes of these movements from a developmental perspective requires acknowledging the complexity of this endeavor. Our data suggest that in infants, head movements cannot be considered in a straightforward manner as a "trait" (the HR cohort does not always have "noisier" movements). That is because statistical features of head movements in very young 1-2 mo-old infants interact with the experimental condition (i.e., whether infants are sleeping or listening to native language). To emphasize, the LR cohort reveals greater sensitivity to context relative to the HR cohort, whose head movements were similar across both conditions (Fig. 1). Thus, at 1–2 months, LR infants seem to react differentially to distinct conditions (language vs. sleep) whereas HR infants do not.

The idea that head movements can provide insight about the developing human mind is, of course, not new. The head turning procedure (e.g., (Kemler Nelson et al., 1995)) (also: 'preferential looking' (Teller, 1979) in the visual perception domain, which "elicits differential behavior towards differential stimuli" (Atkinson and Braddick, 2013)) is a widely used paradigm in developmental cognitive science, used to infer competence in cognitive and perceptual abilities in non-verbal neonates and infants and used to reveal occasions for learning (Stahl and Feigenson, 2015) (Fig. 2; (Schulz, 2015)). In addition, in early life, spontaneous movements in particular during sleep, have a functional value for the neonate, and are thought to help newborns build sensorimotor maps of the extra-uterine environment (discussed in (Denisova and Zhao, 2017); (Blumberg et al., 2015)). These considerations reveal the complex role of head movements during development. Note that because standardization of MR protocols worldwide produces ample quantities of data acquired under similar and relatively well-controlled conditions, studying statistical features of estimates of head movements during a functional or resting-state MRI scan in diverse infant populations, in particular using already existing datasets, is scientifically informative, free, and accessible (Open Science Infant Research protocol; (Denisova and Zhao, 2017)).

Thus, there are at least two key issues, from a developmental perspective, regarding differences in head movements during an MRI scan. First, head movements corrupt raw data and affect the output of analytics and statistical inference. Second, head movements in infants are not random: they vary depending on the experimental task and autism risk. I discuss this latter issue and the potential ways to study neurobiological causes of atypical head movement signatures using quantitative MRI (qMRI) in section 4.4. I next focus on the technical aspects of mitigating movement and the main limitations of current approaches, which may induce what I refer to as the BOLD mosaic effect.

2.3. Current approaches to address head movement issues and main limitations of standard techniques

Volumes in functional and resting-state fMRI studies are acquired in rapid succession (e.g., every 2 s) using an Echo-Planar Imaging (EPI)

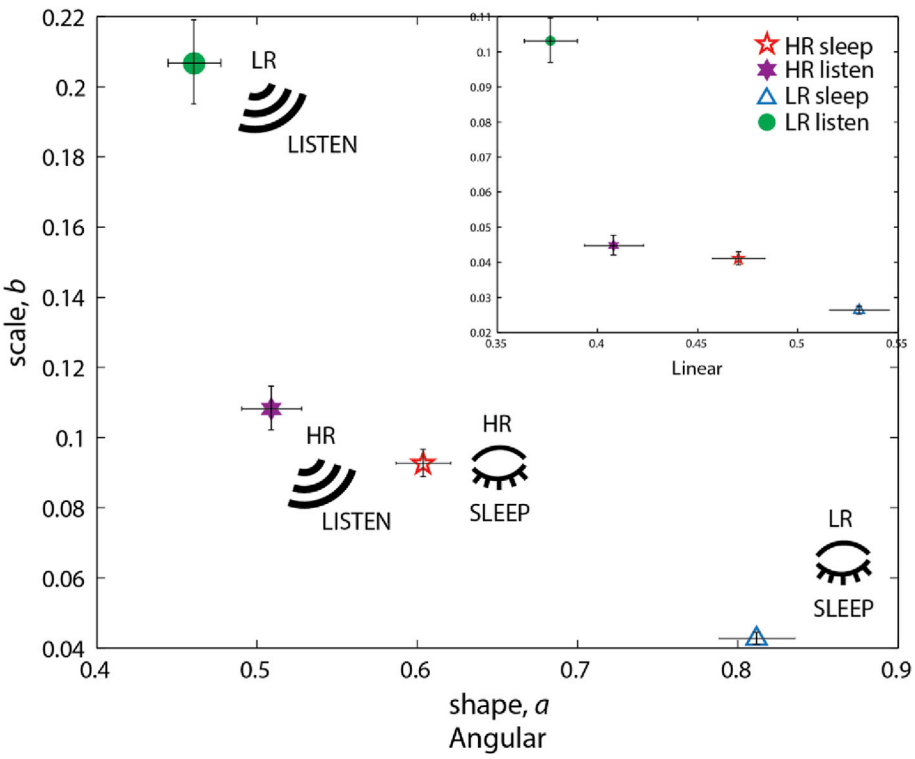


Fig. 1. Existence of autism risk- and task-sensitive head movement signatures during MRI scans from a study in which 1-2 month-old infants at high risk (HR) and low risk (LR) for developing Autism Spectrum Disorders (ASD) underwent 2 scans, a resting-state sleep fMRI scan and an fMRI scan during which infants heard native language (Denisova and Zhao, 2017). HR infants showed more noisy (higher *b* parameter, y-axis) and less symmetrical (lower *a* parameter, x-axis) movement signatures during sleep relative to 1-2 month-old LR infants. However, relative to the HR cohort, LR infants showed the noisiest, least symmetric signatures during wakefulness, when native language was presented to them. Note that HR infants' patterns to both conditions were more similar relative to data from LR infants. Shown are parameter estimates of angular speed (consistent pattern for linear speed; inset) on the Gamma parameter plane for each cohort and condition (sleep: $N = 28_{HR}$, $N = 28_{LR}$; native language listening: $N = 27_{HR}$, $N = 28_{LR}$). Error bars denote 95% CIs. The dissociation of these patterns as a function of risk status and task offers a clue about nascent neurobiological atypicalities that may underlie or contribute to atypical perceptual sensitivity to evolutionarily important inputs, which may precede atypical development (see text). The causes and sequelae of atypical neurobiology can be probed precisely using advanced conceptual frameworks and analytical approaches and tools including quantitative MRI. Figure adapted from Inflexible neurobiological signatures precede atypical development in infants at high risk for autism, Kristina Denisova and Guihu Zhao, Scientific Reports, Volume 7, Article number: 11285 (2017); https://doi.org/10.1038/s41598-017-09028-0.

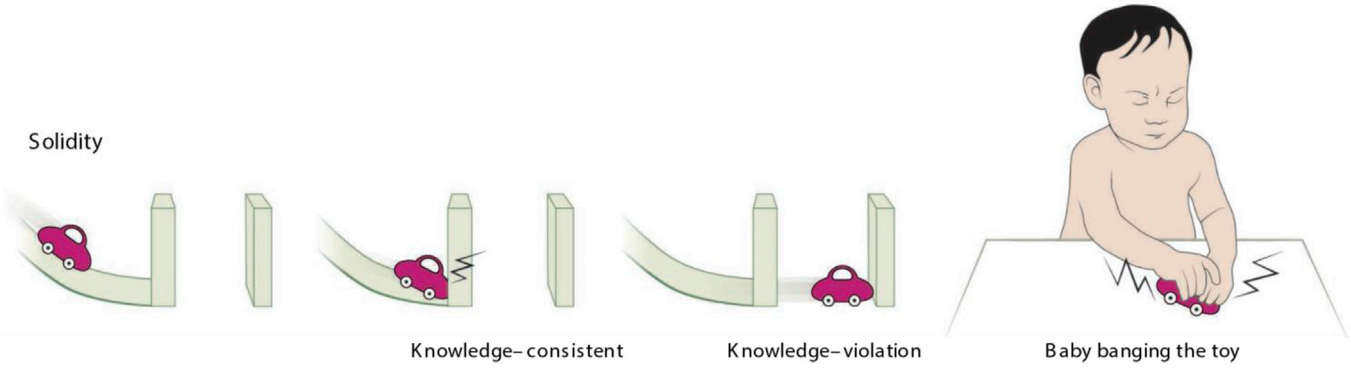


Fig. 2. Head movements (and/or eye movements) are used as an index of differential sensitivity, such as violation of an expectation in non-verbal neonates, infants, and toddlers. These indices can be used to infer infants' competence on a particular construct. This illustration shows that 11-month old infants seek to explore objects that violated their expectations with respect to how the object "should" behave and learned more about the object's other accompanying properties due to exploring the object that was inconsistent with prior knowledge. Infants expect a solid object to collide with a wall, and not to pass through it. When it appears to pass through the wall, infants seek to explore this unexpected behavior, an example of "knowledge-violation" (Stahl and Feigenson, 2015). The contribution of atypical, or atypically maturing, brain substrates (including hemodynamic response and tissue structure of brain matter) subserving normal development of cognitive concepts is not well understood in high risk infants, but can be studied using advanced imaging techniques. Figure from Infants explore the unexpected, Laura Schulz, Science 03 Apr 2015: Vol. 348, Issue 6230, pp. 42–43. Reprinted with permission from AAAS; https://doi.org/10.1126/science.aab0582.

pulse sequence sensitive to T2* BOLD contrast. Because the head may move between successive volume acquisitions, the EPI volumes are coregistered (Friston et al., 1995) to a reference volume (e.g., this is the 1st volume in SPM and middle volume in FSL). While the details of the process differ slightly depending on the software used to process the data, in general, the alignment step computes a rigid-body transform of the head's position for all time points during the scan, outputting a matrix with 6 columns (translations in x, y, z and rotations about the x, y, and z axes or pitch, roll, and yaw respectively) and a variable number of rows depending on the number of acquired volumes (scans). These realignment parameters are generated as a text file; movement time series data are probed in various ways, including simple plots for visualization and advanced computations and statistics on the data.

The role of in-scan movement in imaging analyses is a well-known and studied issue (Friston et al., 1995, 1996). The traditional approach to motion correction in fMRI involves regressing out the realignment

motion parameters obtained during volume registration procedure; doing so "discounts" their impact on the neuroimaging analyses (Friston et al., 1996). This is done by including 'nuisance' regressors in the overall model, that is, in addition to the main regressors of interest pertaining to the event- or block conditions relevant for the fMRI experiment. Thus, at a minimum, all six motion parameters are included as regressors of non-interest in the (general linear) model. Further, for example, expansion terms (Friston et al., 1996) are often included. These are quadratic terms of the original realignment parameters, as well as parameters describing position at a previous time point and the corresponding quadratic terms (Friston et al., 1996).

Recently, investigators from different groups (Power et al., 2012; Satterthwaite et al., 2013; Van Dijk et al., 2012) have probed the ways in which increased movements during the scan impact subsequent analyses and findings. For example, when participant groups differ in the amount of movement, this pattern affects connectivity metrics in rs-fMRI data and results can mimic high level effects of interest. Thus, researchers have proposed guidelines for the 'permitted' amount of movement (Power et al., 2012; Satterthwaite et al., 2013; Van Dijk et al., 2012). In particular, this includes a recommendation to exclude any volumes with movement exceeding 0.2 mm on the Framewise Displacement (FD) metric (Power et al., 2012) (cf. (Power et al., 2015)) (Siegel and colleagues noted 0.2 mm as "floor" in still subjects during an fMRI scan (Siegel et al., 2014)). After movement correction (e.g., (Power et al., 2012)) (approaches vary by investigator; this process could involve scrubbing or interpolating using adjacent volumes, or zeroing out corrupted timepoints), the volume time series are re-run, a process that once again generates realignment parameters that can be quantified.

