NeuroImage 273 (2023) 120057

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Review

Not with a "zap" but with a "beep": Measuring the origins of perinatal experience

Joel Frohlich[a,*], Tim Bayne[b,k], Julia S. Crone[c,d], Alessandra DallaVecchia[c], Asger Kirkeby-Hinrup[e,f], Pedro A.M. Mediano[g,h], Julia Moser[i,j], Karolina Talar[a], Alireza Gharabaghi[a,†], Hubert Preissl[i,†]

[a] Institute for Neuromodulation and Neurotechnology, University Hospital and University of Tübingen, Germany
[b] School of Philosophical, Historical and International Studies, Monash University, Melbourne, Victoria, Australia
[c] Department of Psychology, Pritzker Hall, University of California Los Angeles, Los Angeles, CA, USA
[d] Vienna Cognitive Science Hub, University of Vienna, Vienna, Austria
[e] Department of Philosophy and Cognitive Science, Lund University, Sweden
[f] Cognitive Neuroscience Research Unit, Center for functionally Integrative Neuroscience, Aarhus University, Denmark
[g] Department of Computing, Imperial College London, London, UK
[h] Department of Psychology, University of Cambridge, Cambridge, UK
[i] IDM/fMEG Center of the Helmholtz Center Munich at the University of Tübingen, Division of Diabetology, Endocrinology and Nephrology, Department of Internal Medicine, German Center for Diabetes Research (DZD), Tübingen, Germany
[j] Masonic Institute for the Developing Brain, University of Minnesota, Minneapolis, MN, USA
[k] Program on Brain, Mind, and Consciousness, Canadian Institute for Advanced Research (CIFAR), Toronto, Ontario, Canada

ARTICLE INFO

Keywords:
Infant
Fetus
Perinatal
Consciousness
Perturbational complexity
MEG

ABSTRACT

When does the mind begin? Infant psychology is mysterious in part because we cannot remember our first months of life, nor can we directly communicate with infants. Even more speculative is the possibility of mental life prior to birth. The question of when consciousness, or subjective experience, begins in human development thus remains incompletely answered, though boundaries can be set using current knowledge from developmental neurobiology and recent investigations of the perinatal brain. Here, we offer our perspective on how the development of a sensory perturbational complexity index (sPCI) based on auditory ("beep-and-zip"), visual ("flash-and-zip"), or even olfactory ("sniff-and-zip") cortical perturbations in place of electromagnetic perturbations ("zap-and-zip") might be used to address this question. First, we discuss recent studies of perinatal cognition and consciousness using techniques such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and, in particular, magnetoencephalography (MEG). While newborn infants are the archetypal subjects for studying early human development, researchers may also benefit from fetal studies, as the womb is, in many respects, a more controlled environment than the cradle. The earliest possible timepoint when subjective experience might begin is likely the establishment of thalamocortical connectivity at 26 weeks gestation, as the thalamocortical system is necessary for consciousness according to most theoretical frameworks. To infer at what age and in which behavioral states consciousness might emerge following the initiation of thalamocortical pathways, we advocate for the development of the sPCI and similar techniques, based on EEG, MEG, and fMRI, to estimate the perinatal brain's state of consciousness.

1. Introduction

Research into the level or state of human consciousness often focuses on fields with strong medical applications and/or unmet needs, such as disorders of consciousness (Bourdillon et al., 2020; Chennu et al., 2014; Engemann et al., 2018; Jean-Remi King et al., 2013; Lutkenhoff et al., 2020; Monti et al., 2010; Sitt et al., 2014) and anesthesia monitoring (Colombo et al., 2019; Sarasso et al., 2015). Nonetheless, a scientific understanding of consciousness is incomplete without an account of when and how consciousness emerges in early human development. Indeed, as the science of consciousness expands, it encounters a number of new frontiers. A recent review (Seth and Bayne, 2022) recognized new directions for consciousness research, including inferring consciousness in non-human animals, cerebral organoids, and, most importantly for this

* Corresponding author.
E-mail address: jfneuro@pm.me (J. Frohlich).
† These authors contributed equally (senior coauthorship)

https://doi.org/10.1016/j.neuroimage.2023.120057.
Received 5 October 2022; Received in revised form 24 March 2023; Accepted 27 March 2023
Available online 30 March 2023.

Table 1
Comparisons of cerebral organoids, fetuses, newborns, and adults. *Cerebral organoids* or "minibrains" have as many as 6 million neurons using current organoid techniques, more than that of insects such as honey bees or fruit flies (Greely, 2021). At present, they are generally thought to lack consciousness (Lavazza, 2021; Muotri, 2021), though this could change with increasing sophistication in the near future. Massive brain growth occurs during *fetal development*, with the total number of neurons peaking around 30 weeks gestation and then declining by approximately 70% before birth due to apoptosis (Rabinowicz et al., 1996). *Neonates* are born with slightly more neurons than an adult. Both fetuses and infants exhibit an abundance of active or rapid eye movement (REM) sleep and spend the majority of their day sleeping. By contrast, *adults* sleep eight hours a day, the majority of which is non-rapid eye movement (NREM) sleep. As adults, we can produce evidence of our own consciousness through verbal reports. How can neural mechanisms responsible for consciousness—if indeed present—be inferred or manipulated in fetuses, infants, and adults? Anesthesia can generally be used safely in adults to reversibly switch consciousness off, but its use is discouraged during pregnancy and early in postnatal development, except for when absolutely necessary for surgery. For safety reasons, brain stimulation in fetuses and infants is limited to sensory stimulation that perturbs neural circuits using discrete stimuli such as light flashes or auditory tones. Tools for measuring neural activity in fetuses are limited to fetal magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI), with electroencephalography (EEG) also available for recording neural activity in infants. Some techniques used in adults, such as electrocorticogram (ECoG) and local field potentials (LFP) in neurosurgery patients, as well as positron emission tomography (PET), are not used to study fetuses or infants for ethical and safety reasons.

	Cerebral organoids	Fetuses	Newborns	Adults
Number of neurons	1 - 6 million	65 billion (18 weeks) 280 billion (30 weeks) >86 billion (40 weeks)	>86 billion	86 billion
Modalities	LFP, single unit recordings	fMRI, MEG	fMRI, fNIRS, EEG, MEG	fMRI, fNIRS, PET, EEG, ECoG, LFP, MEG
Sleep/wake cycle	None using current techniques	Mostly active sleep, analogous to adult REM sleep (Nijhuis et al., 1982)	15 h per day (Parmelee Jr et al., 1964)	8 h per day
Anesthesia	Used for research (Logan et al., 2020)	Discouraged for health/safety reasons (see Van de Velde and De Buck, 2012)	Discouraged for health/safety reasons (see Davidson, 2011)	Used for painful procedures in patients, research in volunteers
Stimulation	Optogenetic, pharmacological	Sensory (visual/auditory)	Sensory (visual/auditory)	Electromagnetic, pharmacological, focused ultrasound, sensory

manuscript, early human development. In light of this last goal, basic and translational research into perinatal consciousness is a promising direction for scientific inquiry and may ultimately catalyze the development of new techniques for detecting consciousness in early human development. Results stemming from such work may also be applied to the measurement of consciousness in adults, e.g., by introducing new approaches for perturbing the thalamocortical system and/or introducing new data prompting updates to existing theories of consciousness (see Box 1).

Which developmental stage is most valuable for understanding the emergence of consciousness (Table 1)? Initially, infancy is the natural target for most investigations, as it is the developmental stage at which overt behavior emerges and, furthermore, common approaches for measuring brain activity, such as electroencephalography (EEG) or functional magnetic resonance imaging (fMRI), are generally easier when data are recorded ex utero. Specifically, one may wish to record early in postnatal development, e.g., from newborns or preterm infants, as a means of starting close to "square one" (Ciaunica et al., 2021). Can we go earlier—even closer to square one?

Despite the technical challenges of in utero recordings, there are scientific reasons to also pursue functional brain data from human fetuses. One such reason is that the womb is, in some respects, a more controlled environment than the cradle. The former environment isolates the fetal nervous system from many environmental stimuli and controls arousal levels using sedating chemicals such as adenosine, allopregnanolone, pregnanolone, and prostaglandin D2 (Mellor et al., 2005). By contrast, the cradle is a less controlled environment that often requires parental intervention when the infant becomes agitated, as occurs often. The consequences of the less controlled ex utero environment can be seen when comparing auditory habituation in fetuses with full-term newborns. Despite the fact that full-term newborns are more developed than fetuses, fetuses more reliably show evidence of habituation to auditory tones, likely because they are isolated in the womb from most other environmental stimuli, including outside sounds (Muenssinger et al., 2013). Given the above considerations, fetal data are promising for testing hypotheses concerning perinatal cognition and/or consciousness, especially when recording magnetoencephalography (MEG) signals, which allow cortical activity to be studied with high temporal resolution. However, we emphasize that spatial resolution is limited in standard fetal MEG recordings, in which only a few channels record cortical signals (Fig. 1A). To look for rich spatiotemporal patterns of perinatal cortical activity suggestive of consciousness, next-generation brain imaging technologies may offer new possibilities. One such solution is MEG recorded with optically pumped magnetometers (OPMs), which can be deployed flexibly in an ad hoc manner (Brookes et al., 2022; Escalona-Vargas et al., 2020), e.g., with sensor placement optimized for a given gestational period and fetal orientation in the womb (Fig. 1B). However, it is unclear whether OPM-based MEG alone is sufficient to capture rich spatiotemporal patterns of cortical activity without advanced beamformer approaches combined with anatomical information from structural magnetic resonance imaging (MRI). Another possible solution is fetal fMRI, which offers vastly superior spatial resolution and is considered safe for both the fetus and the mother-to-be (Ray et al., 2016; van den Heuvel and Thomason, 2016). Given that fetal MEG studies are currently limited to only a few cortical channels and currently only two dedicated data collection sites (Little Rock, Arkansas, USA and Tuebingen, Germany, Fig. 2), other approaches such as fetal fMRI and infant EEG/MEG/fMRI are also needed to fully understand the perinatal period.

In this article, we will give our perspective on a new frontier of both cognitive neuroscience and consciousness research—the perinatal period—and advocate for a new approach to quantifying perinatal consciousness using sensory perturbational complexity. Such a neural measure would be especially valuable for inferring perinatal consciousness given recent claims that infant behavior is subcortically mediated—and thus unreliable for inferring consciousness (Tononi and Koch, 2008)—until three to six months after birth (Blumberg and Adolph, 2023). This approach builds on recent findings obtained with fetal MEG and fMRI and can be realized in the near term. First, in Section 2 "SARA and her SQUIDs: an overview of fetal MEG", we re-

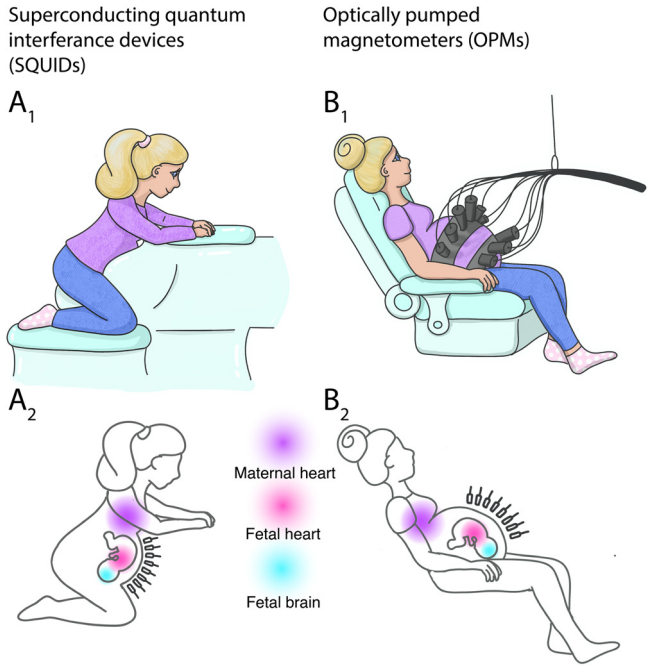

Fig. 1. Fetal MEG techniques. Optically pumped magnetometers (OPMs) are a recent innovation in MEG technology. Whereas conventional MEG devices (A) detect weak magnetic brain signals using SQUIDs (Superconducting Quantum Interference Devices) that must be cooled by liquid helium to ~4 Kelvin (−269 Celsius), OPMs (B) use room temperature sensors utilizing lasers inside vapor cells filled with rubidium or cesium gas to detect weak magnetic fields (Brookes et al., 2022); the vapor atoms are "pumped" by the laser, meaning that they become magnetized. This allows them to interact with and thus trigger the detection of very weak external fields. Unlike SQUIDs, OPMs do not require a fixed helmet or dewar containing cryogenic coolant but can instead be applied flexibly in an ad hoc manner. For example, one may use 3D-printed caps that accommodate different head sizes, e.g., as seen in a video directed by Brady Haran for the University of Nottingham: https://youtu.be/9FrsYjkKhBI?t=247 (Haran, 2022). Given their flexible deployment, the application of OPMs to MEG hardware is motivated in part by the need for improved MEG recordings in infants and young children (Brookes et al., 2022). Furthermore, an OPM sensor array may also be applied to the abdomen of a pregnant woman to record fetal cortical signals (B). OPMs have already been applied in this way to record fetal heart signals (MCG) (Escalona-Vargas et al., 2020), as fetal MEG devices detect a mixture of fetal brain signals (cyan), fetal heart (magenta), and maternal heart (purple) signals (Fig. A_2, B_2). We anticipate that OPMs will increase the accessibility of fetal brain activity to researchers in the near future. In their application to infant data, OPM-based MEG will yield far better head-coverage than SQUID based MEG, yielding higher spatial resolution (see Fig. 4A_1, cf. Fig. 3E). Artwork by Katrin Sippel.

view insights on perinatal consciousness and cognition obtained with fetal MEG (sometimes referred to as fMEG). Next, in Section 3 "Weak fields and strong fields: what MRI adds to the picture", we review the insights into perinatal cognition and consciousness obtained from neuroimaging. Having considered the above evidence, we then give our view of what an objective, validated measure of felt experience in the earliest stage of human life might look like in Section 4 "Sensory perturbational complexity: an index of perinatal consciousness?" Following this section, we consider how such a measure could be validated for use as an EEG/MEG measure of perinatal consciousness in Section 5 "A roadmap toward the development of sPCI". In Section 6 "An alternative perturbational complexity approach using fMRI", we consider how a perturbational complexity measure of perinatal consciousness could also be implemented using neuroimaging. Finally, in Section 7 "Conclusions", we end with reflections on the epistemological limitations of measuring perinatal consciousness.

Box 1. Perinatal consciousness and theories of consciousness

One way to approach the question of perinatal consciousness is to consider predictions made by leading theories of consciousness. Although theories of consciousness can be grouped in various ways, for present purposes, the most illuminating divide is between what we call 'low-bar' views and 'high-bar' views. Low-bar views hold that perceptual and sensory consciousness requires little in the way of cognitive machinery, whereas high-bar views hold that consciousness presupposes significant amounts of cognitive machinery.

One of the most influential low-bar views is the *integrated information theory* (IIT) (Tononi, 2004; Tononi et al., 2016). The central idea behind IIT is that consciousness should be understood in terms of 'cause-effect power' that reflects the amount of maximally irreducible integrated information generated by a physical system. Integrated information, in turn, is associated with the information theoretic quantity Φ (Phi), which measures the amount of information that is generated by a system as a whole (as compared to its parts considered in isolation). Given that the requirements for having some level of Φ are relatively easy to satisfy, it seems likely that IIT would point to an early origin for fetal consciousness. Another influential 'low-bar' theory of consciousness is the recurrent processing theory or RPT (Lamme, 2018, 2006). RPT has mostly been discussed in relation to visual consciousness, and holds that visual consciousness requires only localized recurrent processing within the visual system, and that although parietal and frontal regions might be required for reporting and using the contents of visual experience, they are not required for visual experience itself. RPT also points towards an early onset for visual consciousness.

Perhaps the most influential high-bar approach is the global workspace theory (GWT), first proposed by Baars (1997) and since developed in neurobiological detail by Dehaene and others (Dehaene et al., 1998; Dehaene and Changeux, 2011; Mashour et al., 2020). According to GWT, sensory information becomes conscious when it is 'broadcast' within an anatomically widespread neuronal workspace that is implemented across higher-order cortical association areas, with a particular (though not exclusive) emphasis on prefrontal cortex. Activation of the global workspace is achieved through nonlinear network 'ignition' in which recurrent processing amplifies and sustains neuronal representations. Given the emphasis that GWT places on long-range amplification and integration, it would point towards a late date for the emergence of consciousness.

Another influential high-bar approach to consciousness is the higher-order approach, according to which representations are conscious when they are the targets of a certain meta-representational process (Brown et al., 2019). The higher-order view is more of an approach than a particular theory, and there are a variety of views within its ranks as to what kinds of metarepresentational processes are required for consciousness. Some higher-order theorists focus on meta-representational states that are conceptualized and involve an explicit theory of mind (Rosenthal, 2005); others focus on the abstract states within a generative model of perceptual processing (Fleming, 2020; Lau, 2019). Higher-order approaches that focus on conceptualized meta-representations are committed to a late-onset view of human consciousness, whereas those that are couched in neurocomputational terms can allow that consciousness emerges relatively early in development.

Just as low-bar and high-bar approaches make different predictions for when consciousness first emerges, they also tend to make different predictions for where in the brain the critical mechanisms for consciousness are located (posterior and anterior regions, respectively; see Boly et al., 2017; Odegaard et al., 2017). Thus, from the perspective of IIT or RPT, an experiment showing maturation of posterior cortical regions might increase the plausibility of the developmental stage being studied supporting consciousness. On the other hand, from the perspective of GWT of higher-order theories, an experiment would likely need to show

maturation of pre-frontal or frontoparietal areas to give plausibility to consciousness occurring at the developmental stage under investigation. Note, however, that all of the above theories attribute consciousness to a distributed network process (Seth and Bayne, 2022), in which other cortical areas beyond those emphasized by the theory may also play a role, even if they are not strictly necessary for consciousness within a framework. Finally, despite their differences, all of the above theories emphasize cortical mechanisms of consciousness (Seth and Bayne, 2022) and view neural correlates of consciousness located in the midbrain or hindbrain (Parvizi and Damasio, 2001) as enabling factors or background conditions which are, at best, necessary, but never sufficient, for consciousness (Tononi and Koch, 2008).

2. SARA and her SQUIDs: an overview of fetal MEG

2.1. Introduction to perinatal MEG and EEG

MEG is a noninvasive technology for measuring magnetic neural activity (Barnes et al., 2010). Because magnetic fields, unlike electric fields, are never blocked but only redirected, skull, scalp, and other tissues minimally attenuate magnetic fields, giving MEG an advantage over its less expensive and much older sister technology, EEG. Like EEG, the MEG signal is generated by synchronous currents in millions of pyramidal cell apical dendrites, the parallel architecture of which is conducive to signal summation. Yet the unique physics of magnetic fields, which, unlike electric fields, pass nearly unimpeded through tissues as emphasized above, allows for noninvasive fetal imaging via magnetic sensors positioned around a pregnant woman's abdomen or an infant's head. As with most other MEG systems, the magnetic sensors of current fetal MEG devices are extremely sensitive superconducting quantum interference device (SQUID) coils capable of detecting biomagnetic fields on the order of femtoteslas (Keune et al., 2019). However, next-generation devices will likely use OPMs (Escalona-Vargas et al., 2020; Wakai, 2014) to record fetal MEG signals in a flexible manner, with sensor placement unconstrained by the cryogenic dewar used in SQUID-based systems (Fig. 1).

The first fetal MEG signal was recorded in 1985 using a single SQUID channel which detected auditory event-related responses from the fetal cortex in a study by Blum et al. (1985). Since then, the application of MEG to detect fetal and neonatal cortical signals has grown, albeit modestly. Of the > 100 MEG centers worldwide that are registered on Biomag Central (Biomag Central, 2017), only four are capable of detecting biomagnetic fetal signals (Fig. 2), and of these, only two are dedicated to fetal MEG (Keune et al., 2019). As mentioned above, recent advances in room-temperature OPMs which do not require a fixed-size helmet may expand the currently small number of sites with fetal MEG capabilities, as the OPM equipment does not need to be custom-built for fetal applications but can instead be adapted for new purposes (Brookes et al., 2022).

When dedicated to fetal brain signals using current-generation technology, the MEG system is referred to as a SQUID array for reproductive assessment (SARA), and its general application to fetal imaging is referred to as fetal MEG (Fig. 1A, Fig. 3). Of the two SARA systems in operation today, one was installed in the Department of Obstetrics and Gynecology at University of Arkansas for Medical Sciences in Little Rock, Arkansas, USA in 2000, followed by the more advanced SARA II system installed at the fMEG Center at the University of Tübingen, in Tübingen, Germany in 2008 (Keune et al., 2019). Another system capable of recording fetal MEG is an 83-channel fetal biomagnetometer primarily dedicated to magnetocardiography at the University of Kansas Medical Center, in Kansas City, Kansas, USA (Memar, 2019), and a similar device has also been used at the Biomagnetic Center of Jena University Hospital in Germany (Schneider et al., 2001) to record from fetuses, but neither of these are SARA systems.[1] A larger number of MEG systems ex-

[1] In the past, several sites used non-dedicated systems to record fetal MEG signals, but it seems that they are not operational anymore.

Fig. 2. Map of global MEG systems. MEG systems from Biomag Central (Biomag Central, 2017) were categorized according to the developmental period they are built to study. This map is not exhaustive but provides a general overview of how many systems are dedicated to each developmental period worldwide. Whereas many systems can record MEG signals from adults or children (cyan), only nine MEG systems that we know of are capable of recording from infants (yellow). Even fewer systems (four) are capable of recording from fetuses. Of these, two are SARA systems (red) and two are general system for recording fetal biomagnetic signals, including magnetocardiogram (MCG, magenta). The global scarcity of MEG systems capable of recording from fetuses and/or infants underscores the difficulty of studying this developmental period. However, next generation MEG systems based on optically pumped magnetometers (OPMs) may improve the availability of fetal and infant MEG (Wakai, 2014) by allowing for ad hoc recordings that do not require custom-built cryogenically cooled devices (see Fig. 1).

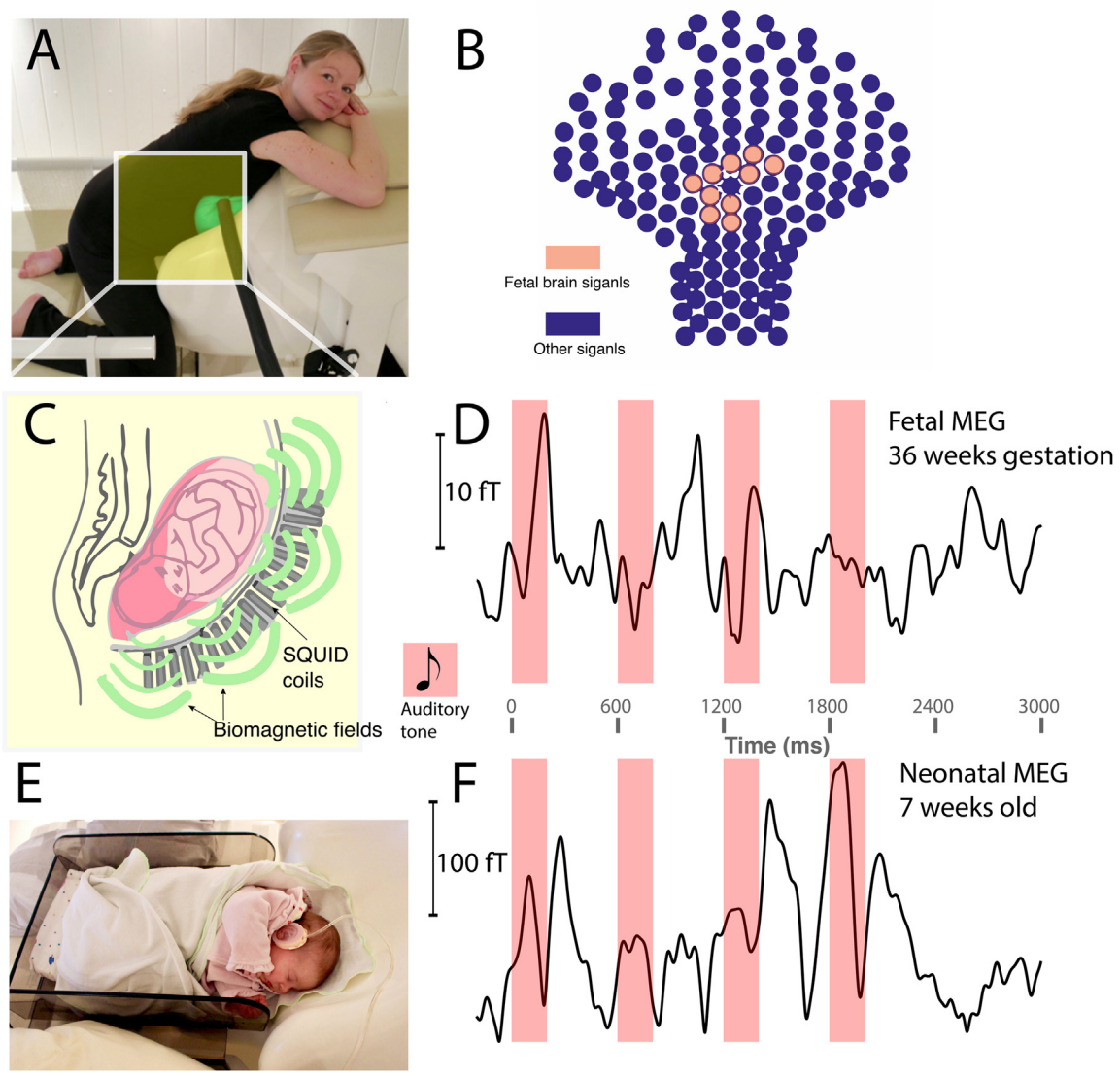

Fig. 3. Measurement of fetal brain signals using a SQUID array for reproductive assessment (SARA) system. A mother-to-be kneels in front of the SARA device with her abdomen positioned within the concavity containing the sensor array (A). A sound balloon is placed between the maternal abdomen and the sensors to deliver auditory stimuli. Only a subset of fetal MEG channels receive detectable signals from the fetal brain (pink), whereas other channels generally receive signals from other physiological activity and noise sources (B). The fetus is situated near the SQUID coils (C), which are positioned to detect biomagnetic fields from the fetus on the order of femtoteslas (D). Besides fetal cortical signals, the SARA device can also detect cortical signals from infants, e.g., when an infant is placed in a cradle head-first toward the sensor array and wearing infant-friendly headphones to delivery auditory stimuli (E). Cortical signals recorded from infants are similar to fetal cortical signals but with a higher SNR and large amplitude (F). In both (E) and (F), examples of trial-averaged auditory-evoked MEG signals from a fetus and newborn, respectively, are shown, with pink highlights denoting auditory tones. Note that (A) and (E) depict examples of participants and not the actual subjects who volunteered the data in (D) and (F).

ist for studying later periods of development, e.g., at least nine systems worldwide are used to record MEG signals from infants (Fig. 2).

Each SARA system can detect both spontaneous fetal signals as well as fetal visual and auditory event-related fields (ERFs), with stimuli presented to the fetal nervous system via a sound balloon (auditory) or light-emitting diodes (visual) placed between the maternal abdomen and the SQUID array (Keune et al., 2019). In the case of the sound balloon, speakers are placed outside of the magnetically shielded room housing the SARA system to avoid magnetic artifacts, and auditory tones are transmitted through an air-filled plastic tube to the inflated plastic balloon placed between the maternal abdomen and the SQUID array (Niepel et al., 2020). Sound attenuation by the maternal abdomen is accounted for in the stimulus delivery, and the volume is thus calibrated at 20 – 30 dB higher than the target volume that will reach the fetus (Gerhardt et al., 1990; Querleu et al., 1988). In the case of visual stimulation, red LED lights are placed between the maternal abdomen and the SQUID array, as lower frequencies of light pass more easily through tissue than higher frequencies toward the blue end of the spectrum. The SARA system can also be used to detect neural signals from infants, including neonates, with the infant lying in a crib positioned head-first toward the SQUID array (Niepel et al., 2020; Preissl et al., 2004); sensory stimuli can then be delivered as necessary, e.g., using infant-friendly earmuffs to deliver auditory tones (Keune et al., 2019; Preissl et al., 2004).

Given the biophysical advantages of MEG discussed at the beginning of this section, its sister technology, EEG, has rarely been used for recording prenatal cortical activity in humans, the acquisition of which requires recordings from the fetal scalp during labor after rupture of the amniotic membranes (Thaler et al., 2000). Given this limitation, EEG is not particularly useful for studying fetal brain activ-

ity, but similar electrophysiology methods, e.g., local field potentials (LFPs), may be applied to cerebral organoids to study the early development of neural oscillations (Trujillo et al., 2019). In addition to cerebral organoids, electrophysiology can be applied to preterm infants (Wallois et al., 2021) as a means of studying early development before full term gestational age. These EEG studies are boosted by a higher SNR than infant MEG recordings using a SARA device. For instance, Mahmoudzadeh et al. (2017) used EEG to study the spatial scalp topography of event-related responses in preterm infants with a mean gestational age of 30 weeks. The authors discovered reproducible topographies occurring at each of several event-related potential (ERP) peaks in response to phonetic stimuli, as well as a mismatch response (see Glossary in Box 2) to deviant stimuli that differed from standard stimuli according to syllable or the speaker's gender. Thus, EEG can be used to show phonetic processing and discrimination prior to full term maturation. Importantly, however, preterm infants should not be conceptualized as ex utero fetuses, as the chemical environment of the womb sedates the fetus and may thus constrain its capacity for cognition and awareness (Lagercrantz, 2009; Lagercrantz and Changeux, 2009; Mellor et al., 2005). For a discussion of other EEG studies in infants, see Section 4.3 "Sensory perturbational complexity: an index of perinatal consciousness?".

Box 2. Glossary

Conceptual age: fetal age referenced to the time of fertilization (also known as post-conceptual age), cf. gestational age (defined below).

Consciousness: subjective experience, which may occur in the absence of self-awareness or meta-cognition. An organism is conscious if there is "something it is like" to be that organism (Nagel, 1974).

Default mode network (DMN): a spontaneous fMRI connectivity network active during higher cognitive functions and commonly reduced during focused attention. Its principal nodes include the posteromedial cortex, middle temporal cortex, medial prefrontal cortex, and angular gyrus (Smallwood et al., 2021). The DMN is altered during unconscious states, but it is neither necessary nor sufficient for consciousness.

Entropy: the number of ways in which a system or signal can be arranged. Signal entropy is often referred to as "complexity", and increased EEG/MEG signal entropy is generally associated with consciousness (Sarasso et al., 2021).

Gestational age: fetal age referenced to the time of last menstruation, cf. conceptual age (defined above). In infants, the gestational age is added to the chronological age (age after birth) to give the postmenstrual age.

Local-global: a stimulation paradigm with two levels of deviant or oddball stimuli, within trials (local oddballs) and between trials (global oddballs), in which detection of a global oddball may require consciousness (Bekinschtein et al., 2009)

Mismatch response: the early cortical response to a low probability or "oddball" stimulus (defined below) which is generally preconscious (Näätänen et al., 2001). In EEG, it is referred to as the mismatch negativity (MMN) and in MEG, it is referred to as the mismatch field (MMF).

Oddball: a deviant, low probability stimulus or irregularity in a sequence of stimuli.

P300: a late cortical response, as recorded with EEG or MEG, to a stimulus, generally associated with a reorienting of attention (Polich, 2007). In the context of an oddball paradigm, it occurs after the mismatch response. Its late component (P3b) is often associated with consciousness (but see criticism noted in Section 2.3 of the text). Although it is named for its 300 ms latency in adults, a later yet analogous response has also been observed in infants (McIsaac and Polich, 1992) and fetuses (Moser et al., 2021).

PCI algorithms: algorithms for quantifying the complexity of the EEG/MEG response to a cortical perturbation, as a means of computing the PCI or sPCI (defined below). In principle, the same algorithms may be used for PCI and sPCI, though in practice, different algorithms may be better suited for each.