A fundamental, underexamined issue that I focus on here in the context of infants and more generally with regard to child cohorts, is that corrected EPI time series data retains imprints of mechanisms that caused the data corruption in the first place. I postulate that these imprints differ between individuals and cohorts. There is reason to think that imprints remain since despite harnessing multi-echo EPI acquisitions and an independent component analyses (ICA) technique, recent work could not fully tease out non-BOLD 'noise' from BOLD-like 'signal' (Power et al., 2018). This is a problem because these EPI data are used as input into analytic approaches that actually exploit subtle individually-driven variations in these data (e.g., correlational analyses, or 'fingerprinting'/(dis) similarity metrics; e.g., (Finn et al., 2015)). Thus, caution is warranted as these procedures may lead to incorrect higher-level inference and interpretation. Subtle differences in connectivity metrics may also result if contiguous snips or segments from the original time series differ in length in one cohort relative to another cohort. One may wonder whether variations of this kind, in EPI time series data from infants at risk for atypical development, may actually stem from maturational or developmental differences in the sensorimotor system or from other causes, including atypical sensitivity to evolutionarily important input such as the human voice (see section 4).

While we did not have enough subjects remaining to conduct connectivity analyses of BOLD data (e.g., after removing volumes with excessive movements using objective criteria such as in (Denisova et al., 2016)), it is instructive to consider how subsequent brain-based statistical inference could be affected by intrinsic HR vs. LR differences in head movement signatures. For example, recent work by Emerson and colleagues (Emerson et al., 2017) has prospectively studied HR infants (N = 59) who underwent a resting-state fMRI scan collected during natural sleep at 6 months of age, and rigorous quality checks (QC) preceded seed-based connectivity analyses. The infants were grouped into 2 subgroups, those who developed ASD as 24 mo-olds (11 males, ASDpos) and those who did not (N = 48, ASDneg). Out of at least 2 runs with resting-state fMRI data, a fixed total number of uncensored volumes, 150, was used for analyses, but due to length limitations of each run (130 vol), subtle differences in the way the segments were combined may have differed in important ways between the 2 groups. That is, fewer segments containing original BOLD data could have been strung together from a single run for HR ASDpos relative to HR ASDneg infants, or contiguous segments could have been shorter for HR ASDpos group (vs. longer for HR ASDneg infants), thereby introducing heterogeneities in continuity of the BOLD time series in the stitched sequence.

As a result, the new BOLD time series representing the QC-passed volumes may have differed between HR ASDpos and HR ASDneg groups, and these heterogeneities could have affected BOLD time series extracted from each region-of-interest seed. While it is difficult to predict precisely whether greater or reduced connectivity would be expected overall across other infant-sibling samples, it is relatively straightforward to expect that heterogeneities in BOLD time series would manifest as a variety of atypical connections (i.e., increased between some pairs of seeds and reduced between others), which is exactly what the authors found (Emerson et al., 2017).

Regardless of whether the summary statistic of the amount of movement between two groups are similar, they could still differ with regard to sleep states (active or quiet sleep) for intermittent periods of time. That is, it is possible that HR ASDneg could have a similar amount of movements relative to the HR ASDpos group: some infants could actually be more awake (and show noisier movements than usual) or in REM (rapid eye movement) active sleep (and thus show more movements relative to segments of infants who are in a quiet, non-REM sleep). As we have argued previously, it is difficult to ascertain sleep states during an MR scan (Denisova and Zhao, 2017). In this sense, brain-based connectivity analyses performed with input data that have undergone subjective treatment would not reflect brain function *per se* but would instead represent an epiphenomenon of preprocessing. On the other hand, and arguably more informative at a fundamental level, what we are observing with these data may actually reflect important and underlying group differences in neurobiology.

2.4. Knowledge gaps and recommendations for future work

First, it should be noted that interpretational difficulty could arise if similar preprocessing steps are taken in other cohorts (e.g., in awake participants other than neonates and children) if between- and within-group differences exist. If data fragmentation processes produce a mosaic-like BOLD time series for one cohort, what is the contribution of this effect to the between-group differences on a given brain metric, and subsequent high-level interpretation? How such data preprocessing approaches affect statistical inference, interpretation and hypothesis testing in clinical imaging research with multiple cohorts, including children, is thus an open question. A related point is that given a fixed duration of BOLD runs (~5–6 min scan for infants and children), the current practice of using a fixed cut-off threshold (e.g., ranging from 75 to 80% of all volumes/frames) for the number of volumes remaining that do not require or undergo QC may also lead to the mosaic effect for some participants. This can occur because it is not possible to end up with long contiguous BOLD blocks from a participant who for instance, showed movement spikes throughout the scan.

Second, with regard to infant studies, a concerted effort is needed to collect information on sleep states (e.g., by video-recording the infant during the scan and then coding sleep states or by obtaining in-tandem heart-rate, respiration and/or electroencephalography (EEG) data). At a minimum, it would be helpful to have an independent measure of the infants' eye status during the scan: open or closed. If some infants present with more fragmented sleep patterns, then this strategy would lead to stitching of (BOLD time series) segments from runs that could nevertheless vary systematically in head movements. To help avoid a data fragmentation effect whereby cuts are made without regard to the physiological state of the infant, implementing matching on sleep state and equating both the length of the segment (number of volumes) and the number of segments, may help ensure that the segments are qualitatively and quantitatively similar between cohorts. That is, stitching blocks of BOLD time series that are similar in physiological state, and then comparing blocks across cohorts may help render subsequent inference

scientifically valid.

Third, researchers are advised to follow nuanced guidelines and to objectively limit between-group differences in head movements in infant cohorts. After frame censoring and "scrubbing" (Power et al., 2012), any between-group differences must be (1) non-significant (alpha = 0.05), (2) less than 0.004 mm when using a summary statistic approach (as suggested in Van Dijk et al., 2012), and, additionally (3) not differ on measures of variability when considering the entire time series (Denisova et al., 2016). The statistical character of time series can be computed readily in MATLAB using the "fitdist" function, as follows. Specifically, in addition to computing a summary statistic (i.e., a single value representing an average Root Mean Square (RMS), Framewise Displacement (FD), or speed) one can take the time series of FD, RMS, or speed values over the scan and fit a probability distribution function (e.g., Lognormal or Gamma) to obtain parameter estimates for each participant. Various variability estimates (e.g., variance or coefficient of variation) may also be computed. These estimates should not differ significantly (alpha = 0.05) between HR cohorts or related subgroupings (HR vs. LR cohorts) in order to exclude the possibility that non-linear signatures exist, as subtle movements may affect the integrity of BOLD modeling and subsequent statistical inference with such data. The lengths of contiguous BOLD segments should be similar when comparing cohorts (also see section 5.2 and section 7). Note that these guidelines are relevant for data acquired with single-echo EPI sequences (most fMRI and rs-fMRI studies) as well as with multi-echo EPI acquisitions.

Addressing head movement issues is very important as high field (7 T) scanners are becoming increasingly more common in research settings. Such increases in field strength bring about new sets of technical challenges, including an increased susceptibility to in-scan movement, furthering the importance of controlling for body movement (see (Zaitsev et al., 2017) and (Goense et al., 2010, 2016) for review). Distortions of the main magnetic field that are caused by movements of the body are much more pronounced at 7T compared to 3T, (where it has not been much of an issue), and these distortions can be difficult to correct. The effects of body movement (e.g., image distortion) in the absence of head motion on fMRI time series acquired at 7T, have been illustrated in investigations using awake monkeys (Goense et al., 2010, 2016). By the end of the 1st year, a human infant weighs on average 9–10 kg (kg) and thus, ranging between 7 and 15 kg for adults, the macaque may be a good model to draw comparisons relative to human infants. The increased interest in higher magnetic fields and higher spatial resolution is driving a renewed interest in motion correction, with the development of a number of new methods for (prospective) motion and distortion correction (Zaitsev et al., 2017) (for discussion of prospective motion correction (PMC) in the context of qMRI, see section 5.1). It is crucial that we address head and body movement issues in functional and resting-state fMRI studies as these problems are exacerbated at 7T.

Nevertheless, an important concern in the field is that head movements cause artifacts which cannot be fully "cleaned" from BOLD time series data (e.g., because of spin history) (Zaitsev et al., 2017). That is, QC and related strategies do not adequately eliminate bias between infant groups with different non-linear movement signatures. As such, one of the key priorities for grant-giving agencies must be devoted to the advancement of new technologies and techniques for imaging human infants, including optical prospective motion correction. Additionally, scanner manufacturers should support the development of, and should make available for routine use, 32 and/or 48 channel head coils sized for neonate, infant and toddler participants ((Keil et al., 2011); cf. (Deen et al., 2017)). With regard to obtaining in-tandem physiological data, appropriate physiological measures, including heat-rate, respiration, as well as video should be included together along with the imaging data when datasets are deposited as part of required data sharing agreements with the funding agencies. These steps will help make acquired data comparable across sites, make the interpretation of imaging data more transparent, and advance the discovery of neurobiologically-grounded bases of atypically developing brain function in humans.

3. Hemodynamics

3.1. The problem

The BOLD signal is an *inference* about brain function, reflecting metabolic demands of the brain and it is a proxy, an indirect measure of neural activity. The measured T2* signal reflects changes in the deoxyhemoglobin concentration in the blood and is affected by changes in cerebral blood flow, blood volume and tissue oxygen consumption (see illustration of human brain's neurovasculature in the coronal view, in Fig. 3). It is problematic from a BOLD modeling perspective, that neurovasculature is not well developed in a newborn brain (Kozberg and Hillman, 2016b), yet creative techniques have shown evidence for higher-level cognitive functioning even in fetuses and newborns. For example, fetuses prefer human face-like stimuli before birth (Reid et al., 2017) and in twin pregnancies, fetuses display proto-predictive capacities in movements towards their other twin (Castiello et al., 2010). Typically developing newborns are sensitive to evolutionarily important stimuli such as the human voice (DeCasper and Spence, 1986).

3.2. Hemodynamic response variability issues specific to children and development

While in human adults the BOLD response exhibits an overshoot due to an inflow of oxygenated blood following a stimulus, human infants often show an inverted or negative BOLD response due to increases in deoxygenated (paramagnetic) hemoglobin, as noted in (Kozberg et al., 2013). Studies with human infants using fMRI reveal individual differences in this pattern for subgroups of infants within the same study (Anderson et al., 2001), as well as developmental differences in terms of timing when a mature, adult-like positive BOLD response is detected (Arichi et al., 2012), and differences as a function of task condition (May et al., 2011) using functional near-infrared spectroscopy (fNIRS) (fNIRS is discussed in section 3.3.3).

Investigations of these patterns in rodents have shown that neural activity in newborns is sustained in a "unique metabolic environment" (Kozberg and Hillman, 2016b; Kozberg et al., 2016). In particular, Kozberg and colleagues found that as "neural events drive local oxygen depletion" (Kozberg et al., 2016), they do not trigger increases in oxygenated blood flow, as would be expected under adult-like neurovascular coupling. Further, Kozberg and colleagues found that systemic blood pressure confounds the shape of the hemodynamic response in newborns (Kozberg et al., 2013) (Fig. 4a). Overall, postnatally, neural activity appears to be sustained in an oxygen-impoverished environment, and an oxygen-impoverished environment may support blood vessel growth (Kozberg and Hillman, 2016b) during "activity-linked angiogenesis" (Kozberg et al., 2016): Kozberg and Hillman (2016)a,b note that "vascular growth appears optimized to regions of higher neural activity" (Kozberg and Hillman, 2016a). Thus, the development of neurovasculature follows behind and along with developing neural function, and eventually, supports neural activity with robust adult-like neurovascular coupling (Kozberg and Hillman, 2016a) (Fig. 4b). In addition, Kozberg and colleagues detected spatial differences in the maturation of 'adult' BOLD (i.e., hyperemia, which represents a "robust oversupply of oxygenated blood" (Kozberg et al., 2013)). In neonate mice, nascent hyperemia is confined to the capillary bed in the deeper layers of the cortex, "without recruiting pial arteries" as would be expected in adults (Kozberg et al., 2013). Hemodynamic response may also vary by brain region (Hillman, 2014; Iadecola, 2017).

The findings that the neurovasculature co-develops with neural function during normal development have implications for estimating and inferring functional brain development in young humans at risk for atypical development. Of note, this co-development occurs during critical or sensitive periods for the development of important functions including perceptual processing and language acquisition, capacities that become difficult to acquire if one is deprived of normal early experience. For

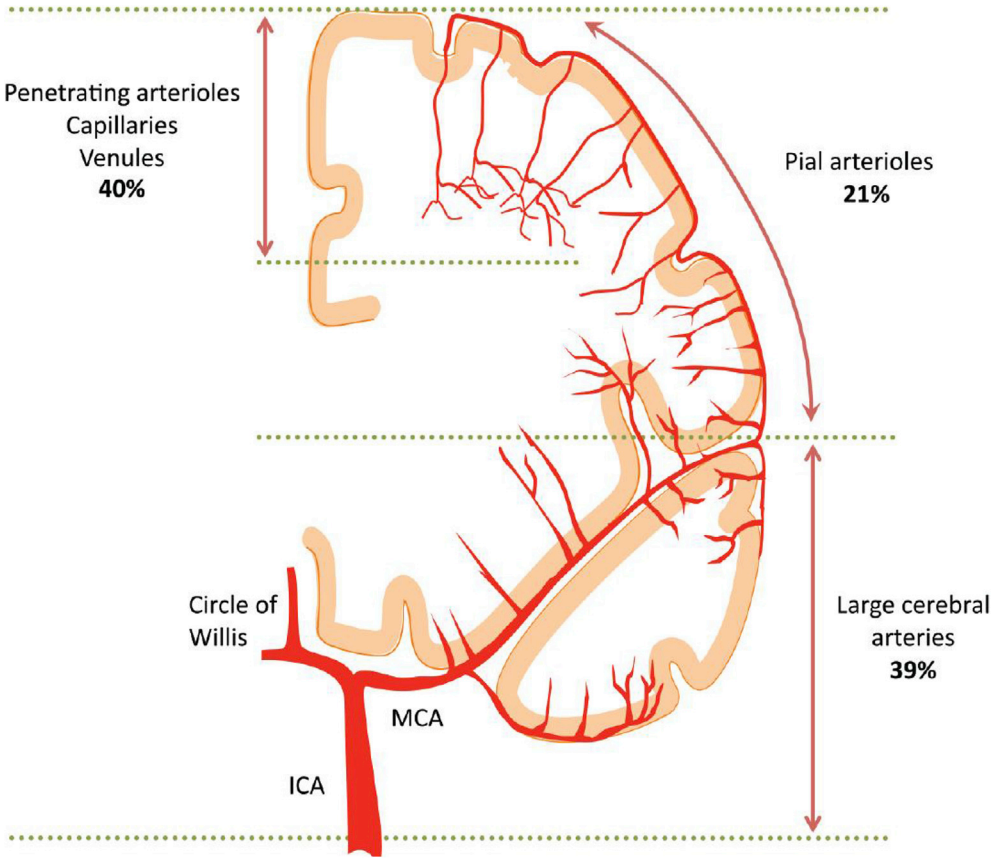


Fig. 3. Illustration of the anatomy of the vascular system of the cerebrum in the coronal view. The blood supply to the cortex arrives via the internal carotid artery (ICA) and continues via the middle cerebral artery (MCA), whose pial arteries and arterioles penetrate the surface of the cortex (see Iadecola, 2017 for additional details). Note: from Fig. 3, Iadecola, Neuron 96 (2017). Reprinted from Neuron, Vol. 96, Costantino Iadecola. The neurovascular unit coming of age: A journey through neurovascular coupling in health and disease, pp. 17-42, Copyright (2017), with permission from Elsevier; https://doi.org/10.1016/j.neuron.2017.07.030.

some infants at risk for atypical development, one may hypothesize the presence of a dysregulated mechanism involving atypical neural firing and accompanying atypical neurovascular development, and may involve dysregulation of blood pressure and blood flow as well as atypical development and function of astrocytes and pericytes that support neurovascular coupling (Kozberg and Hillman, 2016a).

3.3. Current approaches for modeling brain function and main limitations of standard techniques

Because these variations in development are not well understood but may have consequences for interpreting fMRI and resting-state fMRI data, researchers should carefully consider the choice of BOLD models in high risk and related developmental cohorts.

3.3.1. Functional MRI (fMRI)

A canonical hemodynamic response function (HRF) refers to a model with specific assumptions about the shape of a hemodynamic response. The shape is a linear combination of two gamma functions (one, to model the latency of the peak, and another, to model the undershoot), that is, a double gamma function. The HRF shape is then convolved with an event (involving the presentation of a stimulus to participants, to which neural activation is assumed to have occurred) to estimate the underlying hemodynamic response to the stimulus, representing a gradual rise after stimulus onset, and followed by a fall. As noted by Lindquist et al. (2009), the double gamma HRF is generally appropriate when the population under study involves adults and when the main interest is to estimate the magnitude of activation (Lindquist et al., 2009). However, it may not accommodate certain aspects of variability in the shape.

Note that including the temporal derivative and/or dispersion derivative, as well as modeling time on task (Grinband et al., 2008) in experiments that record response latency (relevant for older children), are reasonable approaches that allow flexibility in modeling the hemodynamic response and have been recently used in fMRI studies involving atypically developing children (Denisova et al., 2016). The many additional approaches to model hemodynamic responses are reviewed in (Lindquist et al., 2009) and details pertaining to group-level comparisons are in (Steffener et al., 2010). In particular, it is important to consider performing permutation testing when data may not meet normality assumptions, such as using FSL's 'randomise' (Winkler et al., 2014) which can also be used as a standalone tool when main analyses are conducted using other software, such as SPM; cf. (Denisova et al., 2016).

However, researchers investigating brain function in atypical infant cohorts may consider using an infant-specific or infant-sensitive HRF (Arichi et al., 2012). For example, FLOBS (FMRIB's linear optimal basis sets) (cf. (Arichi et al., 2012)) implemented in FSL makes few prior assumptions about the underlying shape of the HRF, specifically, with regard to potential variability, including in the dispersion of the HRF shape, or its onset. To ensure that FLOBS' HRFs are physiologically plausible and to avoid overfitting, Woolrich et al. (2004) utilize "soft constraints to weight the subspace spanned by the basis set to only include sensible HRF shapes within a linear time-invariant system" (Woolrich et al., 2004). To model data using FLOBS, researchers choose a flexible basis set (e.g., 3 basis functions with default parameters) which is then convolved with the stimuli presented during an experiment. For example, modeling data using a general linear model (GLM), Arichi and colleagues used an "optimal" basis set comprised of three functions with "pre-specified parameters" which accommodates differences in the range in the delay and height of the HRF (Arichi et al., 2012) (see Fig. 5a).

For additional details on incorporating variability into a modeled HRF shape when the underlying hemodynamics are uncertain, see (Lindquist et al., 2009). Future work is needed to develop a more complete understanding of the most appropriate HRF model for different high risk cohorts, such as between prematurely born infants and infants at risk for ASD relative to infants born at term. For example, a double gamma

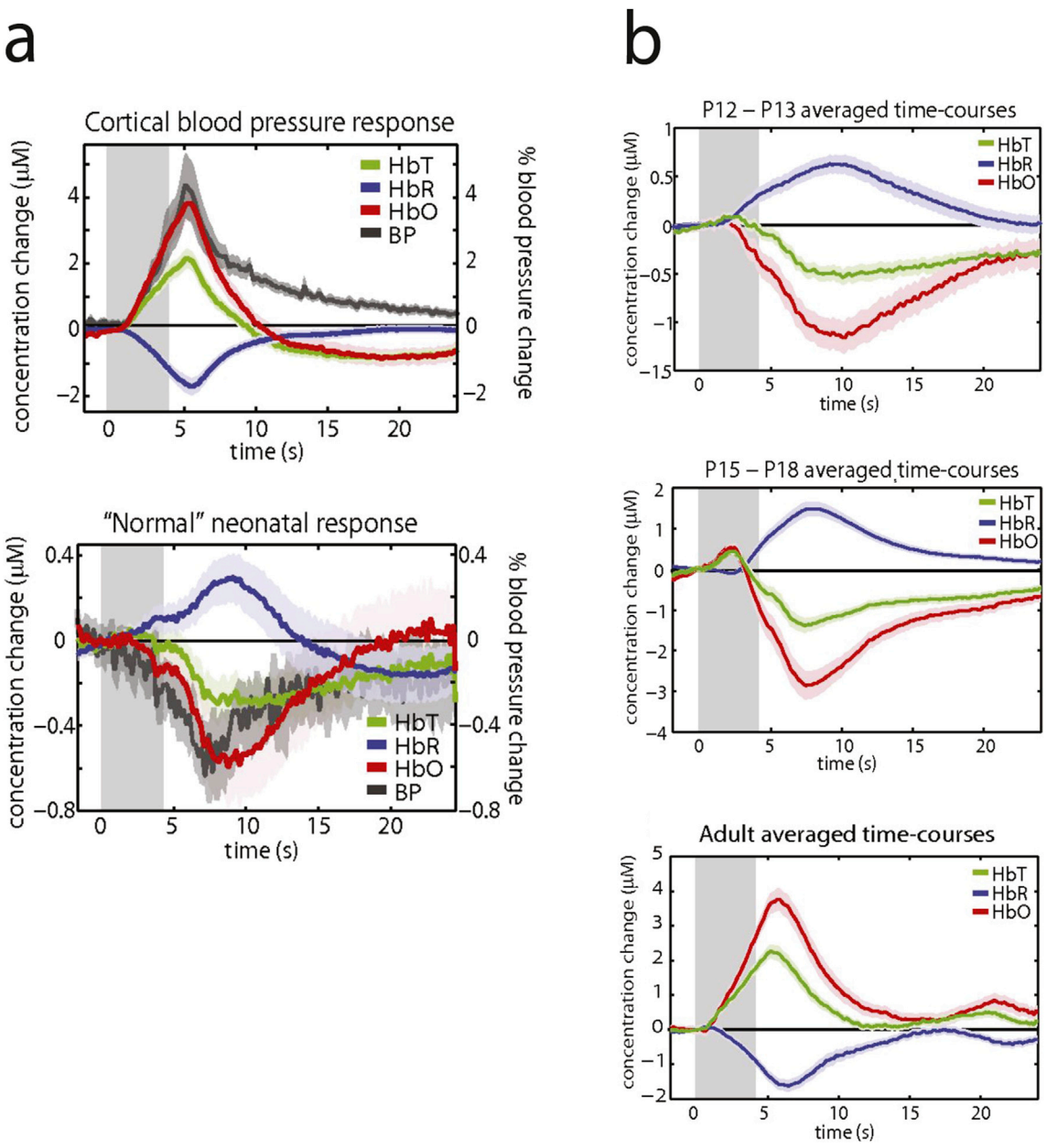
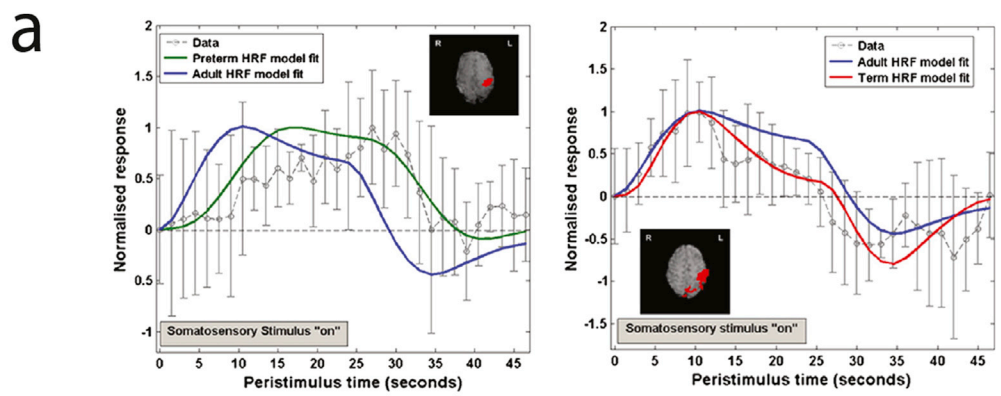