Perturbational complexity index (PCI): the complexity of the EEG response to a TMS pulse or "perturbation" as first introduced by Casali et al. (2013) as an objective and robust measure of consciousness.

Sensory PCI (sPCI): A variation of the original PCI that uses the complexity of EEG or MEG responses to sensory, rather than electromagnetic, perturbations.

SQUID array for reproductive assessment (SARA): An MEG device built for recording fetal MEG signals, but which may also be used to record infant MEG signals (SQUID = superconducting quantum interference device). Note that some sources (e.g., Moser et al., 2019) refer to data recorded with a SARA device as fMEG regardless of whether the subject is a fetus or an infant.

Topographic information analyzed in the above study by Mahmoudzadeh and colleagues would not be obtainable with a SARA system, which generally only records cortical MEG signals from a few channels (Moser et al., 2020). Alternatively, systems dedicated exclusively to infant MEG (Fig. 2) may record high resolution topographic data, e.g., the 375-channel "BabyMEG" installed at Boston Children's Hospital in Massachusetts, USA (Okada et al., 2016). In addition to dedicated systems for infant MEG, EEG is also a valuable tool for studying the spatial dimension of infant cortical activity that would not be otherwise obtainable with a SARA system. For studies requiring even higher spatial resolution (< 1 cm), either advanced MEG source localization techniques or fMRI is required. The latter can be used to study both fetuses and newborns (Anderson and Thomason, 2013; Yates et al., 2021) (see Section 3 "Weak fields and strong fields: what MRI adds to the picture"). Unlike EEG and MEG, fMRI records hemodynamic activity as a proxy for neural activity. A related technology, functional near infrared spectroscopy (fNIRS), also records hemodynamic brain activity in infants (Emberson et al., 2015), but is deployed using a cap of wired sensors in a manner more similar to EEG than fMRI; it is thus portable and appropriate for experiments that cannot be conducted in the MRI scanner. However, fNIRS lacks the high spatial resolution of fMRI. For an overview of imaging modalities available at different developmental stages, see Table 1.

2.2. Fetal cognition

In the past two decades, MEG has been successfully deployed to study cognition in fetuses. In an early fetal MEG study, an "oddball" paradigm was used to study sound frequency change detection in a small sample of fetuses and infants. Nearly half of fetal recordings showed a mismatch field response to oddball or deviant stimuli, which was observed as early as 33 weeks gestational age, i.e., nearly the earliest gestational age studied (Draganova et al., 2005). The proportion of "responders" increased in the neonatal data, with 80% of recordings showing the mismatch response. Several fetal and neonatal recordings also showed a late discriminative negativity response occurring roughly 100 – 200 ms following the earlier mismatch response. A subsequent study detected the mismatch response as early as 28 weeks and demonstrated a non-significant decrease in response latency with gestational age using regular sampling of longitudinal data (Draganova et al., 2007). Besides sound frequency discrimination, fetal MEG has also been used to demonstrate numerosity discrimination in fetuses and newborns using auditory tones. All newborns and roughly three quarters of fetuses in such a study (Schleger et al., 2014) showed a mismatch response between sequences of two versus four tones, and fetuses showed a significant decrease in response latency of 8.1 ms per week.

While the above studies all used MEG to demonstrate discriminative abilities in fetuses and newborns, MEG has also been used to ele-

gantly demonstrate perinatal learning. In a study of auditory habituation, Muenssinger et al. (2013) used MEG to demonstrate dishabituation to a deviant auditory tone following five identical tones in fetuses and newborns. Three criteria were used for habituation: 1) a decrement in response amplitude between the second and fifth tone, 2) a response increment between the fifth and sixth tone due to the new stimulus (stimulus specificity), and 3) a response increment between the fifth and seventh tone due to dishabituation. Statistically significant effects were found in fetuses for criteria 1 and 2, and in newborns for only criterion 2. Although this might be partially explained by the larger fetal sample (i.e., the neonatal group might have been underpowered), somewhat surprisingly, the proportion of fetuses that showed evidence of criterion 1 was larger (27 out of 36, or 75%) than the proportion of newborns that showed the same decrement (10 out of 15, or 66.7%). Why was habituation learning easier to demonstrate in a less mature population (fetuses) compared to a more mature population (newborns)? This counterintuitive finding appears to support a point made in the introduction: fetal arousal is regulated by maternal hormones and the isolation of the womb, whereas neonatal arousal is far more varied and influenced by a greater number and intensity of environmental stimuli. The authors (Muenssinger et al., 2013) note that, while recording from newborns, "[parental] intervention was necessary during almost all measurements at a certain point" and that "[*t*]hese distractions from the environment might have served as 'natural dishabituators' which interfered with the habituation process" in the neonatal condition. Put simply, newborns in the cradle frequently move and cry for their caregiver, whereas fetuses are largely sedated and isolated from confounding environmental stimuli. The above study supports the stance that fetuses are often valuable subjects for studies of perinatal cognition.

2.3. Possible evidence of fetal consciousness

Although the preceding studies provide evidence of learning and perceptual discrimination in infants and fetuses, their results are perhaps consistent with a lack of perceptual awareness. However, recent studies using a hierarchical learning "local-global" paradigm (Moser et al., 2021, 2020) do appear to provide specific evidence of perceptual consciousness in both newborn infants and fetuses from 35 weeks gestation. This paradigm, based on (auditory) prediction errors or "oddballs", has already been used as a marker of consciousness in adult neurological patients (Bekinschtein et al., 2009; Jean-Rémi King et al., 2013; Sitt et al., 2014), and it can also distinguish general anesthesia from consciousness in neurosurgery patients (Nourski et al., 2018) and macaque monkeys (Uhrig et al., 2016). For definitions of terms relevant to this approach (e.g., oddball, P300), please see the Glossary (Box 2).

As presently implemented, the local-global paradigm is a non-behavioral task that trains the subject to anticipate the final tone in a sequence of auditory stimuli to be either the same or different from the subsequent three or four tones within the same sequence. For instance, a tone that is identical to the preceding tones despite an expectation that it should be different is a local standard/global deviant. A tone that is different from the preceding tones, as expected given earlier training stimuli, is a local deviant/global standard. Detecting global rule violations requires integration of information over a longer temporal duration than that of first-order rule violations and may depend on perceptual consciousness and working memory (Marchi and Hohwy, 2020). According to some theoretical frameworks (e.g., Seth, 2018) which hypothesize that consciousness depends on predictive coding, an error signal in response to global deviants is highly suggestive of perceptual consciousness.

This prediction error signal appears as the P3b component of the P300 response seen in the ERP or ERF recorded during an oddball paradigm. However, the P300 response as conventionally implemented as a signature of perceptual consciousness has been criticized both for low sensitivity (Dembski et al., 2021; Faugeras et al., 2012) and low specificity (Cavinato et al., 2012; Doradzińska et al., 2020; Schubert et al., 2020; Silverstein et al., 2015; Tzovara et al., 2015). While we acknowledge these concerns, the presence of a P300-like response at least raises the possibility of perceptual consciousness in fetuses.

Considering the foregoing, successful detection of second-order or "global" rule violations, evidenced by large signal deflections in the trial-averaged ERF, is suggestive of consciousness, as was recently reported in studies of fetuses and neonates conducted at the SARA site in Tübingen (Moser et al., 2021, 2020). These responses were only reliably detected in fetuses starting from 35 weeks gestational age, and the amplitude of the response was modulated by heart rate variability, i.e., arousal, suggesting that fetuses who were in a quiet sleep state during the experiment were unconscious and thus unable to be "surprised" (in a Bayesian sense) by the deviant tones. To the best of our knowledge, the above study is the first ever to explicitly claim evidence of consciousness in utero based on recorded brain activity.

3. Weak fields and strong fields: what MRI adds to the picture

While fetal MEG records extremely weak magnetic fields on the order of femtoteslas, MRI uses very powerful magnetic fields on the order of teslas to noninvasively image the brain. In particular, fMRI infers changes in blood oxygenation and can be applied to fetuses to map intrinsic brain network development in utero (Anderson and Thomason, 2013). Although pregnancy is sometimes listed as a contraindication for certain MRI protocols, safe protocols have been developed specifically for fetal imaging, which incorporate parameters such as a low number of slices and high repetition time to decrease the rate of heat absorption by fetal tissue (van den Heuvel and Thomason, 2016). Follow-up studies of children who were scanned as fetuses during the third trimester of pregnancy did not find any harmful effects of fetal MRI (Baker et al., 1994; Kok et al., 2004). Although the loud volume of MRI scanning noise is another potential safety concern for fetuses, the maternal abdomen attenuates acoustic energy by 20 - 30 dB, i.e., a factor of 100 - 1000, nearly comparable to the level of sound protection afforded by earplugs (Abel and Lam, 2004), and no hearing problems have been reported in children who were scanned as fetuses (Baker et al., 1994).

One of the greatest contributions of fMRI to our understanding of fetal brain development is the discovery of early functional connectivity within the default mode network (DMN) in late gestation (Thomason et al., 2015). The DMN is a network of spontaneous and strongly correlated hemodynamic fluctuations across cortical regions (sometimes referred to as an intrinsic connectivity network) which, in adults, is implicated in many different cognitive functions due to its integrative role and unique topographic characteristics (Smallwood et al., 2021) (see the Glossary in Box 2 for further definition). Properties of the DMN are altered during unconscious states, including diminished resting-state connectivity and entropy within the DMN, anticorrelations between DMN nodes and other regions of the brain, and task-based DMN deactivations (Crone et al., 2015, 2011; Deshpande et al., 2010; Luppi et al., 2019; Norton et al., 2012; Threlkeld et al., 2018). On the other hand, however, DMN connectivity has been detected, albeit disrupted (Norton et al., 2012), in subjects that show no signs of consciousness (Bodien et al., 2017; Boly et al., 2008; Vincent et al., 2007), and, conversely, consciousness may persist even when the DMN is not detected (Bodien et al., 2019). Furthermore, non-ordinary states of consciousness are often associated with weakened DMN connectivity, e.g., in a stimulus-free environment (Al Zoubi et al., 2021) or in the psychedelic state (Carhart-Harris et al., 2016). Thus, identifying DMN connectivity does not necessarily mean the subject is conscious and an unconscious subject does not necessarily have no detectable DMN. Rather than serving as a direct indicator of consciousness, the DMN may indicate the level of information integration, which is a key component of consciousness within some theoretical and pragmatic frameworks (Mediano et al., 2022).

With the foregoing in mind, the study cited above by Thomason et al. (2015) demonstrated evidence of fMRI connectivity between two important nodes of the DMN–the prefrontal cortex and the posterior cingulate cortex–in fetuses older than 35 weeks conceptual age (37 weeks gestational age, see Glossary in Box 2), thus establishing the possibility that this network is already active before birth. Similarly, two recent, large sampled fMRI studies of newborns found evidence of DMN connectivity mere weeks after birth (Hu et al., 2022; Sylvester et al., 2022). Furthermore, increasing functional connectivity within the DMN is supported by increases in regional cerebral blood flow in the first two years of life (Yu et al., 2023). The DMN present during the perinatal period might be interpreted as a weaker, immature version of the adult DMN, as Hu et al. (2022) found that the neonatal DMN and other fMRI networks had less within-network connectivity compared to adults. Indeed, the DMN may not mature to adult-like connectivity patterns until two years of age (Gao et al., 2009). Thomason et al. (2015) also found that, beyond the DMN, long-range fMRI connectivity increased with gestational age in the cohort of 39 fetuses they studied cross-sectionally between 24 and 38 weeks gestational age, and early evidence of other intrinsic connectivity networks, such as the motor, visual, auditory, and thalamic networks, was also reported in older fetuses.

Indeed, the DMN is not the only fMRI connectivity network present during the perinatal period. In the Hu et al. study cited above (2022), within the first year of life, not only the DMN, but also the dorsal attention network (DAN) and executive control network (ECN) were already active in both full-term infants and term-equivalent infants born prematurely, with the reciprocal relationships seen in adults between DMN activity and activity in the other two networks already present. Before term-equivalent age, only the DAN was online as a distinct network, leading the authors to speculate that processes sometimes associated with consciousness (Mediano et al., 2022), such as “integration of information across diverse sensory and high-order functional modules”, are absent prior to term-equivalent age. In another study (Huang et al., 2020), resting state fMRI networks were examined in newborns no more than several weeks old and compared to adults. The authors reported that sensorimotor areas were the most active and well-connected of the neonatal brain and, in fact, the only region examined that the authors did *not* describe as having much lower dynamic connectivity with other regions as compared to adults. Given this finding and the role of global information propagation (Baars, 1997; Dehaene et al., 1998) and integration (Tononi et al., 2016) in prominent theories of consciousness (see Box 1), it is possible that bodily perception—dependent on sensorimotor connectivity, which matures early in infants—is one of the first dimensions of consciousness to arise human development (see also Ciaunica et al., 2021). Finally, besides functional connectivity, fMRI can also be used to map brain activation during the perinatal period. In another fMRI study (Goksan et al., 2015), newborns less than seven days old were exposed to mild noxious stimuli (a pinprick on the foot), and their fMRI responses were compared to those of adults in a similar experiment. In 90% of the anatomical brain regions that yielded pain responses in adult participants (18 out of 20), infants also demonstrated similar responses. This substantial overlap suggests similar pain perception in infants and adults.

4. Sensory perturbational complexity: an index of perinatal consciousness?

4.1. Complexity and consciousness

Convergent evidence from many studies has pointed toward the entropy or complexity of EEG and MEG signals as an accurate, experimentally useful readout of consciousness (Frohlich et al., 2021, 2022a; Sarasso et al., 2021). Complexity can be conceptualized as informational content (Gell-Mann and Lloyd, 1996), and is generally quantified as either the entropy of the signal (i.e., the number of ways in which states of the signal can be arranged), or as the compressibility of the signal, usually measured as the number of unique "patterns” in the signal, which is, in fact, bounded by the signal’s ground truth entropy (Cover and Thomas, 2012). Entropy is commonly quantified in anesthesiology using approaches such as state entropy and response entropy (Viertiö-Oja et al., 2004), and more commonly in research using approaches such as permutation entropy (Li et al., 2008; Olofsen et al., 2008) and sample entropy (Wei et al., 2013). EEG compressibility is generally quantified using the Lempel-Ziv complexity (LZc) algorithm (Hudetz et al., 2016; Lempel and Ziv, 1976; Zhang et al., 2001). In a diverse range of contexts, including NREM sleep (Abásolo et al., 2015; Frohlich et al., 2022a; Schartner et al., 2017b; Tosun et al., 2017), general anesthesia (Bai et al., 2015b; Hudetz et al., 2016; Schartner et al., 2015; Zhang et al., 2001), drowsiness (Mediano et al., 2021), and absence seizures (Bai et al., 2015a; Mateos et al., 2018), numerous studies have demonstrated that EEG/MEG complexity decreases with a reduction in or loss of consciousness. Conversely, EEG/MEG complexity increases with changes and intensifications of phenomenology, such as those during hallucinatory or psychedelic states (Schartner et al., 2017a; Timmermann et al., 2019), lucid dreaming (relative to non-lucid dreaming; Baird et al., 2022), or musical improvisation (Dolan et al., 2018).

Although the above studies focused on adults and children, entropy is also known to correlate with conscious states in infancy. For example, Wielek et al. (2019) achieved above-chance classification of sleep stages in newborns with machine learning using multiscale permutation entropy features, and the performance accuracy using these entropy features was significantly greater than that achieved using spectral EEG features. Using dimensionality measures of neural complexity, two earlier studies also reported differences in signal complexity between infant sleep stages (Janjarasjitt et al., 2008; Scher et al., 2005). Taken together, the above cited literature supports a strong experimental link between consciousness and signal complexity in adults and infants.

4.2. The perturbational complexity index (PCI)

The studies described above quantify consciousness based on the complexity of spontaneous brain signals. In addition to those studies, evidence has accumulated for a specific measure of complexity dubbed the perturbational complexity index, or PCI (Casali et al., 2013).