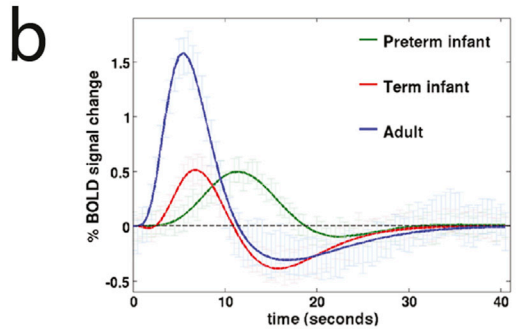
Fig. 4. The hemodynamic response is complex and is affected by multiple variables including blood pressure and maturation status. **(a)** The existence of different hemodynamic response profiles in newborn rats when blood pressure was simultaneously recorded with an optical imaging technique in behaving rats (ages: postnatal, P12-P13). When blood pressure increases were observed (upper panel), the responses were more adult-like (see (**b**), last panel), but when no blood pressure increases were observed (lower panel), the responses were as would be expected for a neonate, an increase in deoxygenated hemoglobin. **(b)** The hemodynamic responses shown for 3 age groups of rats: neonatal (P12-13), "intermediate" (P15-18), and adult, showing a gradual emergence of the 'adult-like' hemodynamic response. For additional details, see text. HbT: total hemoglobin; HbR: deoxygenated hemoglobin; HbO: oxygenated hemoglobin; BP: blood pressure. Note: **(a)** is from Fig. 1C and 1D and **(b)** is from Fig. 2A, B, 2C from Kozberg et al. (2013). Reused with permission from Resolving the transition from negative to positive blood oxygen level-dependent responses in the developing brain, Mariel G. Kozberg, Brenda R. Chen, Sarah E. DeLeo, Matthew B. Bouchard, and Elizabeth M. C. Hillman, PNAS, Vol. 110 (2013), pp. 4380-4385; https://doi.org/10.1073/pnas.1212785110.

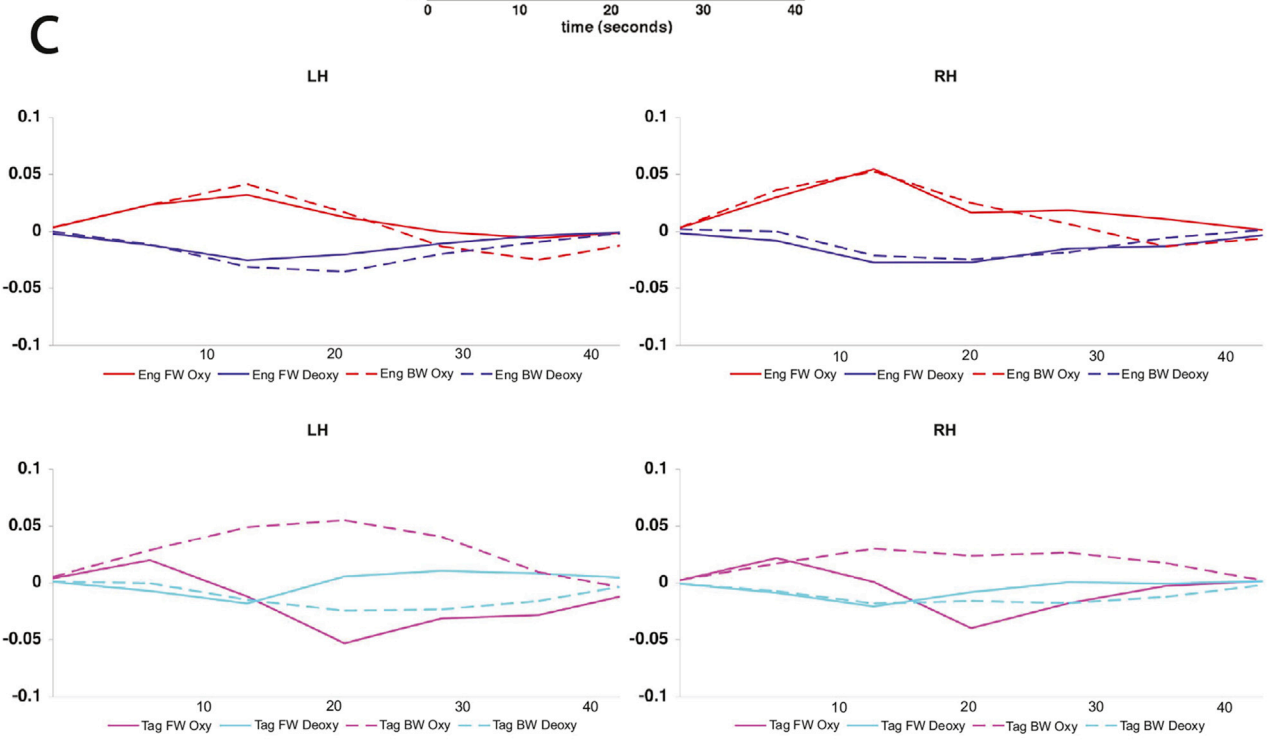
HRF has been used when fitting such data and visualizing trends (see Fig. 5b), and permutation techniques can be used to test statistical significance between cohorts when using cohort-specific HRFs. The study and characterization of the hemodynamic response and its parameters in human infants at risk for atypical development and understanding how this response evolves with age, under different experimental tasks and for different brain areas and systems is an important, underexplored area that requires future research.

3.3.2. *Resting-state functional MRI (rs-fMRI)*

Addressing hemodynamic variability in resting-state fMRI studies is a distinct and challenging issue compared to fMRI, and is underexamined in atypical development in humans. Importantly, an EPI pulse sequence sensitive to T2* is used to acquire both functional as well as resting-state fMRI data. A fundamental difference concerns the step that selects which waveforms are used for input for subsequent inference analyses, and whether or not the HRF is explicitly modeled. Unlike fMRI scans (infants may be engaged in a 'task': viewing visual stimuli, listening to auditory stimuli, or being presented with somatosensory stimulation; the experiment can be implemented using an event-related or block design) for which the hemodynamic response to stimuli is explicitly modeled, resting-state fMRI studies do not explicitly model hemodynamic







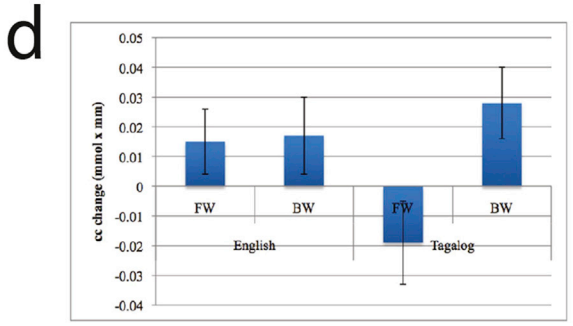


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Fig. 5. The nature of the hemodynamic response in human neonates differs relative to the hemodynamic response in adults and can also vary as a function of a specific task (and/or condition). **(a)** The left panel shows fMRI BOLD data from a somatosensory task from a prematurely born infant, fitted with either an individualized hemodynamic response function (HRF) or a 'canonical', adult HRF (the double gamma HRF). The right panel shows data from an infant at term corrected post-menstrual age, fitted with either an individualized HRF or a canonical HRF model. In both cases, individualized or infant-specific models provide a closer fit relative to the adult model (Arichi et al., 2012). **(b)** Average (group) data from preterm neonates, term neonates, and adults fitted with the same canonical model, the double gamma HRF (Arichi et al., 2012). Note: **(a)** is from Fig. 5 and **(b)** is from Fig. 2d, reused from Development of BOLD signal hemodynamic responses in the human brain, Tomoki Arichi, Gianlorenzo Fagiolo, Marta Varela, Alejandro Melendez-Calderon, Alessandro Alievi, Nazakat Merchant, Nora Tusor, Serena J. Counsell, Etienne Burdet, Christian F. Beckmann, and A. David Edwards, NeuroImage, Vol. 63, pp. 663-673 (2012); https://doi.org/10.1016/j.neuroimage.2012.06.054. **(c)** fNIRS oxy- and deoxyhemoglobin group average data from a language task presented to newborns, who heard either forward (FW) or backward (BW) filtered (retaining lower frequencies) speech in native (English) or non-native (Tagolog) language (y-axes show oxy- and deoxyhemoglobin concentration changes and x-axes indicate time in seconds; the left panel shows data for the left hemisphere (LH) and the right panel shows data for the right hemisphere (RH)). **(d)** shows the same data as in **(c),** plotted as a function of change in oxyhemoglobin concentration, revealing that neonates were differentially sensitive to non-native vs. native language, in particular to forward Tagolog relative to the other 3 conditions (May et al., 2011). Note: **(c)** is from Fig. 5 and **(d)** is from Fig. 7, reused from Language and the newborn brain: Does prenatal language experience shape the neonate neural response to speech? Lillian May, Krista Byers-Heinlein, Judit Gervain, and Janet F. Werker, Frontiers in Psychology, Vol. 2, 222 (2011); https://doi.org/10.3389/fpsyg.2011.00222.

response. Specifically, data are processed as "rs-fMRI" when the scan involves no obvious task, such as when an infant is sleeping, while awake but not doing a specific task, or when older individuals and children are asked to lie still inside the scanner with their eyes open or closed.

Traditionally, rs-fMRI BOLD data are temporally filtered to retain slow frequencies (recommendations on whether to use a range or a band-pass filter (e.g., 0.009–0.08 Hz; (Power et al., 2011); or 0.01–0.1 Hz; (Satterthwaite et al., 2013)) or cutoffs (e.g., high-pass filtering only: (Smith et al., 2013)) vary across investigators), creating new time series before subsequent analyses, including functional connectivity analyses and statistical inference on these data. These recommendations have been derived largely from studies with typically developing adults. For example, in a study by Cordes et al. (2001), which included a total of $N = 4$ adult subjects between 20 and 25 years old and used a relatively high sampling rate (TR) of 400 ms (2.5 Hz, which gives Nyquist frequency of 1.25 Hz), the researchers recommended a cutoff of 0.1 Hz, as frequencies lower than this value contributed to 90% of the correlation coefficient (Cordes et al., 2001). However, none of the assumptions underlying the choice of the appropriate bandwidth or a frequency cutoff have been examined from a neurodevelopmental perspective, neither for typically developing human infants nor for those at risk for atypical development.