Experimentally, PCI is calculated as the complexity or, more specifically, the compressibility (LZc in the original PCI algorithm) of the EEG response to a cortical perturbation using transcranial magnetic stimulation (TMS)—hence the nickname “zap-and-zip” (Koch, 2019). PCI has been demonstrated to have near-perfect accuracy for inferring the presence/absence of consciousness in adults (Casarotto et al., 2016). PCI values are specific to awareness, rather than arousal or wakefulness; this is evidenced by the fact that, in adults, the PCI can distinguish states of behavioral unresponsiveness which do not yield subjective reports upon awakening (e.g., NREM sleep, propofol anesthesia) from those which do yield such reports (e.g., REM sleep, ketamine anesthesia) (Casarotto et al., 2016). Furthermore, subanesthetic doses of ketamine with psychedelic effects suggest that PCI tracks the general capacity for consciousness rather than the richness of conscious content (Farnes et al., 2020). There is some evidence that PCI may even be capable of detecting consciousness when it is otherwise dissociated from EEG oscillations, as occurs following pharmacological challenge with the antiepileptic drug tiagabine (Darmani et al., 2021). The possibility that complexity metrics are even more effective in discriminating states of consciousness after a perturbation (as in PCI) than they are in spontaneous activity would indicate a crucial role for perturbations in the experimental assessment of one’s conscious state. Two main algorithms for PCI exist, the original algorithm based on LZc (Casali et al., 2013), and a newer algorithm based on state transitions (PCIst) that can be deployed in real time (Comolatti et al., 2019).

Beyond its empirical effectiveness, at a theoretical level PCI is also well supported. PCI fits well with a “weak” or pragmatic version

(Mediano et al., 2022) of integrated information theory (IIT) that highlights the interplay between integration and differentiation in neural dynamics for consciousness (Box 1). Experimental studies using variations of IIT's flagship measure, Φ, have found decreased Φ in humans under anesthesia and disorders of consciousness (Luppi et al., 2020), as well as in macaques under anesthesia (Afrasiabi et al., 2021). In perinatal development, a recent study (Isler et al., 2018) analyzed EEG recordings from a large sample of preterm infants and found that Φ was lowest in quiet sleep (analogous to adult NREM sleep), intermediate in active sleep (analogous to adult REM sleep), and greatest in wakefulness, and, furthermore, increased with postmenstrual age in infants.[2]

4.3. Sensory perturbational complexity

Given the empirical power of PCI, it is natural to ask whether a measure similar to PCI could be deployed in infancy or even in fetuses to infer consciousness in a very young developing brain. Although both infant and fetal development are of major interest to us, a large part of the discussion here will focus on applications in infancy, as a PCI-like measure will be substantially easier to apply to infants as compared with fetuses. Unfortunately, since PCI computes the LZc of TMS-evoked potentials, such stimulation would likely be unethical to apply to the perinatal brain, given that the long-term consequences of electromagnetic stimulation in infants are unknown, and many investigators and research participants are hesitant even to apply TMS to the maternal brain during pregnancy, despite an absence of evidence regarding harm (Pridmore et al., 2021). Thus, a solution to this problem might be to develop an index analogous to the PCI for inferring perinatal consciousness that uses sensory stimulation rather than magnetic stimulation to perturb the cortex (Fig. 4), i.e., a sensory PCI, or sPCI. The logic of PCI, aligned with weak IIT (see Box 1), should also allow for non-magnetic perturbations from which the balance between cortical differentiation and integration can be judged. For instance, one might calculate signal complexity after perturbing the infant cortex using visual stimuli ("flash-and-zip") or auditory stimuli ("beep-and-zip"), resulting in a proxy measure that approximates the well-established PCI. Indeed, our group has taken a similar approach in a recent study (Frohlich et al., 2022b) that found significant changes in the entropy of auditory-evoked MEG signals with maturation using fetal and neonatal recordings (see Section 5.3.2 "Current work" below).

Despite using sensory, rather than magnetic, perturbations, sPCI should be highly similar to PCI both in terms of how it is measured and what it is measuring. Like PCI, sPCI should be computed using the temporospatial activity pattern spanning all cortical recording sites in order to capture neural integration. Thus, while different theories of consciousness place different emphases on posterior or anterior cortical regions (Box 1), both sPCI and PCI take all cortical areas into account. Indeed, while both sPCI and PCI are inspired by IIT—which predicts greater involvement of posterior cortex in the neural substrate of consciousness (Tononi et al., 2016)—they are also compatible with other theories of consciousness, such as global workspace theory (Mashour et al., 2020)—which predicts greater involvement of anterior cortex in the neural substrate of consciousness (Baars, 2005). In this sense, our proposal for sPCI can still be considered "theory neural", even while drawing inspiration from weak IIT. Furthermore, just as PCI and sPCI are measured similarly, they also measure the same construct: both approaches should track the presence of awareness rather than other factors such as arousal or wakefulness. As in the original PCI, cortical responses to sensory stimulation can be recorded with EEG to capture the fast dynamics of evoked responses; unlike the original PCI, however, MEG (which shares the high temporal resolution of EEG) is also compatible with sPCI. Furthermore, while magnetic perturbations are already compatible with fMRI (Bestmann et al., 2008), sensory (in particular, olfactory) perturbations may be more practical to combine with neuroimaging, e.g., if one wishes to maximize spatial resolution (see Section 6 "An alternative perturbational complexity approach using fMRI"). For use with low-density EEG/MEG recordings in which source localization is infeasible, sPCI should use an algorithm that can be applied in sensor-space, such as PCIst (Comolatti et al., 2019) or variations of the LZc-based approach (Dallavecchia et al., 2021; see Section 5.2 "Computing complexity from low SNR MEG recordings").

The application of sPCI to infants is expected to offer information above and beyond conventional approaches to analyzing sensory event-related responses. Conventional approaches based on component latencies and topographies are often unreliable for the purpose of inferring consciousness at the level of an individual subject (see criticism cited above in Section 2.3 "Possible evidence of fetal consciousness"). However, PCI evaluates the signal's complexity holistically and does not depend on components having specific latencies or topographies, helping in part to overcome the limitations of a conventional sensory ERP/ERF approach. For this reason, we are optimistic that a perturbational complexity approach may improve the ability to detect consciousness based on sensory irregularities. Nonetheless, we should not expect sPCI or any other individual metric of consciousness to yield 100% accuracy. Indeed, the strongest approach is likely one in which multiple indices of consciousness converge on the same classification. The sPCI approach is thus only a beginning toward the development of indices for perinatal consciousness, and we expect it to be part of an eventual toolkit for inferring consciousness in early development.

4.4. Development of the thalamocortical system and the possible onset of consciousness

The sPCI can also allow us to hypothesize about what stage of development consciousness might begin in. For example, computational evidence from *in silico* brain models suggests that thalamocortical coupling is crucial to reproduce the characteristic complex dynamics that follow TMS in conscious (adult) brains (Bensaid et al., 2019). Experimentally, electrophysiological studies have shown that inclusion of the thalamus is crucial to obtain Φ estimates (see Box 1) that align with the predictions of IIT (Afrasiabi et al., 2021). These PCI- and IIT-specific studies join a growing body of experimental and theoretical research pinpointing the thalamocortical system as a key brain structure that allows consciousness to emerge (Alkire et al., 2008; Bachmann et al., 2020; Mashour and Alkire, 2013).

What are the implications of this research for perinatal consciousness? Most importantly, it suggests that consciousness is very unlikely to develop before the establishment of thalamocortical connectivity at roughly 26 weeks gestation (Kostović and Judaš, 2010) (Fig. 5). The thalamus itself is likely to be an enabling factor for consciousness; it provides information that contributes to conscious content, but the thalamus alone is not sufficient for consciousness, despite its important role therein (Fuller et al., 2011; Koch et al., 2016). Furthermore, it is currently unknown precisely when after the establishment of thalamocortical connectivity at 26 weeks gestation consciousness emerges and, on this front, different theories offer different predictions (Ciaunica et al., 2021). The experimental application of sPCI might shed new light on this debate, by tracing the developmental trajectory of neural complexity. However, near future application of sPCI will most likely focus on infancy given both practical and conceptual challenges in fetuses (see below).

[2] Note, however, that this finding appears to be at odds with that of Wielek et al. (2019), who found that another measure of EEG complexity, multiscale permutation entropy, actually decreases in infants (born full term) from week 2 to week 5. Thus, while the relationship between complexity/entropy and the level of consciousness appears to be positive under nearly all circumstances, the relationship between the former quantity and maturation is more ambiguous in early development (see also Frohlich et al., 2022b). Further work is necessary to disentangle the influences of maturation and conscious level on EEG/MEG entropy.

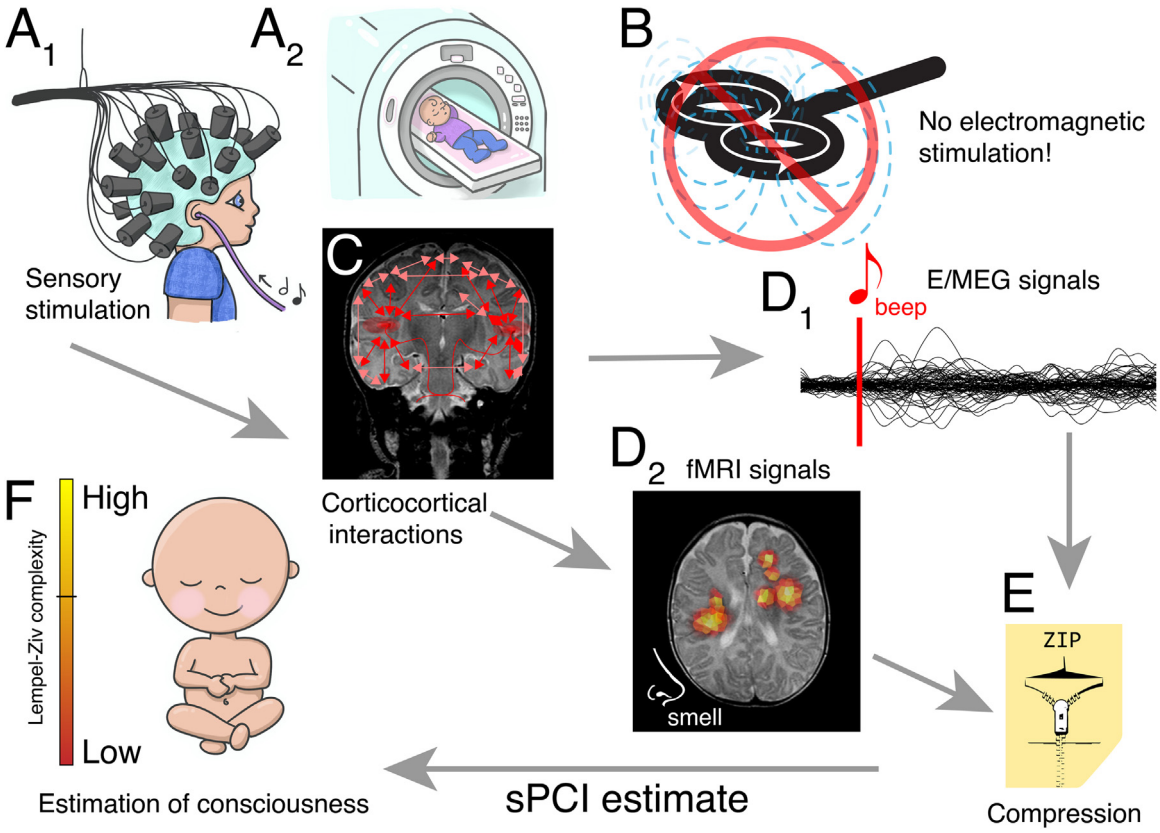

Fig. 4. How can consciousness be measured in infants? The above diagram illustrates two plausible approaches for estimating the presence of consciousness in infants using sensory stimulation. In one approach, infant-friendly earphones are used to deliver auditory stimulation while either EEG or, in the illustrated example above, OPM-based MEG signals are recorded. (A_1) In another example, olfactory stimuli are delivered in an MRI scanner while fMRI is recorded. (A_2) Because both approaches use sensory stimulation, the infant is not exposed to any electromagnetic stimulation (e.g., no TMS), the effects of which in very early development are unknown. (B) Sensory perturbations and, in particular, Bayesian prediction errors, lead to corticocortical interactions, causing the original perturbation to propagate across cortex. (C) In the first approach, the cortical responses to sensory stimulation are recorded using EEG or MEG, with good temporal resolution and adequate spatial resolution. (D_1) In the second approach, the cortical responses to chemosensory stimulation are recorded using fMRI, with good spatial resolution and adequate temporal resolution. (D_2) The complexity of the spatiotemporal pattern in response to the perturbation is estimated using a compression algorithm, e.g., Lempel-Ziv. (E) The resulting value is the sensory perturbational complexity index (sPCI), which can be used to infer consciousness in the infant subject (F). This may help inform decisions about whether analgesics or anesthetics are needed in the neonatal intensive care unit. Note: the neonatal structural MR images in (C) and (D_2) are from a publicly available pediatric brain atlas (Jelacic et al., 2006); the MEG responses in (D_1) are semi-simulated, i.e., real channel-averaged signals from different fetal subjects were combined to simulate a multichannel response from a single fetal subject; the activation map in (D_2) is arbitrarily simulated. Artwork (A_1, A_2, F) by Katrin Sippel.

5. A roadmap toward the development of sPCI

Given that infants cannot self-report their conscious state, how might sPCI be validated as an index of consciousness? In this section we sketch an outline of experimental challenges and questions that need to be met for sPCI to be established as a valid index of perinatal consciousness.

5.1. Stimuli and external perturbations

Before sPCI is tested and validated, we must choose an appropriate sensory modality for perturbations. The two most natural choices for stimulus modalities are auditory and visual, which in both cases can be easily and safely delivered. Auditory stimulation can be delivered to infants via appropriate headphones (Fig. 3E) or to fetuses via a sound balloon, and visual stimulation can be delivered to both infants and fetuses using light-emitting diodes. However, in both cases, the repeated stimulation needed to acquire a number of trials large enough for data analysis risks inducing habituation, thus reducing the amplitude of the evoked response and compromising the efficacy of the perturbation.

A more promising option is to rely on different types of signals given by Bayesian prediction errors (Friston, 2019). Prediction errors represent a difference between the brain's expectations (or predictions) of incoming information and the actual incoming information. For example, oddballs elicit a stronger response than standard stimuli both in terms of the early mismatch response (Garrido et al., 2009) and the later P300 response (Rosenfeld et al., 2005). As such, sensory irregularities may be suitable candidates for perturbations used to implement sPCI. Implementation of standard and deviant stimuli in both auditory and visual modalities can be easily achieved, for example, by including stimuli that differ along a particular dimension (e.g., auditory frequency or visual pattern) from standard stimuli presented in the majority of trials.

5.2. Computing complexity from low SNR MEG recordings

Calculation of LZc for PCI conventionally relies on source-reconstructed data obtained from high-density EEG (Casali et al., 2013). In infants, high-density EEG can be acquired using a geodesic sensor net (Johnson et al., 2001). However, experimental setup time is faster in infants using MEG, and MEG is still the only option for noninvasive, direct measurements of neural activity from fetuses. Although some MEG devices allow for high-density recordings from infants (Okada et al., 2016), SARA devices do not, and fetal MEG cannot be recorded at high

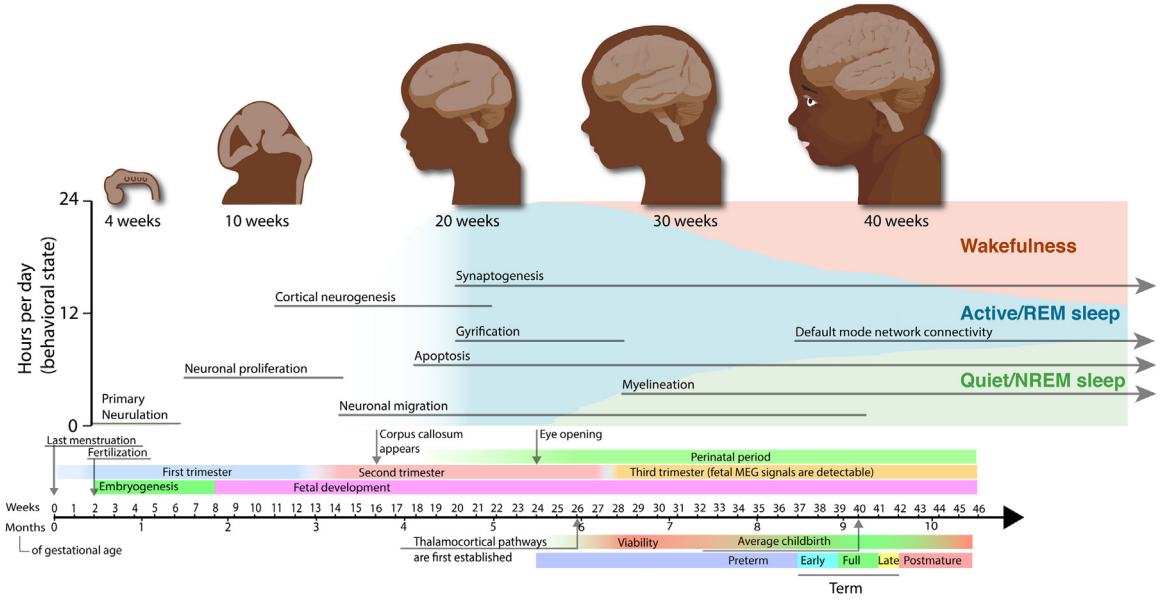

Fig. 5. Developmental timeline. Milestones in fetal development include formation of the corpus callosum at 16 weeks gestation (Richards et al., 2004), eye opening at 24 weeks gestation (Kurjak et al., 2007), establishment of thalamocortical pathways at 26 weeks gestation (Kostović and Judaš, 2010), cortical gyrification at 20 – 28 weeks gestation (Rajagopalan et al., 2011), and default mode network (DMN) synchronization at 37 weeks gestation (Thomason et al., 2015). Note that ages here are given as gestational age, which differs from conceptual age (commonly used in other sources) by two weeks; the former is referenced to the time of last menstruation, while the latter is referenced to the time of fertilization. The timing of other events (neurulation, proliferation, cortical neurogenesis, migration, apoptosis, synaptogenesis, gyrification, and myelination) is from Tau and Peterson (2010) and Keeney et al. (2015). Material for this figure was adapted from public domain and Creative Commons licensed images. Timeline of fetal development was adapted from Häggström (2014). Timeline of sleep development was adapted from Hobson and Friston (2012). Images of the developing embryonic/fetal head/body were adapted from Padilla and Lagercrantz (2020).

density with current technology (Fig. 3B). Thus, the first obstacle toward computing sPCI from perinatal subjects will often be that of spatial resolution. Given that PCI relies on estimating both the temporal *and* spatial complexity of the cortical response to a perturbation after source reconstruction, how much can neural complexity tell us about consciousness if the spatial dimension is excluded? At least in the case of spontaneous (i.e., unperturbed) activity, LZc in adults can be useful for inferring consciousness when only single EEG/MEG channels are considered (Toker et al., 2022; Zhang et al., 2001) or when complexity is averaged across channels (Frohlich et al., 2022a), and so the temporal dimension alone may be useful. However, if one wishes to use spontaneous complexity to infer consciousness, MEG recordings acquired with SARA systems will likely still require further SNR improvements (see Moser et al., 2019) . Additionally, it is dubious whether single channel LZc is appropriate or otherwise sufficient in the context of perturbational complexity, which is conventionally defined as spatiotemporal complexity spanning all cortical recording sites. Thus, developing a suitable complexity metric for sPCI will require an investigation of alternatives to LZc that are applicable to low-density, sensor-space data – some of which are available (e.g., PCIst, see Comolatti et al., 2019).

Additionally, again due to the SNR concerns given above, computing sPCI from such data may require a very large number of ERP/ERF trials to increase the SNR of the recorded brain signals by averaging over many trials, thereby decreasing the presence of non-time-locked, environmental noise. Even without trial-averaging, signals recorded during sensory stimulation may be more informative for inferring consciousness than the entropy of spontaneous signals, at least using current fetal MEG approaches. For example, Moser et al. (2019) showed that, in fetuses, two separate measures of cortical complexity varied from control channels when applied to MEG signals recorded during auditory stimulation without trial averaging, while this difference was not seen for spontaneous signals. Overall, future research will need to explore both experimental and computational methods to extract event-related responses from low-SNR signals.

5.3. Future and ongoing studies

Even if a common algorithm such as PCIst can be used, there are many differences in the experimental methods of PCI and sPCI, including sensory versus magnetic stimulation and adult versus perinatal subjects (infants or fetuses). Additionally, sPCI allows cortical responses to perturbations to be recorded using MEG, whereas the conventional PCI approach is limited to EEG. A successful validation strategy will involve progressively changing each element (perturbation method, data acquisition method, and target population) that differs between PCI and sPCI.

5.3.1. Validating sPCI

The first stage of validation should involve studies in adults, contrasting data from conscious wakefulness to states of low or no consciousness (e.g., NREM sleep or general anesthesia). These initial studies should also compare sPCI values derived from auditory and visual perturbations to determine which modality of stimulation yields the best performance (Table 2). Although it is unclear, at present, whether sensory perturbations will meet the extremely high accuracy (Casarotto et al., 2016) of TMS-based PCI for differentiating consciousness from unconsciousness, sPCI must show sufficient specificity to consciousness in order to pass this stage of validation. In this regard, a reasonable goal would be to compare sPCI head-to-head with conventional sensory ERP measures used to estimate consciousness, e.g., a P3b global (Bekinschtein et al., 2009). If the LZc of sensory evoked potentials is more specific to consciousness than other neural measures, then sPCI should proceed to the next stage of validation. As stated earlier, the goal of this initial validation study is not to meet or exceed the performance of TMS-based PCI, yet it may nonetheless be useful to also compare sensory perturbations to TMS perturbations as a reference in the same subjects. For this reason, cortical signals should first be recorded using EEG rather than MEG for compatibility with TMS. However, follow up experiments may then be necessary to confirm that sensory perturbations yield similar results in adults when cortical responses are recorded with MEG as

Table 2
Stages of development for validating the sPCI as a measure of consciousness. NREM = non-rapid eye movement; sPCI = sensory perturbational complexity index. TMS = transcranial magnetic stimulation.

Stage	Stage 1: Adults	Stage 2: Children	Stage 3: Infants
Perturbation modality	Visual (light flashes) Auditory (simple tones) Auditory (prediction errors) Magnetic (TMS)	Visual (light flashes) Auditory (simple tones) Auditory (prediction errors)	Visual or auditory (auditory prediction errors preferred)
Cortical signals	EEG (for compatibility with TMS)	EEG or MEG	EEG or MEG
State comparisons	Wakefulness vs. NREM sleep Wakefulness vs general anesthesia	Wakefulness vs. NREM sleep	Wakefulness vs. quiet sleep

opposed to EEG, as the former is sensitive to tangential sources in sulcal walls, whereas the latter is sensitive to radial sources atop cortical gyri (Fuchs et al., 2017).

Should such an experiment successfully validate one or both sensory modalities in adults, the next step would be to also validate sPCI in young children who are old enough to self-report their conscious experience. At this stage, data may be acquired using either EEG or MEG. If both visual and auditory modalities perform equally well in adults, auditory stimulation is likely preferable, as it can be easily delivered using earphones, whereas bright light flashes must be delivered through closed eyelids and may thus cause flinching, leading to discomfort and muscle artifacts. TMS perturbations are likely unnecessary and possibly unethical at this stage of validation, given that we do not expect that sensory perturbations can or should fully match the performance of TMS perturbations. A number of prior studies have already measured EEG responses to TMS in children (Kallioniemi et al., 2022), but in contexts unconcerned with PCI or consciousness. Although two such studies did report on the "complexity" of TMS evoked potentials in children (Määttä et al., 2019, 2017), the authors apparently defined complexity informally, e.g., based on the number of peaks in the TMS evoked potential, rather than using formal measures such as entropy or LZc. Furthermore, while one large sample, single site study concluded that MRI-guided TMS is safe overall in clinical pediatric populations (Braden et al., 2022), administering TMS to children who do not directly benefit from such stimulation may still be ethically ill-advised, as adverse events do occasionally occur during TMS sessions with children (Braden et al., 2022), a risk which is unlikely to be acceptable when TMS has no direct benefit for the child. Furthermore, while the above study was conducted as a retrospective chart review, a longitudinal study is likely needed to rule out long-term developmental effects of TMS in young children. As such, validation efforts in children should only use sPCI without a TMS-based comparison. Consequently, cortical signals could be recorded using either EEG or MEG at this stage of validation. Furthermore, unlike validation studies in adults, unconsciousness—or at least, diminished consciousness (see Nilsen et al., 2022)—in children will only be induced by natural means (i.e., NREM sleep) for obvious ethical reasons, unless pediatric patients undergoing general anesthesia for medically necessary surgery could also be recruited.

Ultimately, once sPCI has been shown to accurately discriminate consciousness from unconsciousness in children, a threshold sPCI value separating consciousness from unconsciousness may be determined. By extrapolation, this threshold could then be applied to perinatal populations to infer consciousness in infants. Indeed, the ultimate goal of sPCI is application to infant subjects (Table 2). Here, as in the last stage of validation, data may be acquired using either EEG or MEG. Although the state of consciousness during infant wakefulness is uncertain, one might anticipate that sPCI would stratify infants according to whether signals were recorded during wakefulness (presumably high sPCI), quiet sleep (analogous to NREM sleep, with presumably low sPCI), or active sleep (analogous to REM sleep, with presumably intermediate sPCI). A negative finding at this stage of development would be difficult to interpret, either indicating that sPCI lacks sensitivity to conscious state in infants or that consciousness does not meaningfully vary in infancy between these states. In this event, and as a last resort, studies could also recruit infants undergoing general anesthesia for medically necessary surgery, as in the childhood stage of validation. Once sPCI has been validated in infants, it could then also be applied to fetuses using MEG, though interpreting PCI values in fetuses would likely be even more difficult than doing so in infants because fetuses depart even more from the population used in the prior stage of validation (children) and, moreover, due to the difficulty of ground-truthing in fetuses (see Section 7. "Conclusions" below). As such, this is beyond the scope of the current discussion. Finally, a significant challenge for progressing from one stage of validation to the next is the fact that PCI may be influenced by factors unrelated to consciousness which change with development. This precludes the use of a fixed threshold boundary value of PCI that would separate consciousness from unconsciousness across all developmental stages.

5.3.2. *Current work*

Our research group recently conducted an analysis of auditory evoked fields in fetuses and newborns inspired by PCI (Frohlich et al., 2022b). As we have advocated for here, our study examined cortical entropy in response to auditory irregularities in a large sample of more than 40 unique fetal subjects—many with multiple recordings—and 20 newborn subjects, with all data recorded using the SARA system at the Tuebingen fMEG Center. We used these data to test the hypothesis that cortical entropy would increase as the capacity for consciousness increases in early development. Although this analysis came very close to computing the sPCI measure we have outlined in this manuscript, two subtle differences should be noted: 1) we performed spatial averaging of MEG signals acquired with SARA systems to overcome SNR limitations and, as such, we do not regard our entropy computations as true measurements of sPCI since there was no spatial dimension to these data and 2) although we examined LZc (the compression algorithm used in the original PCI, Casali et al., 2013), our strongest finding was obtained using the permutation entropy of 4 – 10 Hz signals.

Indeed, a crucial issue revealed by the above study is whether cortical responses to sensory irregularities will behave the same as cortical responses to TMS—will their complexity increase during consciousness, or might they instead decrease? In the above study (Frohlich et al., 2022b), we attempted to resolve this issue using an entropy decomposition which disentangles the effects of signal amplitude, phase, and their interaction (Mediano et al., 2020). Elsewhere, we have shown that changes in EEG entropy between wakefulness and NREM sleep are driven by non-amplitude factors (signal phase and its interaction with amplitude) in children with Angelman syndrome (Frohlich et al., 2022a). Similarly, in our MEG study of fetuses and infants, we indeed found that changes in non-amplitude factors drove increases in permutation entropy with maturation, suggesting that the emergence of con-

sciousness with maturation is the ultimate driver of this particular entropy increase. However, changes in signal amplitude with maturation drove decreases in permutation entropy, suggesting that the maturation of ERFs may mask the possible influence of consciousness which is mediated by non-amplitude factors. Indeed, the classic P300 response in adults is longer and relatively homogeneous across the scalp (Jean-Remi King et al., 2013; Ragazzoni et al., 2019) compared with TMS-evoked potentials (Sulcova et al., 2022), which might mean that sPCI will behave quite differently from TMS-based PCI, e.g., requiring an algorithm that disentangles phasic effects from those of amplitude.

Finally, there has been only one pilot study of sPCI in adults to date that we are aware of (DallaVecchia et al., 2021), which investigated three different PCI algorithms in 21 healthy young participants during a low arousal state (eye closed) versus a high arousal state (eyes open) using two types of stimulation (somatosensory and auditory; although the former used median nerve stimulation that would not be suitable for infants or fetuses). Auditory perturbations (1000 Hz tones) could successfully distinguish between states using one of the algorithms, and somatosensory perturbations appeared to be slightly more useful than auditory perturbations, as they could distinguish between states using two different algorithms. A shortcoming of this pilot study is that it did not examine large changes in conscious state, but rather compared two conscious states that varied in the level of visual content and arousal, so it remains possible that auditory perturbations are equally or perhaps even more useful than somatosensory perturbations when distinguishing wakefulness from states of low (Nilsen et al., 2022) or no consciousness (e.g., NREM sleep).

While it remains unknown whether sensory stimulation produces a sufficiently large cortical perturbation to reliably approximate perturbational complexity measures of consciousness in infants, we believe the sPCI approach is a promising option for developing a measure of infant consciousness (Fig. 4F). Experimentally, to ensure a sufficiently large cortical perturbation with a high SNR, the sPCI could use a large number of deviant trials that generate Bayesian prediction errors.

6. An alternative perturbational complexity approach using fMRI

Any measure of perturbational complexity should account for both temporal and spatial entropy, yet, as discussed in Section 5.2, estimation of spatial complexity from MEG recorded using a SARA device is highly challenging. Recordings with EEG (Johnson et al., 2001) or dedicated infant MEG systems (Okada et al., 2016) may offer some improvement. However, to obtain optimal spatial resolution, fMRI is required. Although the most common protocols for fMRI in infants require the infant to sleep in the scanner to minimize movement (Ellis and Turk-Browne, 2018), thus presenting the infant subject when consciousness might vanish during quiet/NREM sleep, protocols for awake infant fMRI have also been successfully implemented (Yates et al., 2021), and one fMRI study to date has investigated awake newborns at 7 weeks of age (Biagi et al., 2015). Thus, states of infant wakefulness, active/REM sleep (abundant in infants, see Fig. 5), and quiet/NREM sleep can all be studied using fMRI. Furthermore, as mentioned in Section 3, fetal fMRI is also feasible and offers useful clues regarding perinatal consciousness.

Whereas MEG and EEG are challenged by their low spatial resolution, fMRI is limited by its low temporal resolution. Both scanning speed and the hemodynamic response function (HRF) generally limit the temporal resolution of fMRI to > 0.5 s. Furthermore, given the loud environment in the MRI scanner, paradigms that rely on auditory stimulation (e.g., the auditory oddball paradigm) are not an optimal choice. Both of these limitations (temporal resolution and loud environment) might be addressed by using olfactory perturbations in place of auditory perturbations, as the cortical response to olfactory stimuli is much slower, starting only after a few seconds and lasting around 10 s (Georgiopoulos et al., 2018).

Perhaps as much or even more so than other sensory modalities, olfaction is of crucial importance to the survival of a neonate, who must use to smell to recognize kin and breastfeed immediately after birth (Schaal et al., 2020). As such, olfaction is likely to be a strong modality for perturbing the infant nervous system. Human olfaction is unique compared to the other major senses. The majority of olfactory information never passes through the thalamus. In fact, the primary (direct) pathway sends afferents directly from the olfactory bulb to the orbitofrontal cortex via the olfactory piriform cortex bypassing the thalamus (Tham et al., 2009). A minor indirect pathway first passes from the olfactory piriform cortex to the thalamus before reaching the cortex (Nevelle and Haberly, 2004). Thus, sensory information is first processed in the paleocortex and then in the neocortex. Despite these differences with other sensory modalities, for olfactory content to become conscious, it requires a large-scale network that facilitates information integration (Merrick et al., 2014) which makes it a viable candidate for sPCI. Additionally, studies in the context of recovery from unresponsive wakefulness syndrome (also known as the vegetative state) after severe brain injury have shown that olfactory stimulation can be used to detect consciousness (Arzi et al., 2020). Finally, a recent study demonstrated that chemosensory stimuli delivered to pregnant women influence fetal arousal and behaviors and might, in principle, also serve as useful perturbations to study the fetal brain. Chemosensory stimuli were delivered to pregnant women and influenced subsequent facial movements in fetuses as measured with 4D ultrasonography (Ustun et al., 2022). Although pregnant women in this study were given flavor capsules with shells that took time to first dissolve in the small intestine before a fetal response could be observed, odorant stimuli should reach the placenta faster for a much more immediate effect.