With regard to the upper bound, the highest frequencies that could be identified in principle are not fixed, but depend on the actual sampling rate during the scan; the Nyquist frequency is half that value. While the TR (the effective sampling rate) has conventionally been around 2 s, s (or 2.5 or 1.5 s), for newer pulse sequences and hardware this value can be less than 1 s (e.g., multiband imaging; ~0.7 s in the Human Connectome Project). Thus, at $TR = 2$ s, the highest frequency that could be identified would be around 0.25 Hz (1/TR/2) while for $TR = 0.7$ s, this value is around 0.71 Hz. These considerations reflect the maximum based on the physical limitations of the equipment.

On the other hand, lower frequency waveforms may overlap with those from certain physiological processes that continue maturing in young humans, and that could be particularly notable in atypical development. What is the developmentally-rooted basis for selecting a specific low frequency range, and does it appropriately serve as a proxy for the underlying, nascent neural activity in the developing human brain? We need deliberate, carefully designed studies with children participants to probe and establish a reasonable range of frequencies to retain for sleeping rs-fMRI and, separately, for awake rs-fMRI scans.

In particular, in addition to investigating simultaneous neural and hemodynamic response underlying stimulus-evoked events in mice, Kozberg and colleagues studied spontaneous neural activity and the corresponding hemodynamics during a 'condition' in which no stimuli were presented. The authors found that in the youngest mice studied (approximately corresponding to a premature infant: mice of postnatal age P7-P8), spontaneous neural events "occur infrequently", and that hemodynamic fluctuations are global but are not coupled to the "local neural activity" (Kozberg et al., 2016). Kozberg et al., 2016 found "a lack of local hemodynamic coupling during spontaneous activity in the youngest age groups" relative to adult mice (Kozberg et al., 2016). These findings have implications for our understanding of the significance of the waveforms detected with rs-fMRI in young humans. In human adults, the waveforms representing heart-rate and respiration (~0.15–0.40 Hz) normally fall outside the range of frequencies retained for connectivity analyses performed with rs-fMRI data (~0.01–0.08 Hz). (As the heart rate is even faster in infants and children compared to adults, those frequencies *per se* would normally be filtered out when using the current standard for the highest cutoff, 0.08 Hz). However, additional processes of interest ascribed to lower frequencies considered in rs-fMRI analyses warrant investigation in infants.

The frequencies within the 0.04–0.15 Hz range in measures of heart-rate variability reflect the baroreflex by which baroreceptors regulate blood pressure (Shaffer and Ginsberg, 2017). This mechanism "includes transmission of nerve impulses from the baroreceptors to the medulla in response to a change in blood pressure and that produces vasodilation and a decrease in heart rate when blood pressure increases and vasoconstriction and an increase in heart rate when blood pressure decreases" (https://www.merriam-webster.com/medical/baroreflex). Given that studies in newborn mice, as compared to adults, (e.g., (Kozberg et al., 2013)) indicate atypical relationship between blood pressure, hemodynamics, and neural activity, and studies in human infants indicate ongoing maturation of the baroreflex (e.g., (Andriessen et al., 2005; Witcombe et al., 2012; Yiallourou et al., 2010)), the role of baroreflex waveforms' contribution to the range of frequencies typically considered in rs-fMRI functional connectivity studies in infants should be investigated. One prediction is that a substantive portion of variability in BOLD fluctuations during rest in atypically developing neonates and infants may be due to a variable function of the baroreflex, and not to the metabolic processes accompanying neural activation *per se*, fundamentally changing our interpretation of BOLD fluctuations in infants.

It may be helpful to investigate the nature of signal variability in rs-fMRI data in response to physiological changes by explicitly modeling some of these events or pseudo-events when available (such as sleep vs. awake states during a session, heart rate variability (periods), but also head movements, etc.). For example, Satterwaite and colleagues used a Finite Impulse Response (FIR) to model head movement spikes during a scan and found a reduction in BOLD signal, in particular in the volume immediately following the instance of heightened movement (Satterthwaite et al., 2013). In infants, rather than FIR or a canonical HRF, an individual basis set such as FLOBS that allows for variability in the HRF properties can be used in order to gain both an understanding as to the role (or interaction) of non-neural variables during the scan as well as to gain a sense of variability of BOLD signal over the scan. Additional approaches that estimate hemodynamic response in rs-fMRI (e.g., (Wu et al., 2015)) deserve attention in infants.

It is beyond the scope of the current work to address intensely debated aspects of rs-fMRI time series processing, such as global signal regression or subtraction, denoising approaches (such as ones leveraging

multi-echo EPI acquisitions and ICA (Kundu et al., 2013; Power et al., 2018)), and important concerns about the order of the processing steps that are performed on the time series (Carp, 2013). However, it should be noted that a major new research direction, from a developmental perspective in humans, is the focus on gaining a neurobiologically-grounded understanding of which features most closely represent neural signal in functional neuroimaging data, including rs-fMRI scans.

3.3.3. Functional near infrared spectroscopy (fNIRS)

Relevant for our discussion on infant hemodynamics is a different *in-vivo* technique to study brain function in infants, the functional Near-Infrared Spectroscopy (fNIRS) (Aslin et al., 2015; Gervain et al., 2011). Near-infrared spectroscopy (NIRS) "takes advantage of the different optical absorption spectra of oxygenated hemoglobin (HbO) and HbR (deoxygenated hemoglobin) to measure relative changes in each across the cortex using different wavelengths of near-infrared light" (Kozberg and Hillman, 2016a).

Because fNIRS isolates the two contributions (HbO and HbR) comprising the hemodynamic response, this technique permits a more nuanced approach to the variability and evolution of the hemodynamic response in early life in humans. For example, we may be able to study the transition from less to more mature hemodynamic response in infants from HR and LR cohorts and the conditions under which different responses may occur (May et al., 2011) (Fig. 5c and Fig. 5d) as well as to probe the hemoglobin phase of oxygenation and deoxygenation (Watanabe et al., 2017). The fNIRS technique is also well suited for use at bedside, a very important consideration when studying vulnerable infants, in particular, those born prematurely who are cared for in a neonatal intensive care unit (NICU).

However, the light from the NIRS system does not penetrate deeper structures of the brain and this precludes the study of functional links of significant interest between the cerebral cortex and important subcortical structures that participate in learning processes, including the basal ganglia and hippocampus. Additionally, this limitation precludes the possibility of using NIRS to study regional and task-driven variation in hemodynamics. As infants' skull thickness increases with age, this further affects the depth of the penetration of the signal obtained with fNIRS (Gervain et al., 2011). Obtaining recordings from other modalities including electroencephalography (EEG), an electrophysiological technique that non-invasively measures electrical activity near the surface of the cortex, along with (or subsequently with) fNIRS can provide additional information about evolution of the hemodynamic response in high risk infant populations. For example, Mahmoudzadeh and colleagues used both fNIRS and EEG to reveal atypical neurovascular coupling, relative to the neural response itself, in prematurely born infants to speech syllables (Mahmoudzadeh et al., 2018).

3.4. Knowledge gaps and recommendations for future work

In fMRI event-related or block designs it is recommended to use an individualized BOLD model (e.g., FLOBS) that considers variability in the HRF. Investigations are needed to model HRFs in different populations and as a function of a specific task and condition, as well as for different brain regions and systems. For rs-fMRI designs, we need studies that probe the nature and appropriate bandwidth of the frequencies comprising "signal" when studying BOLD fluctuations in infants at rest or during sleep. Our knowledge base on this subject is sparse.

In the future, with regard to dissecting sources of BOLD signal within a voxel, high-resolution human infant scanning at higher fields (7T) may increase our understanding about contributions from different "compartments" such as veins, arteries, and capillaries and the associated differences in metabolism, in combination with using pulse sequences that are sensitive to these different compartments (e.g., Cerebral Volume Flow (CVF) or Cerebral Blood Flow (CBF) sequences (Goense et al., 2016)).

An additional consideration is the use of inotropic medication in some vulnerable (e.g., premature) infant populations. Inotropic drugs help manage circulatory function but may affect the nascent neurovascular system (Cox and Groves, 2012), thereby potentially affecting the BOLD signal (i.e., an effect that would be unrelated to the underlying neural activity). Whether or not participants have been administered these medications in early life should be noted in research studies if this information is available.

In order to obviate limitations of a specific functional technique, studies in infants may consider combining different functional techniques when studying the developing brain function (also see section 4.4 on multi-modal imaging). For example, magnetoencephalography (MEG) is a magnetic imaging technique that uses superconducting quantum interference devices (SQUIDS) to amplify electrical currents in the brain and can detect signal from deeper tissues, unlike fNIRS and EEG (for review, see (Baillet, 2017)).

In summary, methodological choices in functional imaging need to be rooted in knowledge of the special and transient nature of the neurobiology characterizing early life in humans. Importantly, the properties of the hemodynamic response may depend on the nature of the question and the brain system under study, in particular in neonates. As an example, because the auditory system is relatively more developed at birth relative to the visual system, in neonates fMRI can be used to study hemodynamic response properties accompanying language acquisition and language development, whereas fNIRS may more readily detect subtle nuances of (and thereby deviations from) normal visual system development near birth. Empirical research motivated by these important, outstanding questions is needed to produce the underlying assumptions required for high risk infant research fMRI and rs-fMRI studies in human infants, as well as functional brain imaging using other techniques.

4. Tissue structure

4.1. The problem

I briefly note that even in the context of "normative" or representative development (see Fig. 6 (Kang et al., 2011; Silbereis et al., 2016) and Fig. 7 (Kang et al., 2011)), investigators working at different levels of analysis have reported substantial individual variation and region-specific heterogeneity in brain maturation (e.g., (Kinney et al., 1988; Leroy et al., 2011), cf. (Dehaene-Lambertz and Spelke, 2015)). In the course of typical development, brain regions and structures differ with respect to both the onset as well as the rate of myelination (the sheathing or covering of axons with fatty tissue that facilitates the speed of neural conduction). Histological studies indicate that myelination proceeds non-linearly, for example, with the cerebellum showing microscopic myelin at birth (Kinney et al., 1988), while *in-vivo* neuroimaging work has revealed that some areas of the pre-frontal cortex show earlier maturation of white matter relative to the temporal cortex (Leroy et al., 2011), and a complex developmental profile for key brain metabolites (Bluml et al., 2013). Distinct and complex gene expression trajectories for different brain regions and structures over the human life span have also been reported, in particular for the neocortex, hippocampus, and the cerebellum (Kang et al., 2011).