For the above reasons, we suggest that olfactory stimulation would be well suited for the unique challenges of fMRI in the context of perturbational complexity. Although the onset of an olfactory stimulus is difficult to time precisely as it is influenced by factors such as inhalation, air diffusion, and, in the case of fetuses, placental transfer, that are difficult or impossible to fully control, the margin of uncertainty in stimulus onset timing is much more compatible with the low temporal resolution of fMRI than with the high temporal resolution of MEG or EEG. In fact, olfactory stimulation has successfully been implemented in numerous fMRI studies (Van Regemorter et al., 2022). Thus, with fMRI, one might deliver odors using a block design, e.g., one odor stimulus per 6–10 s block with a TR below 1 s which has been shown to result in the strongest responses across the brain and avoid issues with habituation (Georgiopoulos et al., 2018). One would then compute the spatiotemporal entropy of the block-averaged global cortical response from the infant or fetus as an approximation of perturbational complexity. It is uncertain, however, how many blocks are needed to compute this approximation and whether such a design would benefit from interleaved "deviant" blocks (as in a local-global paradigm) containing new odors that might generate Bayesian prediction errors.

We believe this "sniff and zip" approach is feasible with the modest temporal resolution afforded by fMRI. As an encouraging precedent, analyses of spontaneous resting-state fMRI activity in adults consistently show decreased BOLD signal complexity during unconsciousness, both when measured as LZc, as in the original PCI algorithm (Mediano et al., 2021; Varley et al., 2020), and when measured using the sample entropy algorithm (Luppi et al., 2019), suggesting that the complexity of sensory-evoked fMRI BOLD responses will also be valuable for inferring the presence or absence of consciousness. Furthermore, standard fMRI sequences that increase the temporal resolution to around 0.5 s have already been validated (e.g., the Human Connectome Project sequence with a TR of 547 ms using multiband acquisition in which the signal of 8 slices are acquired simultaneously;Risk et al., 2021). Recent developments have further pushed these limits to a temporal resolution within the range of milliseconds, as demonstrated by the novel scanning technique known as direct imaging of neuronal activity (DIANA) which features millisecond temporal resolution and sub-millimeter spatial resolution (Toi et al., 2022). Although it has been developed for a small animal scanner, DIANA could potentially revolutionize perinatal

imaging. However, because high field strengths are required for DIANA, safety considerations would most likely make this approach infeasible for perinatal imaging in the near future due to the risk of tissue heating in newborns and fetuses (van den Heuvel and Thomason, 2016).

7. Conclusions

Combined with sensory stimulation, MEG, EEG, and fMRI offer paths forward toward "quantifying the unquantifiable" in early development, as the original PCI technique using TMS-EEG has been described in adults (Casali et al., 2013). Nevertheless, inferences of consciousness in early human development face the difficult challenge that investigators do not have access to the ground truth. This is a crucial distinction between inferences of perinatal consciousness, which cannot be confirmed by verbal or behavioral reports, and inferences of consciousness in unresponsive adult patients with severe brain injuries, who might later recall having visited the laboratory after regaining communication, thus confirming the inference made by researchers (Frohlich, 2020).

Accepting this challenge, we believe that data from MEG, EEG, and fMRI recordings can be used to test theories of consciousness in the same way that cosmologists use data from the cosmic microwave background to test theories about the origin of the universe (Dicke et al., 1965), which also cannot be viewed or accessed directly. Furthermore, knowledge of developmental neurobiology can be used to constrain estimates of when consciousness first arises—for example, given that most neurobiologists accept the thalamocortical system as critical to conscious awareness (Tononi and Koch, 2008), one cannot reasonably expect consciousness to emerge prior to the establishment of thalamocortical connections at approximately 26 weeks gestation (Kostović and Judaš, 2010). Going forward, we expect that perturbational approaches based on PCI that deploy sensory stimulation instead of electromagnetic stimulation will provide the most promising tools for reliably indexing perinatal consciousness. However, we by no means exclude other approaches, but rather expect sPCI to be only one of several tools that will soon be used for inferring consciousness in infants and perhaps even fetuses.

Data and code availability statement

This is a review manuscript. No data or code were used in this work, with the minor exception of MEG data traces displayed in Fig. 3 and Fig. 4. These data are already publicly available (fetal data: https://zenodo.org/record/4541463#.ZB2chfbMKHu; neonatal data: https://zenodo.org/record/4018827#.ZB2c8fbMKHs).

Declaration of Competing Interest

The authors declare no competing financial interests.

Acknowledgements

We would like to thank Katrin Sippel for creating artwork in Fig. 1 and Fig. 4., and we also thank Yuri G. Pavlov for a useful discussion regarding olfactory stimulation.

We gratefully acknowledge the following funders: 1) the FET Open Luminous project (H2020 FETOPEN-2014–2015-RIA under agreement No. 686764) as part of the European Union's Horizon 2020 research and 2014 – 2018 training program, 2) the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD01GI0925), 3) the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation; 493345456), 4) the Australian Research Council (ARC; DP190101805), 5) the Brain, Mind and Consciousness program of the Canadian Institute for Advanced Research (CIFAR), 6) the Open Access Publishing Fund of the University of Tübingen, and 7) the Tiny Blue Dot Foundation.

References

Abásolo, D., Simons, S., Morgado da Silva, R., Tononi, G., Vyazovskiy, V.V., 2015. Lempel-Ziv complexity of cortical activity during sleep and waking in rats. J. Neurophysiol. 113, 2742–2752.

Abel, S.M., Lam, Q., 2004. Sound attenuation of the indoor/outdoor range EAR plug. Mil. Med 169, 551–555.

Afrasiabi, M., Redinbaugh, M.J., Phillips, J.M., Kambi, N.A., Mohanta, S., Raz, A., Haun, A.M., Saalmann, Y.B., 2021. Consciousness depends on integration between parietal cortex, striatum, and thalamus. Cell. Syst 12, 363–373.

Al Zoubi, O., Misaki, M., Bodurka, J., Kuplicki, R., Wohlrab, C., Schoenhals, W.A., Refai, H.H., Khalsa, S.S., Stein, M.B., Paulus, M.P., Feinstein, J.S., 2021. Taking the body off the mind: decreased functional connectivity between somatomotor and default-mode networks following Floatation-REST. Hum. Brain. Mapp 1–12. doi:10.1002/hbm.25429.

Alkire, M.T., Hudetz, A.G., Tononi, G., 2008. Consciousness and anesthesia. Science 322, 876–880.

Anderson, A.L., Thomason, M.E., 2013. Functional plasticity before the cradle: a review of neural functional imaging in the human fetus. Neurosci. Biobehavl. Rev. 37, 2220–2232.

Arzi, A., Rozenkrantz, L., Gorodisky, L., Rozenkrantz, D., Holtzman, Y., Ravia, A., Bekinschtein, T.A., Galperin, T., Krimchansky, B.-Z., Cohen, G., 2020. Olfactory sniffing signals consciousness in unresponsive patients with brain injuries. Nature 581, 428–433.

Baars, B.J., 2005. Global workspace theory of consciousness: toward a cognitive neuroscience of human experience. Prog. Brain Res. 150, 45–53.

Baars, B.J., 1997. In the theatre of consciousness. Global workspace theory, a rigorous scientific theory of consciousness. J. Consciou. Stud. 4, 292–309.

Bachmann, T., Suzuki, M., Aru, J., 2020. Dendritic integration theory: a thalamo-cortical theory of state and content of consciousness. Philosop. Mind Sci. 1.

Bai, Y., Liang, Z., Li, X., 2015a. A permutation Lempel-Ziv complexity measure for EEG analysis. Biomed. Signal. Process. Control 19, 102–114.

Bai, Y., Liang, Z., Li, X., Voss, L.J., Sleigh, J.W., 2015b. Permutation Lempel–Ziv complexity measure of electroencephalogram in GABAergic anaesthetics. Physiol. Meas 36, 2483.

Baird, B., Tononi, G., LaBerge, S., 2022. Lucid dreaming occurs in activated rapid eye movement sleep, not a mixture of sleep and wakefulness. Sleep.

Baker, P.N., Johnson, I.R., Harvey, P.R., Gowland, P.A., Mansfield, P., 1994. A three-year follow-up of children imaged in utero with echo-planar magnetic resonance. Am. J. Obstet. Gynecol. 170, 32–33.

Barnes, G., Hillebrand, A., Hirata, M., 2010. Magnetoencephalogram. Scholarpedia 5, 3172.

Bekinschtein, T.A., Dehaene, S., Rohaut, B., Tadel, F., Cohen, L., Naccache, L., 2009. Neural signature of the conscious processing of auditory regularities. Proceedings Nat. Acad. Sci. 106, 1672–1677.

Bensaid, S., Modolo, J., Merlet, I., Wendling, F., Benquet, P., 2019. COALIA: a computational model of human EEG for consciousness research. Front. Syst. Neurosci 13, 59.

Bestmann, S., Ruff, C.C., Blankenburg, F., Weiskopf, N., Driver, J., Rothwell, J.C., 2008. Mapping causal interregional influences with concurrent TMS–fMRI. Exp. Brain. Res 191, 383–402.

Biagi, L., Crespi, S.A., Tosetti, M., Morrone, M.C., 2015. BOLD response selective to flow–motion in very young infants. PLoS. Biol. 13, e1002260.

Biomag Central, 2017. Lab and research centers. https://www.biomagcentral.org/networking/labs.html

Blum, T., Saling, E., Bauer, R., 1985. First magnetoencephalographic recordings of the brain activity of a human fetus. BJOG 92, 1224–1229.

Blumberg, M.S., Adolph, K.E., 2023. Protracted development of motor cortex constrains rich interpretations of infant cognition. Trends Cogn. Sci. (Regul. Ed.).

Bodien, Y.G., Chatelle, C., Edlow, B.L., 2017. Functional Networks in Disorders of consciousness. Presented at the Seminars in Neurology. Thieme Medical Publishers, pp. 485–502.

Bodien, Y.G., Threlkeld, Z.D., Edlow, B.L., 2019. Default mode network dynamics in covert consciousness. Cortex 119, 571.

Boly, M., Massimini, M., Tsuchiya, N., Postle, B.R., Koch, C., Tononi, G., 2017. Are the neural correlates of consciousness in the front or in the back of the cerebral cortex? Clinical and neuroimaging evidence. J. Neurosci. 37, 9603–9613.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T.T., Moonen, G., Hustinx, R., Maquet, P., Laureys, S., 2008. Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? Ann. N. Y. Acad. Sci. 1129, 119–129.

Bourdillon, P., Hermann, B., Guénot, M., Bastuji, H., Isnard, J., King, J.-R., Sitt, J., Naccache, L., 2020. Brain-scale cortico-cortical functional connectivity in the delta-theta band is a robust signature of conscious states: an intracranial and scalp EEG study. Sci. Rep 10, 1–13.

Braden, A.A., Weatherspoon, S.E., Boardman, T., Williard, T., Adkins, A., Gibbs, S.K., Wheless, J.W., Narayana, S., 2022. Image-guided TMS is safe in a predominately pediatric clinical population. Clin. Neurophysiol. 137, 193–206.

Brookes, M.J., Leggett, J., Rea, M., Hill, R.M., Holmes, N., Boto, E., Bowtell, R., 2022. Magnetoencephalography with optically pumped magnetometers (OPM-MEG): the next generation of functional neuroimaging. Trends Neurosci..

Brown, R., Lau, H., LeDoux, J.E., 2019. Understanding the higher-order approach to consciousness. Trends Cogn. Sci. (Regul. Ed.) 23, 754–768.

Carhart-Harris, R.L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., Tagliazucchi, E., Schenberg, E.E., Nest, T., Orban, C., 2016. Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proceedings Nat. Acad. Sci. 113, 4853–4858.

Casali, A.G., Gosseries, O., Rosanova, M., Boly, M., Sarasso, S., Casali, K.R., Casarotto, S., Bruno, M.-.A., Laureys, S., Tononi, G., 2013. A theoretically based index of consciousness independent of sensory processing and behavior. Sci. Transl. Med 5 198ra105-198ra105.

Casarotto, S., Comanducci, A., Rosanova, M., Sarasso, S., Fecchio, M., Napolitani, M., Pigorini, A., .G, Casali, A., Trimarchi, P.D., Boly, M., 2016. Stratification of unresponsive patients by an independently validated index of brain complexity. Ann. Neurol. 80, 718–729.

Cavinato, M., Rigon, J., Volpato, C., Semenza, C., Piccione, F., 2012. Preservation of auditory P300-like potentials in cortical deafness. PLoS. ONE 7, e29909.

Chennu, S., Finoia, P., Kamau, E., Allanson, J., Williams, G.B., Monti, M.M., Noreika, V., Arnatkeviciute, A., Canales-Johnson, A., Olivares, F., 2014. Spectral signatures of reorganised brain networks in disorders of consciousness. PLoS. Comput. Biol. 10, e1003887.

Ciaunica, A., Safron, A., Delafield-Butt, J., 2021. Back to square one: the bodily roots of conscious experiences in early life. Neurosci. Conscious. 2021, niab037.

Colombo, M.A., Napolitani, M., Boly, M., Gosseries, O., Casarotto, S., Rosanova, M., Brichant, J.-.F., Boveroux, P., Rex, S., Laureys, S., 2019. The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine. Neuroimage 189, 631–644.

Comolatti, R., Pigorini, A., Casarotto, S., Fecchio, M., Faria, G., Sarasso, S., Rosanova, M., Gosseries, O., Boly, M., Bodart, O., 2019. A fast and general method to empirically estimate the complexity of brain responses to transcranial and intracranial stimulations. Brain. Stimul 12, 1280–1289.

Cover, T.M., Thomas, J.A., 2012. Elements of Information Theory. John Wiley & Sons.

Crone, J.S., Ladurner, G., Höller, Y., Golaszewski, S., Trinka, E., Kronbichler, M., 2011. Deactivation of the default mode network as a marker of impaired consciousness: an fMRI study. PLoS. ONE 6, e26373.

Crone, J.S., Schurz, M., Höller, Y., Bergmann, J., Monti, M., Schmid, E., Trinka, E., Kronbichler, M., 2015. Impaired consciousness is linked to changes in effective connectivity of the posterior cingulate cortex within the default mode network. Neuroimage 110, 101–109.

Dallavecchia, A., Micheli, F., Toker, D., Frohlich, J., Monti, M., 2021. Quantifying changes in complexity of the event related response to sensory stimuli in different states of arousal. In: SfN Global Connectome. Presented at the Society for Neuroscience. Virtual Conference.

Darmani, G., Nieminen, J., Bergmann, T., Ramezanpour, H., Ziemann, U., 2021. A degraded state of consciousness in healthy awake humans? Brain Stimul. 14, 710–712.

Davidson, A.J., 2011. Anesthesia and neurotoxicity to the developing brain: the clinical relevance. Pediatr. Anesth. 21, 716–721.

Dehaene, S., Changeux, J.-.P., 2011. Experimental and theoretical approaches to conscious processing. Neuron 70, 200–227.

Dehaene, S., Kerszberg, M., Changeux, J.-.P., 1998. A neuronal model of a global workspace in effortful cognitive tasks. Proceedings Nat. Acad. Sci. 95, 14529–14534.

Dembski, C., Koch, C., Pitts, M., 2021. Perceptual awareness negativity: a physiological correlate of sensory consciousness. Trends Cogn. Sci. (Regul. Ed.) 25, 660–670.

Deshpande, G., Kerssens, C., Sebel, P.S., Hu, X., 2010. Altered local coherence in the default mode network due to sevoflurane anesthesia. Brain Res. 1318, 110–121.

Dicke, R.H., Peebles, P.J.E., Roll, P.G., Wilkinson, D.T., 1965. Cosmic black-body radiation. Astrophys. J. 142, 414–419.

Dolan, D., Jensen, H.J., Mediano, P.A., Molina-Solana, M., Rajpal, H., Rosas, F., Sloboda, J.A., 2018. The improvisational state of mind: a multidisciplinary study of an improvisatory approach to classical music repertoire performance. Front. Psychol. 9, 1341.

Doradzińska, Ł., Wójcik, M.J., Paź, M., Nowicka, M.M., Nowicka, A., Bola, M., 2020. Unconscious perception of one's own name modulates amplitude of the P3B ERP component. Neuropsychologia 147, 107564.

Draganova, R., Eswaran, H., Murphy, P., Huotilainen, M., Lowery, C., Preissl, H., 2005. Sound frequency change detection in fetuses and newborns, a magnetoencephalographic study. Neuroimage 28, 354–361.

Draganova, R., Eswaran, H., Murphy, P., Lowery, C., Preissl, H., 2007. Serial magnetoencephalographic study of fetal and newborn auditory discriminative evoked responses. Early Hum. Dev. 83, 199–207.

Ellis, C.T., Turk-Browne, N.B., 2018. Infant fMRI: a model system for cognitive neuroscience. Trends Cogn. Sci. (Regul. Ed.) 22, 375–387.

Emberson, L.L., Richards, J.E., Aslin, R.N., 2015. Top-down modulation in the infant brain: learning-induced expectations rapidly affect the sensory cortex at 6 months. Proceedings Nat. Acad. Sci. 112, 9585–9590.

Engemann, D.A., Raimondo, F., King, J.-.R., Rohaut, B., Louppe, G., Faugeras, F., Annen, J., Cassol, H., Gosseries, O., Fernandez-Slezak, D., 2018. Robust EEG-based cross-site and cross-protocol classification of states of consciousness. Brain 141, 3179–3192.

Escalona-Vargas, D., Bolin, E.H., Lowery, C.L., Siegel, E.R., Eswaran, H., 2020. Recording and quantifying fetal magnetocardiography signals using a flexible array of optically-pumped magnetometers. Physiol. Meas 41, 125003.

Farnes, N., Juel, B.E., Nilsen, A.S., Romundstad, L.G., Storm, J.F., 2020. Increased signal diversity/complexity of spontaneous EEG, but not evoked EEG responses, in ketamine-induced psychedelic state in humans. PLoS. ONE 15, e0242056.

Faugeras, F., Rohaut, B., Weiss, N., Bekinschtein, T., Galanaud, D., Puybasset, L., Bolgert, F., Sergent, C., Cohen, L., Dehaene, S., 2012. Event related potentials elicited by violations of auditory regularities in patients with impaired consciousness. Neuropsychologia 50, 403–418.

Fleming, S.M., 2020. Awareness as inference in a higher-order state space. Neurosci. Conscious. 2020, niz020.

Friston, K.J., 2019. Waves of prediction. PLoS. Biol. 17, e3000426.

Frohlich, J., 2020. Frames of consciousness: an interview with Martin Monti and Adrian Owen. Knowing neurons. URL https://knowingneurons.com/2020/08/01/frames-of-consciousness/ (accessed 3.25.21).

Frohlich, J., Chiang, J.N., Mediano, P.A., Nespeca, M., Saravanapandian, V., Toker, D., Dell'Italia, J., Hipp, J.F., Jeste, S.S., Chu, C.J., 2022a. Neural complexity is a common denominator of human consciousness across diverse regimes of cortical dynamics. Commun. Biol. 5, 1–17. doi:10.1038/s42003-022-04331-7.

Frohlich, J., Moser, J., Mediano, P.A., Preissl, H., Gharabaghi, A., 2022b. The complexity of event-related MEG signals decreases with maturation in human fetuses and newborns. bioRxiv doi:10.1101/2022.11.21.517302.

Frohlich, J., Toker, D., Monti, M.M., 2021. Consciousness among delta waves: a paradox? Brain 144, 2257–2277.

Fuchs, M., Kastner, J., Tech, R., Wagner, M., Gasca, F., 2017. MEG and EEG dipole clusters from extended cortical sources. Biomed. Eng. Lett. 7, 185–191.

Fuller, P., Sherman, D., Pedersen, N.P., Saper, C.B., Lu, J., 2011. Reassessment of the structural basis of the ascending arousal system. J. Comp. Neurol. 519, 933–956.

Gao, W., Zhu, H., Giovanello, K.S., Smith, J.K., Shen, D., Gilmore, J.H., Lin, W., 2009. Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. Proceedings Nat. Acad. Sci. 106, 6790–6795.

Garrido, M.I., Kilner, J.M., Stephan, K.E., Friston, K.J., 2009. The mismatch negativity: a review of underlying mechanisms. Clin. Neurophysiol. 120, 453–463.

Gell-Mann, M., Lloyd, S., 1996. Information measures, effective complexity, and total information. Complexity 2, 44–52.

Georgiopoulos, C., Witt, S.T., Haller, S., Dizdar, N., Zachrisson, H., Engström, M., Larsson, E.-.M., 2018. Olfactory fMRI: implications of stimulation length and repetition time. Chem. Senses 43, 389–398.

Gerhardt, K.J., Abrams, R.M., Oliver, C.C., 1990. Sound environment of the fetal sheep. Am. J. Obstet. Gynecol. 162, 282–287.

Goksan, S., Hartley, C., Emery, F., Cockrill, N., Poorun, R., Moultrie, F., Rogers, R., Campbell, J., Sanders, M., Adams, E., 2015. fMRI reveals neural activity overlap between adult and infant pain. Elife 4, e06356.

Greely, H.T., 2021. Human brain surrogates research: the onrushing ethical dilemma. Am. J. Bioeth. 21, 34–45.

Haggstrom, M., 2014. Medical gallery of mikael haggstrom 2014. WikiJ. Med. 1, 1–53.

Haran, B., 2022. New Way to Scan Brains - Sixty Symbols, Sixty Symbols. University of Nottingham.

Hobson, J.A., Friston, K.J., 2012. Waking and dreaming consciousness: neurobiological and functional considerations. Prog. Neurobiol. 98, 82–98.

Hu, H., Cusack, R., Naci, L., 2022. Typical and disrupted brain circuitry for conscious awareness in full-term and preterm infants. Brain Commun. 4, fcac071.

Huang, Z., Wang, Q., Zhou, S., Tang, C., Yi, F., Nie, J., 2020. Exploring functional brain activity in neonates: a resting-state fMRI study. Dev. Cogn. Neurosci 45, 100850.

Hudetz, A.G., Liu, X., Pillay, S., Boly, M., Tononi, G., 2016. Propofol anesthesia reduces Lempel-Ziv complexity of spontaneous brain activity in rats. Neurosci. Lett. 628, 132–135.

Isler, J.R., Stark, R.I., Grieve, P.G., Welch, M.G., Myers, M.M., 2018. Integrated information in the EEG of preterm infants increases with family nurture intervention, age, and conscious state. PLoS. ONE 13, e0206237.

Janjarasjitt, S., Scher, M., Loparo, K., 2008. Nonlinear dynamical analysis of the neonatal EEG time series: the relationship between sleep state and complexity. Clin. Neurophysiol. 119, 1812–1823.

Jelacic, S., de Regt, D., Weinberger, E., 2006. Interactive digital MR atlas of the pediatric brain. Radiographics 26, 497–501.

Johnson, M.H., de Haan, M., Oliver, A., Smith, W., Hatzakis, H., Tucker, L.A., Csibra, G., 2001. Recording and analyzing high-density event-related potentials with infants using the Geodesic Sensor Net. Dev. Neuropsychol 19, 295–323.

Kallioniemi, E., Saari, J., Ferreri, F., Määttä, S., 2022. TMS-EEG responses across the lifespan: measurement, methods for characterisation and identified responses. J. Neurosci. Methods 366, 109430.

Keeney, J., Davis, J., Siegenthaler, J., Post, M., Nielsen, B., Hopkins, W.D., Sikela, J., 2015. DUF1220 protein domains drive proliferation in human neural stem cells and are associated with increased cortical volume in anthropoid primates. Brain Struc. Func. 220, 3053–3060.

Keune, J., Eswaran, H., Preissl, H., 2019. Fetal Magnetoencephalography (fMEG). Magnetoencephalography 661–676.

King, Jean-Remi, Faugeras, F., Gramfort, A., Schurger, A., El Karoui, I., Sitt, J.D., Rohaut, B., Wacongne, C., Labyt, E., Bekinschtein, T., 2013a. Single-trial decoding of auditory novelty responses facilitates the detection of residual consciousness. Neuroimage 83, 726–738.

King, Jean-Rémi, Sitt, J.D., Faugeras, F., Rohaut, B., El Karoui, I., Cohen, L., Naccache, L., Dehaene, S., 2013b. Information sharing in the brain indexes consciousness in noncommunicative patients. Current. Biol. 23, 1914–1919.

Koch, C., 2019. The Feeling of Life Itself: Why Consciousness is Widespread But Can't be Computed. Mit Press.

Koch, C., Massimini, M., Boly, M., Tononi, G., 2016. Neural correlates of consciousness: progress and problems. Nat. Rev. Neurosci. 17, 307.

Kok, R.D., de Vries, M.M., Heerschap, A., van den Berg, P.P., 2004. Absence of harmful effects of magnetic resonance exposure at 1.5 T in utero during the third trimester of pregnancy: a follow-up study. Magn. Reson. Imaging 22, 851–854.

Kostović, I., Judaš, M., 2010. The development of the subplate and thalamocortical connections in the human foetal brain. Acta. Paediatr 99, 1119–1127.

Kurjak, A., Azumendi, G., Andonotopo, W., Salihagic-Kadic, A., 2007. Three-and four-dimensional ultrasonography for the structural and functional evaluation of the fetal face. Am. J. Obstet. Gynecol. 196, 16–28.

Lagercrantz, H., 2009. The birth of consciousness. Early Hum. Dev. 85, S57–S58.

Lagercrantz, H., Changeux, J.-.P., 2009. The emergence of human consciousness: from fetal to neonatal life. Pediatr. Res. 65, 255–260.