4.2. Maturational issues specific to children and development

If brain maturation in HR infants is delayed (or differs) in a region-specific manner, then some tissues in a HR infant of the same age relative to a LR infant may still have higher water (vs. lipid) content. Of note, because the MR signal is sensitive to lipid vs. water content in a given tissue (and more myelinated areas have higher lipid content), different brain regions and structures are expected to have different relaxation times following the application of an RF (radio frequency) pulse, yielding transverse magnetization (T2), a decay of which is measured at TE (echo

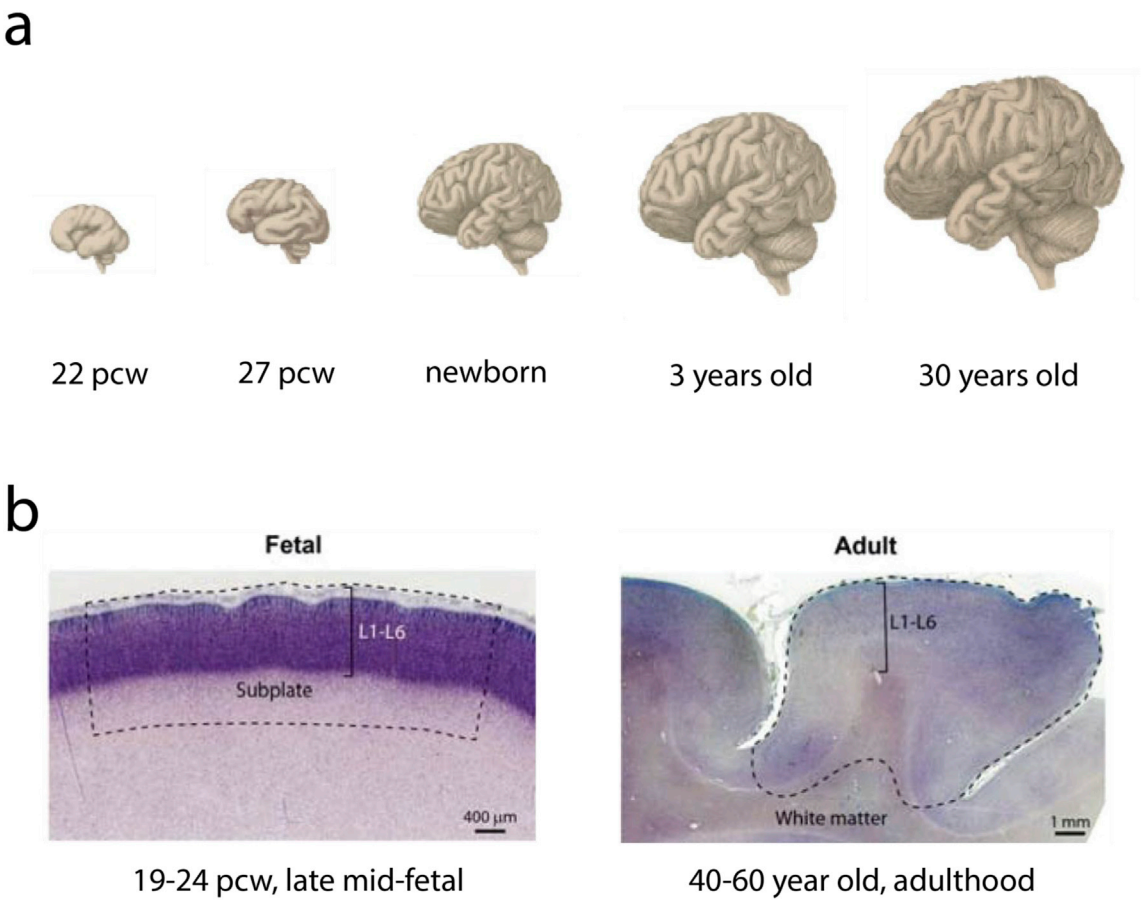

Fig. 6. Illustration of differences in brain anatomy as a function of maturation in humans. **(a)** represents the brain across different ages: ~22 postconceptional weeks (pcw), ~ 27 pcw, around birth, for a 3 year old toddler, and for a 30 year old adult (Silbereis et al., 2016). Note: adapted with permission from Fig. 1 in Silbereis et al., 2016. Reprinted from Neuron, Vol. 89, John C. Silbereis, Sirisha Pochareddy, Ying Zhu, Mingfeng Li, and Nenad Sestan, The cellular and molecular landscapes of the developing human central nervous system, pp. 248-268, Copyright (2016), with permission from Elsevier; https://doi.org/10.1016/j.neuron.2015.12.008. **(b)** histological sample of neocortical tissue from a fetal brain (from a 'late mid-fetal' period, between 19 and 24 pcw) and from an adult brain (from 'middle adulthood' period, between 40 and 60 years old) (Kang et al., 2011). Note: from supplementary Fig. 3b and Fig. 3c, used with permission, from Kang et al., Nature, Vol. 478 (2011). Reprinted by permission from Springer Nature: Nature, Spatio-temporal transcriptome of the human brain, Hyo Jung Kang, Yuka Imamura Kawasawa, Feng Cheng, Ying Zhu, Xuming Xu, Mingfeng Li, Andre M. M. Sousa, Mihovil Pletikos, Kyle A. Meyer, Goran Sedmak, Tobias Guennel, Yurae Shin, Matthew B. Johnson, Zeljka Krsnik, Simone Mayer, Sofia Fertuzinhos, Sheila Umlauf, Steven N. Lisgo, Alexander Vortmeyer, Daniel R. Weinberger, Shrikant Mane, Thomas M. Hyde, Anita Huttner, Mark Reimers, Joel E. Kleinman and Nenad Sestan, Copyright (2011); https://doi.org/10.1038/nature10523.

time) and varies for different tissues (Smith and Lange, 1998). The longitudinal magnetization recovers according to T1 relaxation properties of the different tissues. Because newborns' tissues contain a greater proportion of water overall and there is insufficient contrast between tissues in a T1-weighted image, a T2-weighted pulse sequence (which uses long TR (repetition time) to eliminate T1 contrast, and long TE to develop T2 contrast; (Smith and Lange, 1998)) is used early in life while a T1-weighted sequence is used towards the end of 1st year as water content decreases in both gray and white matter (e.g., (Dubois et al., 2014; Paus et al., 2001)).

Various biological factors and their interactions with risk status and sex are also pertinent for infant brain imaging work. As an example, Hazlett and colleagues' recent report (Hazlett et al., 2017) indicates that the finding of higher total brain volume (TBV) in HR infants who received an ASD diagnosis as toddlers (HR ASD pos) relative to HR ASDneg and LR ASDneg infants failed to reach significance when male-only infants were considered. The idea that HR ASDpos female infants' brain features could be distinct in the early stages of development is supported by another report from the same group on increased extra-axial cerebrospinal fluid (CSF) (Shen et al., 2017) in HR ASDpos infants. It is worthwhile noting that this finding again significantly interacted with risk status and sex, such that the main effect was driven by 2 HR ASDpos female infants who had significantly increased CSF relative to HR ASDpos males.

4.3. *Current approaches to estimate brain maturation and main limitations of standard techniques*

Our lack of knowledge about the patterns of maturation in high risk infants suggests the need for the study of the appropriate biophysical tissue values when imaging this heterogeneous population. Although one aim of MR work is to examine exactly the question of how brain development differs as a function of ASD risk, the current practice of applying qualitative, contrast-weighted pulse sequences and acquisition methods in infants across levels of risk may not be appropriate. Unlike growth charts or other standards of normative maturation and development for which numerical values and ranges have been measured, we actually do not have norms of biophysical brain properties (e.g., T1 and T2 tissue relaxation values) for young humans. If one is interested in obtaining MR signal for a specific structure or region where tissue properties may be expected to differ between HR and LR infants (e.g., the cerebellum or the pre-frontal cortex), then it may be helpful to evaluate T1 and T2 relaxation times directly.