Lamme, V.A., 2018. Challenges for theories of consciousness: seeing or knowing, the missing ingredient and how to deal with panpsychism. Biol. Sci. 373, 20170344.
Lamme, V.A., 2006. Towards a true neural stance on consciousness. Trends Cogn. Sci. (Regul. Ed.) 10, 494–501.
Lau, H., 2019. Consciousness, metacognition, & perceptual reality monitoring.
Lavazza, A., 2021. 'Consciousnessoids': clues and insights from human cerebral organoids for the study of consciousness. Neurosci. Conscious. 2021, niab029.
Lempel, A., Ziv, J., 1976. On the complexity of finite sequences. IEEE. Transac. Inform. Theory 22, 75–81.
Li, X., Cui, S., Voss, L.J., 2008. Using permutation entropy to measure the electroencephalographic effects of sevoflurane. J. Am. Soc. Anesthesiol. 109, 448–456.
Logan, S., Arzua, T., Yan, Y., Jiang, C., Liu, X., Yu, L.-.K., Liu, Q.-.S., Bai, X., 2020. Dynamic characterization of structural, molecular, and electrophysiological phenotypes of human-induced pluripotent stem cell-derived cerebral organoids, and comparison with fetal and adult gene profiles. Cells 9, 1301.
Luppi, A.I., Craig, M.M., Pappas, I., Finoia, P., Williams, G.B., Allanson, J., Pickard, J.D., Owen, A.M., Naci, L., Menon, D.K., 2019. Consciousness-specific dynamic interactions of brain integration and functional diversity. Nat. Commun 10, 1–12.
Luppi, A.I., Mediano, P.A., Rosas, F.E., Allanson, J., Pickard, J.D., Carhart-Harris, R.L., Williams, G.B., Craig, M.M., Finoia, P., Owen, A.M., 2020. A synergistic workspace for human consciousness revealed by integrated information decomposition. BioRxiv.
Lutkenhoff, E.S., Nigri, A., Sebastiano, D.R., Sattin, D., Visani, E., Rosazza, C., D'Incerti, L., Bruzzone, M.G., Franceschetti, S., Leonardi, M., Ferraro, Stefania, Monti, Martin M., 2020. EEG power spectra and subcortical pathology in chronic disorders of consciousness. Psychol. Med. 1–10.
Määttä, S., Könönen, M., Kallioniemi, E., Lakka, T., Lintu, N., Lindi, V., Ferreri, F., Ponzo, D., Säisänen, L., 2017. Development of cortical motor circuits between childhood and adulthood: a navigated TMS-HdEEG study. Hum. Brain. Mapp. 38, 2599–2615.
Määttä, S., Säisänen, L., Kallioniemi, E., Lakka, T.A., Lintu, N., Haapala, E.A., Koskenkorva, P., Niskanen, E., Ferreri, F., Könönen, M., 2019. Maturation changes the excitability and effective connectivity of the frontal lobe: a developmental TMS–EEG study. Hum. Brain. Mapp. 40, 2320–2335.
Mahmoudzadeh, M., Wallois, F., Kongolo, G., Goudjil, S., Dehaene-Lambertz, G., 2017. Functional maps at the onset of auditory inputs in very early preterm human neonates. Cerebral. Cortex 27, 2500–2512.
Marchi, F., Hohwy, J., 2020. The intermediate scope of consciousness in the predictive mind. Erkenntnis 1–22.
Mashour, G.A., Alkire, M.T., 2013. Consciousness, anesthesia, and the thalamocortical system. J. Am. Soc. Anesthesiol. 118, 13–15.
Mashour, G.A., Roelfsema, P., Changeux, J.-.P., Dehaene, S., 2020. Conscious processing and the global neuronal workspace hypothesis. Neuron 105, 776–798.
Mateos, D., Erra, R.G., Wennberg, R., Velazquez, J.P., 2018. Measures of entropy and complexity in altered states of consciousness. Cogn. Neurodyn. 12, 73–84.
McIsaac, H., Polich, J., 1992. Comparison of infant and adult P300 from auditory stimuli. J. Exp. Child. Psychol 53, 115–128.
Mediano, P., Ikkala, A., Kievit, R.A., Jagannathan, S.R., Varley, T.F., Stamatakis, E.A., Bekinschtein, T.A., Bor, D., 2021. Fluctuations in neural complexity during wakefulness relate to conscious level and cognition. BioRxiv.
Mediano, P.A., Rosas, F.E., Barrett, A.B., Bor, D., 2020. arXiv preprint.
Mediano, P.A., Rosas, F.E., Bor, D., Seth, A.K., Barrett, A.B., 2022. The strength of weak integrated information theory. Trends Cogn. Sci. (Regul. Ed.).
Mellor, D.J., Diesch, T.J., Gunn, A.J., Bennet, L., 2005. The importance of 'awareness' for understanding fetal pain. Brain Res. Rev. 49, 455–471.
Memar, K., 2019. Use of Multiscale Entropy to Characterize Fetal Autonomic Development.
Merrick, C., Godwin, C.A., Geisler, M.W., Morsella, E., 2014. The olfactory system as the gateway to the neural correlates of consciousness. Front. Psychol. 4, 1011.
Monti, M.M., Vanhaudenhuyse, A., Coleman, M.R., Boly, M., Pickard, J.D., Tshibanda, L., Owen, A.M., Laureys, S., 2010. Willful modulation of brain activity in disorders of consciousness. New Eng. J. Med. 362, 579–589.
Moser, J., Bensaid, S., Kroupi, E., Schleger, F., Wendling, F., Ruffini, G., Preißl, H., 2019. Evaluating Complexity of Fetal MEG Signals: a Comparison of Different Metrics and Their Applicability. Front. Syst. Neurosci 13, 23.
Moser, J., Schleger, F., Weiss, M., Sippel, K., Dehaene-Lambertz, G., Preissl, H., 2020. Magnetoencephalographic signatures of hierarchical rule learning in newborns. Dev. Cogn. Neurosci 46, 100871.
Moser, J., Schleger, F., Weiss, M., Sippel, K., Semeia, L., Preissl, H., 2021. Magnetoencephalographic signatures of conscious processing before birth. Dev. Cogn. Neurosci 49, 100964.
Muenssinger, J., Matuz, T., Schleger, F., Kiefer-Schmidt, I., Goelz, R., Wacker-Gussmann, A., Birbaumer, N., Preissl, H., 2013. Auditory habituation in the fetus and neonate: an fMEG study. Dev. Sci 16, 287–295.
Muotri, A., 2021. Brains in a Dish. Aeon.
Näätänen, R., Tervaniemi, M., Sussman, E., Paavilainen, P., Winkler, I., 2001. Primitive intelligence'in the auditory cortex. Trends Neurosci. 24, 283–288.
Nagel, T., 1974. What is it like to be a bat? Philos. Rev 83, 435–450.
Nevelle, K., Haberly, L., 2004. Olfactory Cortex in The synaptic organization of the brain, edited by GM Shepherd.
Niepel, D., Krishna, B., Siegel, E.R., Draganova, R., Preissl, H., Govindan, R.B., Eswaran, H., 2020. A pilot study: auditory steady-state responses (ASSR) can be measured in human fetuses using fetal magnetoencephalography (fMEG). PLoS. ONE 15, e0235310.
Nijhuis, J., Prechtl, H., Martin Jr, C.B., Bots, R., 1982. Are there behavioural states in the human fetus? Early Hum. Dev. 6, 177–195.
Nilsen, A.S., Juel, B.E., Thürer, B., Aamodt, A., Storm, J.F., 2022. Are we really unconscious in" unconscious states"? Common assumptions revisited. Front. Hum. Neurosci. 16, 678. doi:10.3389/fnhum.2022.987051.
Norton, L., Hutchison, R., Young, G.B., Lee, D.H., Sharpe, M.D., Mirsattari, S., 2012. Disruptions of functional connectivity in the default mode network of comatose patients. Neurology 78, 175–181.
Nourski, K.V., Steinschneider, M., Rhone, A.E., Kawasaki, H., Howard, M.A., Banks, M.I., 2018. Auditory predictive coding across awareness states under anesthesia: an intracranial electrophysiology study. J. Neurosci. 38, 8441–8452.
Odegaard, B., Knight, R.T., Lau, H., 2017. Should a few null findings falsify prefrontal theories of conscious perception? J. Neurosci. 37, 9593–9602.
Okada, Y., Hämäläinen, M., Pratt, K., Mascarenas, A., Miller, P., Han, M., Robles, J., Cavallini, A., Power, B., Sieng, K., 2016. BabyMEG: a whole-head pediatric magnetoencephalography system for human brain development research. Rev. Scient. Instrum. 87, 094301.
Olofsen, E., Sleigh, J., Dahan, A., 2008. Permutation entropy of the electroencephalogram: a measure of anaesthetic drug effect. Br. J. Anaesth 101, 810–821.
Padilla, N., Lagercrantz, H., 2020. Making of the mind. Acta. Paediatr 109, 883–892.
Parmelee Jr, A.H., Wenner, W.H., Schulz, H.R., 1964. Infant sleep patterns: from birth to 16 weeks of age. J. Pediatr. 65, 576–582.
Parvizi, J., Damasio, A., 2001. Consciousness and the brainstem. Cognition 79, 135–160.
Polich, J., 2007. Updating P300: an integrative theory of P3a and P3b. Clin. Neurophysiol. 118, 2128–2148.
Preissl, H., Lowery, C.L., Eswaran, H., 2004. Fetal magnetoencephalography: current progress and trends. Exp. Neurol. 190, 28–36.
Pridmore, S., Turnier-Shea, Y., Rybak, M., Pridmore, W., 2021. Transcranial Magnetic Stimulation (TMS) during pregnancy: a fetal risk factor. Austral.. Psych. 29, 226–229.
Querleu, D., Renard, X., Versyp, F., Paris-Delrue, L., Crèpin, G., 1988. Fetal hearing. Europ. J. Obstetr. Gynecol. Reprod. Biol. 28, 191–212.
Rabinowicz, T., de Courten-Myers, G.M., Petetot, J.M.-C., Xi, G., de los Reyes, E., 1996. Human cortex development: estimates of neuronal numbers indicate major loss late during gestation. J. Neuropathol. Exp. Neurol. 55, 320–328.
Ragazzoni, A., Di Russo, F., Fabbri, S., Pesaresi, I., Di Rollo, A., Perri, R.L., Barloscio, D., Bocci, T., Cosottini, M., Sartucci, F., 2019. Hit the missing stimulus". A simultaneous EEG-fMRI study to localize the generators of endogenous ERPs in an omitted target paradigm. Sci. Rep 9, 1–15.
Rajagopalan, V., Scott, J., Habas, P.A., Kim, K., Corbett-Detig, J., Rousseau, F., Barkovich, A.J., Glenn, O.A., Studholme, C., 2011. Local tissue growth patterns underlying normal fetal human brain gyrification quantified in utero. J. Neurosci. 31, 2878–2887.
Ray, J.G., Vermeulen, M.J., Bharatha, A., Montanera, W.J., Park, A.L., 2016. Association between MRI exposure during pregnancy and fetal and childhood outcomes. JAMA 316, 952–961.
Richards, L.J., Plachez, C., Ren, T., 2004. Mechanisms regulating the development of the corpus callosum and its agenesis in mouse and human. Clin. Genet. 66, 276–289.
Risk, B.B., Murden, R.J., Wu, J., Nebel, M.B., Venkataraman, A., Zhang, Z., Qiu, D., 2021. Which multiband factor should you choose for your resting-state fMRI study? Neuroimage 234, 117965.
Rosenfeld, J.P., Biroschak, J.R., Kleschen, M.J., Smith, K.M., 2005. Subjective and objective probability effects on P300 amplitude revisited. Psychophysiology 42, 356–359.
Rosenthal, D., 2005. Consciousness and Mind. Clarendon Press.
Sarasso, S., Boly, M., Napolitani, M., Gosseries, O., Charland-Verville, V., Casarotto, S., Rosanova, M., Casali, A.G., Brichant, J.-.F., Boveroux, P., 2015. Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine. Curr. Biol. 25, 3099–3105.
Sarasso, S., Casali, A.G., Casarotto, S., Rosanova, M., Sinigaglia, C., Massimini, M., 2021. Consciousness and complexity: a Consilience of Evidence. Neuroscience of Consciousness.
Schaal, B., Saxton, T.K., Loos, H., Soussignan, R., Durand, K., 2020. Olfaction scaffolds the developing human from neonate to adolescent and beyond. Philosoph. Transac. Royal Soc. B 375, 20190261.
Schartner, M., Seth, A., Noirhomme, Q., Boly, M., Bruno, M.-.A., Laureys, S., Barrett, A., 2015. Complexity of multi-dimensional spontaneous EEG decreases during propofol induced general anaesthesia. PLoS. ONE 10, e0133532.
Schartner, M.M., Carhart-Harris, R.L., Barrett, A.B., Seth, A.K., Muthukumaraswamy, S.D., 2017a. Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD. and. psilocybin. Scient. Reports 7, 46421.
Schartner, M.M., Pigorini, A., Gibbs, S.A., Arnulfo, G., Sarasso, S., Barnett, L., Nobili, L., Massimini, M., Seth, A.K., Barrett, A.B., 2017b. Global and local complexity of intracranial EEG decreases during NREM sleep. Neurosci. Conscious. 2017, niw022.
Scher, M.S., Waisanen, H., Loparo, K., Johnson, M.W., 2005. Prediction of neonatal state and maturational change using dimensional analysis. J. Clin. Neurophysiol. 22, 159–165.
Schleger, F., Landerl, K., Muenssinger, J., Draganova, R., Reinl, M., Kiefer-Schmidt, I., Weiss, M., Wacker-Gußmann, A., Huotilainen, M., Preissl, H., 2014. Magnetoencephalographic signatures of numerosity discrimination in fetuses and neonates. Dev. Neuropsychol 39, 316–329.
Schneider, U., Schleussner, E., Haueisen, J., Nowak, H., Seewald, H.-.J., 2001. Signal analysis of auditory evoked cortical fields in fetal magnetoencephalography. Brain. Topogr 14, 69–80.
Schubert, T.M., Rothlein, D., Brothers, T., Coderre, E.L., Ledoux, K., Gordon, B., McCloskey, M., 2020. Lack of awareness despite complex visual processing: evidence from event-related potentials in a case of selective metamorphopsia. Proceedings Nat. Acad. Sci. 117, 16055–16064.
Seth, A.K., 2018. Consciousness: the last 50 years (and the next). Brain Neurosci. Adv. 2, 2398212818816019.
Seth, A.K., Bayne, T., 2022. Theories of consciousness. Nat. Rev. Neurosci. 1–14.

Silverstein, B.H., Snodgrass, M., Shevrin, H., Kushwaha, R., 2015. P3b, consciousness, and complex unconscious processing. Cortex 73, 216–227.
Sitt, J.D., King, J.-.R., El Karoui, I., Rohaut, B., Faugeras, F., Gramfort, A., Cohen, L., Sigman, M., Dehaene, S., Naccache, L., 2014. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain 137, 2258–2270.
Smallwood, J., Bernhardt, B.C., Leech, R., Bzdok, D., Jefferies, E., Margulies, D.S., 2021. The default mode network in cognition: a topographical perspective. Nat. Rev. Neurosci. 22, 503–513.
Sulcova, D., Salatino, A., Ivanoiu, A., Mouraux, A., 2022. Investigating the origin of TMS-evoked brain potentials using topographic analysis. Brain Topogr. 35, 583–598.
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., 2022. Network-specific selectivity of functional connections in the neonatal brain. Cerebral Cortex.
Tau, G.Z., Peterson, B.S., 2010. Normal development of brain circuits. Neuropsychopharmacology 35, 147–168.
Thaler, I., Boldes, R., Timor-Tritsch, I., 2000. Real-time spectral analysis of the fetal EEG: a new approach to monitoring sleep states and fetal condition during labor. Pediatr. Res. 48, 340–345.
Tham, W.W., Stevenson, R.J., Miller, L.A., 2009. The functional role of the medio dorsal thalamic nucleus in olfaction. Brain Res. Rev 62, 109–126.
Thomason, M.E., Grove, L.E., Lozon Jr, T.A., Vila, A.M., Ye, Y., Nye, M.J., Manning, J.H., Pappas, A., Hernandez-Andrade, E., Yeo, L., 2015. Age-related increases in long-range connectivity in fetal functional neural connectivity networks in utero. Dev. Cogn. Neurosci 11, 96–104.
Threlkeld, Z.D., Bodien, Y.G., Rosenthal, E.S., Giacino, J.T., Nieto-Castanon, A., Wu, O., Whitfield-Gabrieli, S., Edlow, B.L., 2018. Functional networks reemerge during recovery of consciousness after acute severe traumatic brain injury. Cortex 106, 299–308.
Timmermann, C., Roseman, L., Schartner, M., Milliere, R., Williams, L.T.J., Erritzoe, D., Muthukumaraswamy, S., Ashton, M., Bendrioua, A., Kaur, O., Turton, S., Nour, M.M., Day, C.M., Leech, R., Nutt, D.J., Carhart-Harris, R.L., 2019. Neural correlates of the DMT experience assessed with multivariate EEG. Sci. Rep. 9, 16324. doi:10.1038/s41598-019-51974-4.
Toi, P.T., Jang, H.J., Min, K., Kim, S.-.P., Lee, S.-.K., Lee, J., Kwag, J., Park, J.-.Y., 2022. In vivo direct imaging of neuronal activity at high temporospatial resolution. Science 378, 160–168.
Toker, D., Pappas, I., Lendner, J.D., Frohlich, J., Mateos, D.M., Muthukumaraswamy, S., Carhart-Harris, R., Paff, M., Vespa, P.M., Monti, M.M., 2022. Consciousness is supported by near-critical slow cortical electrodynamics. Proceedings. Nat. Acad. Sci. 119, e2024455119.
Tononi, G., 2004. An information integration theory of consciousness. BMC Neurosci. 5, 1–22.
Tononi, G., Boly, M., Massimini, M., Koch, C., 2016. Integrated information theory: from consciousness to its physical substrate. Nat. Rev. Neurosci. 17, 450–461.
Tononi, G., Koch, C., 2008. The neural correlates of consciousness: an update. Ann. N. Y. Acad. Sci. 1124, 239–261.
Tosun, P.D., Abásolo, D., Stenson, G., Winsky-Sommerer, R., 2017. Characterisation of the effects of sleep deprivation on the electroencephalogram using permutation Lempel–Ziv Complexity, a non-linear analysis tool. Entropy 19, 673.
Trujillo, C.A., Gao, R., Negraes, P.D., Gu, J., Buchanan, J., Preissl, S., Wang, A., Wu, W., Haddad, G.G., Chaim, I.A., 2019. Complex oscillatory waves emerging from cortical organoids model early human brain network development. Cell Stem Cell 25, 558–569.
Tzovara, A., Simonin, A., Oddo, M., Rossetti, A.O., De Lucia, M., 2015. Neural detection of complex sound sequences in the absence of consciousness. Brain 138, 1160–1166.
Uhrig, L., Janssen, D., Dehaene, S., Jarraya, B., 2016. Cerebral responses to local and global auditory novelty under general anesthesia. Neuroimage 141, 326–340.
Ustun, B., Reissland, N., Covey, J., Schaal, B., Blissett, J., 2022. Flavor sensing in utero and emerging discriminative behaviors in the human fetus. Psychol. Sci. 33, 1651–1663.
Van de Velde, M., De Buck, F., 2012. Fetal and maternal analgesia/anesthesia for fetal procedures. Fetal. Diagn. Ther. 31, 201–209.
van den Heuvel, M.I., Thomason, M.E., 2016. Functional connectivity of the human brain in utero. Trends Cogn. Sci. (Regul. Ed.) 20, 931–939.
Van Regemorter, V., Rombaux, P., Dricot, L., Kupers, R., Grégoire, A., Hox, V., Huart, C., 2022. Functional imaging in olfactory disorders. Curr. Otorhinolaryngol. Rep. 1–6.
Varley, T.F., Luppi, A.I., Pappas, I., Naci, L., Adapa, R., Owen, A.M., Menon, D.K., Stamatakis, E.A., 2020. Consciousness & brain functional complexity in propofol anaesthesia. Sci. Rep. 10, 1–13.
Viertiö-Oja, H., Maja, V., Särkelä, M., Talja, P., Tenkanen, N., Tolvanen-Laakso, H., Paloheimo, M., Vakkuri, A., Yli-Hankala, A., Meriläinen, P., 2004. Description of the Entropy™ algorithm as applied in the Datex-Ohmeda S/5™ Entropy Module. Acta. Anaesthesiol. Scand. 48, 154–161.
Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., Van Essen, D.C., Zempel, J.M., Snyder, L.H., Corbetta, M., Raichle, M.E., 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447, 83–86.
Wakai, R.T., 2014. Current Status and Future Prospects of Perinatal MEG. Magnetoencephalography. Springer, pp. 641–644.
Wallois, F., Routier, L., Heberlé, C., Mahmoudzadeh, M., Bourel-Ponchel, E., Moghimi, S., 2021. Back to basics: the neuronal substrates and mechanisms that underlie the electroencephalogram in premature neonates. Neurophysiol. Clinique 51, 5–33.
Wei, Q., Liu, Q., Fan, S.-.Z., Lu, C.-.W., Lin, T.-.Y., Abbod, M.F., Shieh, J.-.S., 2013. Analysis of EEG via multivariate empirical mode decomposition for depth of anesthesia based on sample entropy. Entropy 15, 3458–3470.
Wielek, T., Del Giudice, R., Lang, A., Wislowska, M., Ott, P., Schabus, M., 2019. On the development of sleep states in the first weeks of life. PLoS. ONE 14, e0224521.
Yates, T.S., Ellis, C.T., Turk-Browne, N.B., 2021. The promise of awake behaving infant fMRI as a deep measure of cognition. Curr. Opin. Behav. Sci. 40, 5–11.
Yu, Q., Ouyang, M., Detre, J., Kang, H., Hu, D., Hong, B., Fang, F., Peng, Y., Huang, H., 2023. Infant brain regional cerebral blood flow increases supporting emergence of the default-mode network. Elife 12, e78397.
Zhang, X.-.S., Roy, R.J., Jensen, E.W., 2001. EEG complexity as a measure of depth of anesthesia for patients. IEEE. Transac. Biomed. Engin. 48, 1424–1433.

Further Reading

Dalebout, S.D., Fox, L.G., 2001. Reliability of the mismatch negativity in the responses of individual listeners. J. Am. Acad. Audiol 12, 245–253.