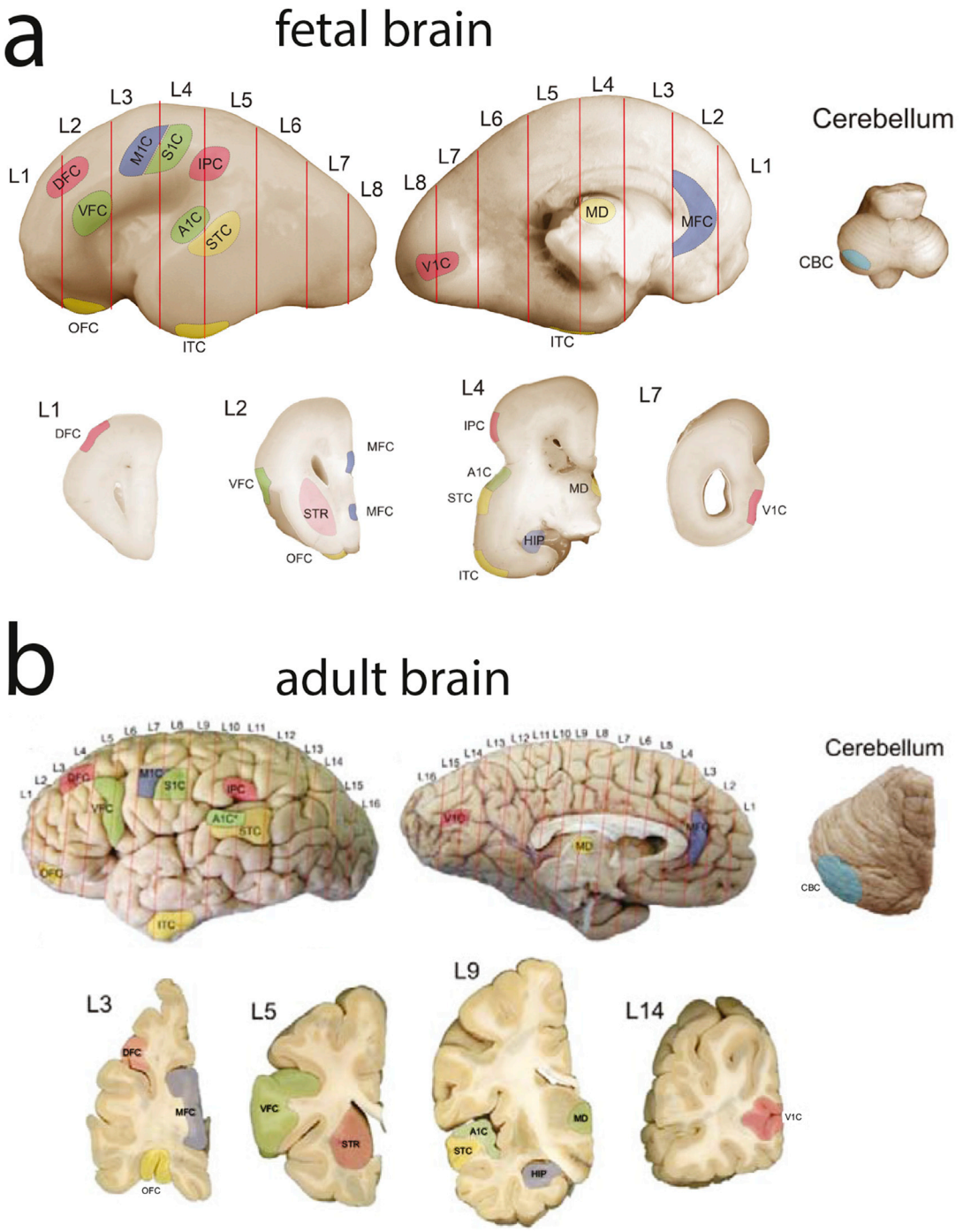

Fig. 7. Distinct fetal and adult gross brain anatomy. **(a)** shows a fetal brain from a lateral and medial view of the left hemisphere and corresponding coronal slices (from a 'late mid-fetal' period, between 19 and 24 postconceptional weeks (pcw)), as well as the whole cerebellum and **(b)** shows an adult brain from a lateral and medial view of the left hemisphere and the corresponding coronal slices. The left cerebellum in the dorsal view is shown. The fetal brain is from a stage prior to the folding of the cortical mantle, i.e., the formation of sulci (indentations in the cortical mantle) and gyri (convex protrusions), in stark contrast to the adult brain specimen, but gyrification would be visible at later fetal stages. Additional coronal slices for both brains are presented in Kang et al. (2011). The names of the regions from Kang et al. (2011) indicate areas used for transcriptional analyses in that study, and here are provided for reference. The following are the abbreviations shown in selected slices for **(a)** and **(b)** and include the regions from the frontal lobe cortex: DFC (dorsolateral prefrontal cortex), OFC (orbital prefrontal cortex), VFC (ventrolateral prefrontal cortex) and MFC (medial prefrontal cortex), from the parietal lobe cortex: IPC (inferior parietal cortex), from the temporal lobe cortex: A1C (primary auditory cortex) and STC (superior temporal cortex), from the occipital lobe cortex: V1C (primary visual cortex), from the subcortical structures: MD (mediodorsal nucleus of the thalamus), STR (striatum), and HIP (hippocampus) as well as from the cerebellum: CBC (cerebellar cortex). Note: (**a**) is adapted from supplementary Fig. 2a, 2b, and 2c and (**b**) is adapted from supplementary Fig. 1a, 1b, and 1c, with permission, from Kang et al., Nature, Vol. 478 (2011). Reprinted by permission from Springer Nature: Nature, Spatio-temporal transcriptome of the human brain, Hyo Jung Kang, Yuka Imamura Kawasawa, Feng Cheng, Ying Zhu, Xuming Xu, Mingfeng Li, Andre M. M. Sousa, Mihovil Pletikos, Kyle A. Meyer, Goran Sedmak, Tobias Guennel, Yurae Shin, Matthew B. Johnson, Zeljka Krsnik, Simone Mayer, Sofia Fertuzinhos, Sheila Umlauf, Steven N. Lisgo, Alexander Vortmeyer, Daniel R. Weinberger, Shrikant Mane, Thomas M. Hyde, Anita Huttner, Mark Reimers, Joel E. Kleinman and Nenad Sestan, Copyright (2011); https://doi.org/10.1038/nature10523.

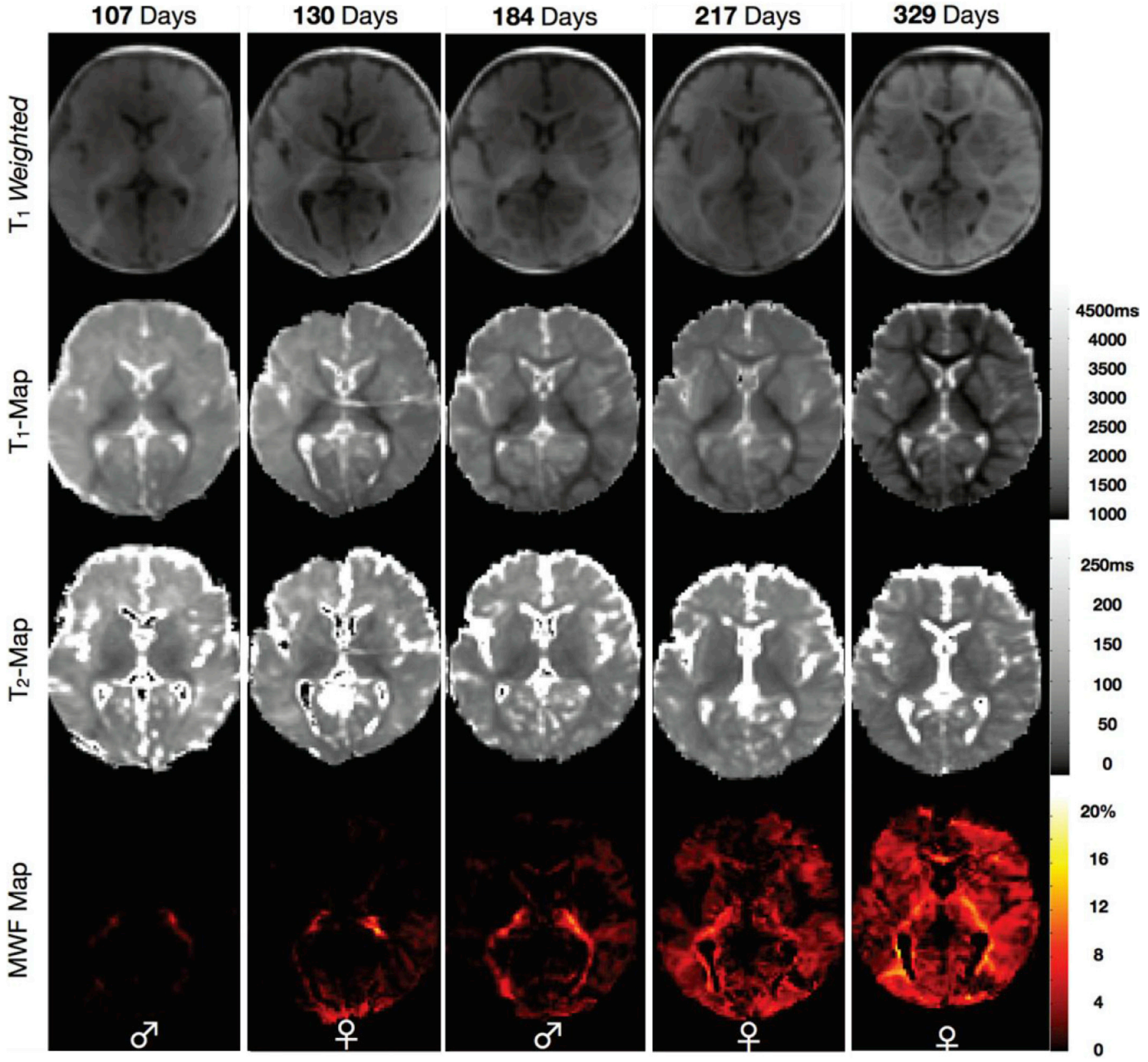

Fig. 8. Regional and maturational heterogeneity in tissue structure or composition detected with different anatomical MRI acquisitions in typically developing infants during the 1st year of life. Shown are selected images (axial view) using different pulse sequences from typically developing infants (ages in days): 107 (male), 130 (female), 184 (male), 217 (female), and 329 (female) (Deoni et al., 2011). Note that the tissue contrast between gray and white matter is relatively weak for the T1-weighted acquisition (row 1) compared to quantitative approaches (rows 2 and 3: T1-Map and T2-Map, respectively), and compared to an approach that maps myelin establishment, shown in the last row ("MWF": myelin water fraction). Note: modified with permission from Fig. 2, from Deoni et al. (2011). Republished with permission of Society of Neuroscience, from Mapping Infant Brain Myelination with Magnetic Resonance Imaging, Sean C. L. Deoni, Evelyne Mercure, Anna Blasi, David Gasston, Alex Thomson, Mark Johnson, Steven C. R. Williams, and Declan G. M. Murphy, The journal of neuroscience: the official journal of the Society for Neuroscience, Vol. 31 (2): 784–791, 2011; permission conveyed through Copyright Clearance Center, Inc.; https://doi.org/10.1523/JNEUROSCI.2106-10.2011.

4.4. *Knowledge gaps and recommendations for future work*

In particular, qMRI (relaxometry), multi-modal imaging (that is, acquiring several MRI and other modalities per session, per participant, including modalities such as Diffusion Tensor Imaging), and approaches such as Macromolecular Tissue Volume (MTV) that can contribute to probing "the macromolecular composition" within a voxel (Mezer et al., 2013), can advance our understanding of atypical brain maturation in at-risk cohorts. For a review of relaxometry approaches and pulse sequences pertinent for clinical imaging, including myelin mapping, see (Deoni, 2010). Several examples of different MR acquisitions for typically developing infants from (Deoni et al., 2011) are shown in Fig. 8; see Mezer et al., 2013 for a different approach and discussion of MTV (Mezer et al., 2013) (see section 5.1 for additional discussion).

Additional MR methods provide distinct and complementary information, including MR Spectroscopy (MRS) (most commonly used to detect hydrogen nucleus (^{1}H) spins, although it can also be used to detect, among others, phosphorus spins), which can inform our understanding

about potential differences in metabolic maturation (e.g., (Bluml et al., 2013)) across different brain structures and regions in at-risk infants. Overall, these acquisitions may help accelerate the study of the maturational process effectively in its own right and accommodate the substantial diversity in infants' brain substrates as a function of risk status, age, and sex.

I suggest that the atypical attunement to different contexts in HR (vs. LR) 1-2 mo-old infants may point to potential atypical neurobiological differences that underlie or contribute to emergent atypical cognition and perception including social competence, social affect, and perceptual sensitivity to evolutionarily important stimuli such as the human voice. One hypothesis is that atypical perceptual sensitivity to important cues in early life may cause problems in many domains that rely on this mechanism, including visual perception and language acquisition. To give an example from the auditory domain, Mueller and colleagues measured mismatch negativity (MMN) patterns to pitch and linguistic rule discrimination in typically developing 3 mo-old infants, and found that "only infants who showed the more mature mismatch response for the pitch deviants (i.e., a negativity) showed a mismatch response to the rule deviants" (Mueller et al., 2012). That is, the ability to detect rule-based dependencies is "related to the polarity of the observed MMRs in response to pitch discrimination and, thus, on the maturational status of auditory perception" (Mueller et al., 2012). Seen in this light, do 1-2 mo-old HR infants show similar head movements during two distinct contexts due to innately atypical or atypically maturing brain substrates?

Using qMRI, for example, one can obtain information about biophysical tissue properties (e.g., T1 relaxation values) of structures and regions thought to underlie the development of social competence, relative to circuitries underlying sensorimotor functioning. For example, it is possible to probe regions underlying the vocal learning circuitry (which subserves both perception and production of speech, and requires normal socialization). Additionally, researchers may probe the integrity of substrates subserving the concepts of numerosity, symbolic processing, face perception, as well as memory. The main point is that quantitative information on tissue properties of the brain in early life can provide unique information about the developing mind (distinct from, and in addition to, computational modeling and cognitive science approaches). This additional and unique information could help us rigorously adjudicate between competing hypotheses for causality and eventually reformulate outstanding questions in the field of atypical development in humans.

5. Interactions between movement, hemodynamics, and tissue structure

To recapitulate, the raw data obtained during image acquisition are corrupted by movement; the issue is complex from a developmental perspective. Once EPI volumes are properly aligned to a reference volume using standard approaches, investigators mitigate the impact of in-scan movement by including motion realignment parameters as regressors of non-interest in the model and use strategies to scrub and interpolate over (or zero out) periods of high movement during the scan. Yet, our data show that movements in the HR cohort are not isolated as spikes during the scan; for instance, HR infants at both age groups (1–2 and 9–10 months) have consistently noisier and more variable signatures during the rs-fMRI sleep scan (Denisova and Zhao, 2017). Further, the signatures do not have the same statistical features—they are not the same—during different tasks, such as when listening to native language vs. when sleeping (Fig. 1). One consequence of including corrupted or movement-imprinted data, or data comprised of differently-sized contiguous segments in subsequent processing and analyses steps is that data obtained during increased movements could reduce BOLD activation in task fMRI and, in rs-fMRI, could increase variability and yield spurious connectivity differences (or 'fingerprinting' differences when (dis)similarity metrics are used) between infant cohorts or as a function of age in rs-fMRI.

These observations present a conceptual problem for post-processing (retrospective) motion correction techniques, including ones that acquire EPI data with multiple echos and apply an ICA technique to separate BOLD and non-BOLD contributions (e.g., (Kundu et al., 2013; Power et al., 2018)). Additionally, there are implications for MR work when investigating atypically maturing hemodynamic response as well as atypically maturing brain tissue in infants at risk for atypical development. Next, I consider how a deeper understanding of several potential interactions between atypical movement, hemodynamic response, and tissue maturation can drive discovery in baby imaging science and transform our conception of atypical development of the central nervous system in human infants.

5.1. Head movements may affect even quantitative relaxometry measurements

Atypical head movement signatures in neonates, infants, toddlers, and older children will impact the quality not only of functional MRI and rs-fMRI data but also of anatomical MRI—both contrast-weighted and quantitative MRI anatomical (structural) acquisitions. In general, head movements present a problem with varying degrees of severity for all imaging, near-infrared spectroscopy, and electrophysiological techniques. If undetected or uncorrected, problematic contributions of movements in raw data will propagate to the subsequent analytical steps where these contributions may bias computational anatomy (e.g., estimates of cortical thickness derived from structural MR may be reduced in cohorts that move more) or correlational metrics in children cohorts with different movement signatures.

Acquiring a single high-resolution anatomical volume requires a longer time due to a larger k-space (e.g., in contrast to relatively rapidly acquired (e.g., every 2 s) single volumes of low-resolution EPI BOLD, which comprise the 4D time series in fMRI and rs-fMRI studies). Further, quantitative anatomical MRI approaches require acquiring more than one volume, and then combining data from multiple acquisitions to obtain estimates of interest (e.g., changing a parameter depending on the specific goal and a given technique, such as the flip angle when acquiring image sets to create quantitative T1 maps). When using variable flip angle mapping strategies, one approach to correct field inhomogeneities is via an additional set of image acquisitions (e.g., (Mezer et al., 2013)). Assuring quality across two independently acquired (inter-scan) volumes is particularly important, as also is quality of acquisitions obtained in multi-site studies (Weiskopf et al., 2013). In the case of anatomical qMRI, movements during a scan can lead to poorer (increased) coefficient of variation (CoV), affecting the "consistency" of quantitative maps (Callaghan et al., 2015) and causing "spatial variability in obtained estimates of R2*" (Castella et al., 2018).

Investigators have noted that retrospective motion correction, which refers to correction offline after the volume has been acquired (see also section 2), cannot correct distortions due to spin history; in addition, such methods also require substantial computational effort (Callaghan et al., 2015). In contrast, methods for prospective motion correction (PMC) utilize adaptive correction techniques on-line, and have already been validated or are under active development (for fMRI and anatomical, including quantitative MRI acquisitions) with typically developing participants (Speck et al., 2006; Zaitsev et al., 2015, 2017). For example, Callaghan and colleagues apply a PMC technique utilizing optical trackers which update the "imaging gradients, radiofrequency, and phase" and report improvements in the CoV of relative to a condition which did not use PMC (Callaghan et al., 2015).

With regard to acquiring high-quality qMRI in particular, and other MRI scans in general, we need developmental studies to test how the impact of atypical movement in at-risk cohorts can be mitigated using the PMC technique. As an interim solution, and as is currently done in many laboratories depending on time availability, it would be important to collect several scans of the same type per participant, with the hope of acquiring one or more high-quality volumes.

5.2. Head movement during a stimulus presentation may influence the ability to characterize the HRF

One concern is that occurrence of head movements while a stimulus is being presented to participants during an fMRI scan, or time-locked to a specific aspect of physiology or environment in the case of an rs-fMRI scan, may interact with the underlying hemodynamic response and thus influence our ability to characterize the hemodynamic response under these conditions. An advantage of fMRI paradigms over rs-fMRI is that the onset of the task stimulus is known and thus can serve as the onset for modeling the hemodynamic response. The fact that the onset of the stimulus is known provides for a straightforward way to model BOLD with an eye towards utilizing low-movement data segments or blocks in data analysis (see (Deen et al., 2017) for an example). In work involving comparisons between children cohorts it would be important to make sure that the length of the segments (or blocks) and contiguity of the original time series are comparable across cohorts. In contrast, no information about what drives BOLD signal is available in principle for rs-fMRI, as such designs, by definition, preclude the participant from participating in a task. The selection of waveforms to represent "signal" in such designs in human infants remains an open empirical question (see section 2 for how to model known events during an rs-fMRI scan).

To obtain enough low motion EPI data with which hemodynamic response can be interrogated, one strategy is to collect more data. This approach is counterintuitive, as the reason for the short duration of fMRI and rs-fMRI scans collected with children participants (~5–6 min) is that children usually do not tolerate scans of long duration. However, if the family is flexible and the scanner is available, then focusing on collecting more runs, that are not fixed in length but are instead guided by infant's comfort level, is recommended. For example, Deen and colleagues studied visual perception in awake infants using fMRI, collected a total of ~23 h of data (N = 17) and were able to use ~17% (~4 h from N = 9) (Deen et al., 2017). It may be recommended to extend the duration of resting-state sleep fMRI scans (instead of terminating each run around 5–6 min and collecting additional runs, each of which requires re-shimming), and to take a similarly flexible approach with task-based fMRI acquisitions, that is, if longer scans are comfortable for the child and the family.

5.3. Alterations in structural maturation may affect how we normalize fMRI activation

An important consideration is how to appropriately align task-evoked fMRI data (which has low spatial resolution) in order to evaluate where in the brain the activation occurs and to compare it to other children in the same cohort, or across cohorts; this procedure is referred to as 'function to structure' registration and normalization. One specific concern in this regard is that maturational differences in neural tissue in infants from different cohorts may influence how we should normalize fMRI activation data. Generally, the process of spatial normalization involves normalizing functional images to a participant's anatomical image and/or an appropriate template. A study-specific template can be made using an average of high-resolution anatomical scans (e.g., T1-weighted) of all children participants in the study. Alternatives include utilizing a population-based template developed in an infant-specific atlas (e.g., (Shi et al., 2011)), and then proceeding to an atlas-based segmentation of data into different tissue classes (as well as brain structures, for reference). Here it may be noted that individualized maps based on activation collected in a separate task in a given modality may not be realistic to be implemented in infants (e.g., similar to retinotopic mapping in visual neuroscience when studying visual perception, but note that the plausibility of this approach may differ for different modalities such as audition, as well as a function of age). Typically, functional analyses proceed on a voxel-wise basis.

Currently, it may be challenging to map task activation to a specific region or area with great precision.

One approach may be to simply approximate the spatial location of the activation, as can be done for fNIRS (e.g., Emberson and colleagues used head measurements as a guide to select appropriate T1-weighted MRI image as a template to which to align their study's fNIRS data (Emberson et al., 2015)), fMRI BOLD (~6 mo-olds; (Deen et al., 2017)), and for EEG (as well as for MEG).

As individual differences in tissue structure (age- or cohort-wise) are revealed (see Fig. 8) and trends are replicated across studies using different quantitative MRI methods, such findings will need to be incorporated into infant-specific pipelines. One implication is that we may need to consider a distribution of quantitative priors even within a given class of tissue, such as the white matter. That is, instead of ignoring individual differences we will need to incorporate them into the tissue models. If this is not done, one consequence could be attributing BOLD activation to white matter and masking it out in a participant with atypically developing gray and white matter tissue.

A less obvious, but exciting implication of this situation is the need to develop new manually-derived tissue dictionaries that would inform automatic segmentation algorithms. Performance of automatic algorithms is normally compared to a "gold standard" of manual segmentation, but these segmentations have been based on T1-and T2-weighted acquisitions. We do not, as of yet, have publicly available, manually segmented datasets from quantitative T1 and T2 maps. Such q-maps from multiple datasets worldwide would provide unbiased estimates of subtle variations of tissue maturation as a function of age and specific brain systems and transform MR research with children at risk for atypical development.

Emerging knowledge about atypical maturation of subcortical areas (for example, the hippocampus and basal ganglia) could also inform our modeling of the corresponding hemodynamic response in those regions. That is, there could be subtle differences in hemodynamic response in infant at-risk cohorts with atypical qMRI measures. The hemodynamic response could interact with differences in tissue maturation, for example, as a function of differences in T2 relaxation values.

6. Neurobiology guides the study of atypical development in humans

Nothing in human cognition makes sense except in the light of neurobiology (a riff on (Dobzhansky, 1973)). The deepest problem as of now is harnessing MR technology to drive the discovery of neurobiological underpinnings of atypical development. This goal is relevant as ASD is currently diagnosed using observational and qualitative assessments and not earlier than 2 years of age. Researchers are interested in understanding brain development in infants at high familial risk for developing ASD as well as in infants who show behavioral markers that precede atypical development. Researchers are also interested in understanding brain development in infants at high familial risk for Attention Deficit/Hyperactivity Disorder (ADHD) and/or in prematurely born infants, as well as the impact of pre-natal and genetically-driven variables (e.g., increased paternal age).

Emerging evidence, including data from our laboratory, suggests that some young humans, as young as 1–2 months after birth, show atypical behavioral sensitivity to important aspects in the environment. Given that our brain normally asserts representational constraints over which aspects of underdetermined and unstructured sensory data are given priority in processing, this evidence for atypical information processing so early in life provides clues for the targeted study of the underlying neural substrates that may cause these atypicalities and, for some children, precede atypical developmental trajectory. How human brain development occurs in the presence of atypically maturing neurobiological tissues and processes must be the leading question to shape future imaging work in infants at risk for atypical development.

What unique information can be recovered by MRI to help us understand the nature of potentially atypically developing properties of the brain in some young humans? Quantitative information would be

powerful because it would provide precision about the properties of the nascent mechanisms that may be atypical in the high risk neonate. Additionally, models of brain function that are infant- and individual-specific can more effectively reveal the underlying principles of the developing mind. In turn, this knowledge could contribute towards a mechanistic understanding of the different types of atypical development in humans and may help inform and formulate new criteria for diagnoses.

7. Conclusions

These considerations inform several pathways to advance our knowledge of atypical development in young humans using MRI, as follows.

(i) Adopt nuanced guidelines for fMRI and rs-fMRI data preprocessing for infant and children cohorts. Ensure that cohorts are similar not only with regard to summary statistic metrics, with between-group differences below 0.004 mm, but also that cohorts are similar on non-linear patterns (quantify the statistical character of head movements as a time series). Do not assume that HR and LR infants are imaged during the same physiological state; obtain in-tandem physiological measures as well as video feeds during scans. Eliminate or reduce the fragmentation effect (i.e., the BOLD mosaic effect) by using similar-length blocks collected during similar physiological states across participants. All else being equal, a participant whose final rs-fMRI time series comprises fewer (but lengthier) contiguous BOLD blocks from the original time series may not be comparable to a participant with more numerous (but shorter) contiguous BOLD blocks.

(ii) Use infant-specific HRF (e.g., FLOBS) when modeling BOLD fMRI. Obtain information on whether inotropic drugs have been administered, which may help minimize variability associated with underdeveloped neurovascular coupling and improve the interpretation of data.

(iii) Consider qMRI (relaxometry) instead of contrast-weighted, qualitative pulse sequences as well as multi-modal imaging to increase precision about biophysical tissue properties in at-risk infants.

The nervous system of newborns from an *at-risk* infant cohort is likely to differ in many subtle ways relative to the nervous system of infants in a *low-risk* cohort. A quantitative approach can provide biophysical specificity about nascent atypicalities in the brain development in these infants. The specificity is particularly crucial as it could help test competing hypotheses and accelerate the development of novel diagnostic classification of atypical development in humans, illuminated by the light of neurobiology.

Conflicts of interest

I have no competing interests, including any financial interests, activities, relationships and affiliations that could have influenced decisions or work on this manuscript.

Authors' contributions

KD wrote paper.

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