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Review article

Early brain activity: translations between bedside and laboratory

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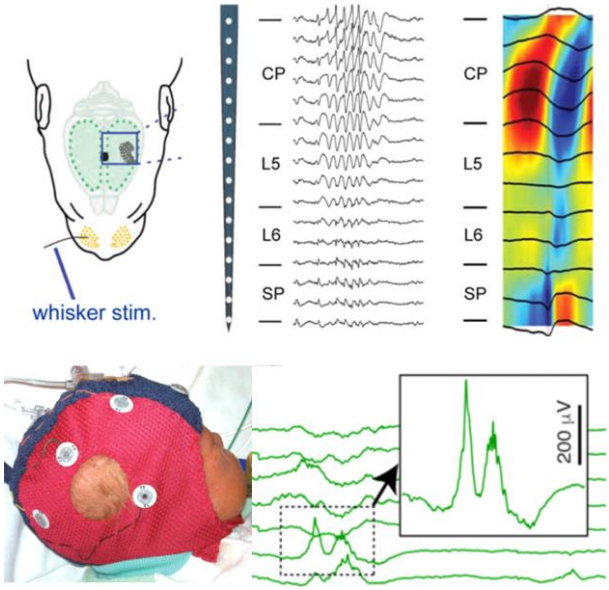
Graphical abstract



Highlights

Early activity is both the cause and the consequence of developmental abnormalities.

Network brain activity can be used as a readout of developmental abnormality.

Transient cortical neurons and circuits shape cortical development.

Translational challenges in understanding and diagnosing developmental brain disorders.

We review (i) what (ii) how and (iii) why the early activity should be measured.

Abbreviations

CR	Cajal-Retzius (neuron)
ECoG	electrocorticogram
EMG	electromyography
FbEEG	Full-band EEG
fMRI	functional magnetic resonance imaging
fUS	functional ultrasound imaging
IVH	intraventricular hemorrhage
IOS	Intrinsic optical signal
L	(cortical) layer
MEA	multi-electrode array
MEG	magnetoencephalography
NICU	neonatal intensive care unit
NIRS	near infrared spectroscopy
NVC	neurovascular coupling
SATs	spontaneous activity transients
VSDI	voltage-sensitive dye imaging

Abstract

Neural activity is both a driver of brain development and a readout of developmental processes. Changes in neuronal activity are therefore both the cause and consequence of neurodevelopmental compromises. Here, we review the assessment of neuronal activities in both preclinical models and clinical situations. We focus on issues that require urgent translational research, the challenges and bottlenecks preventing translation of biomedical research into new clinical diagnostics or treatments, and possibilities to overcome these barriers. The key questions are (i) what can be measured in clinical settings versus animal experiments, (ii) how do measurements relate to particular stages of development, and (iii) how to balance practical and ethical realities with methodological compromises in measurements and treatments.

Keywords: biomarker, development, animal model, human, neuronal activity, cerebral cortex

1. Introduction

Many neurodevelopmental disorders originate during the fetal or neonatal period, but their clinical manifestation becomes apparent only later in childhood with the development of neurocognitive disabilities. The diagnostic lag may be due to the delay in the clinical presentation of the condition *per se*, however it is also challenging to devise diagnostic measures in infants that only have a limited neurological performance repertoire. Here, we aim to identify the origin of translational gaps in understanding early pathophysiology of neural development, and in the development of new diagnostic tools. We also suggest priorities and strategies to bridge these gaps. The focus of our review is the appreciation of neural activity as both a driver of brain development and a readout of developmental processes. Changes in neuronal activity should therefore be considered as both the cause and the consequence of neurodevelopmental abnormalities. For instance, spontaneous activity in the sensory organs (Stellwagen and Shatz, 2002; Sun *et al.*, 2018) as well as spontaneous motor activity during early stages (Lüchinger *et al.*, 2008; Tiriac *et al.*, 2014a) are important for the emergence of spatially organized sensory and motor systems. An infant's spontaneous motor activity is now thought to preempt later emerging neurocognition (Hadders-Algra, 2018). We will review the assessment of neuronal activities in both animal models and clinical situations, with emphasis on issues that most urgently require bridges between preclinical and translational research.

Brain development is a protracted multi-stage process encompassing neural cell generation and differentiation, axon formation, and circuit maturation (Fig. 1). Brain activity emerges and changes concomitant with these processes and thus brain activity can be used as a readout of developmental abnormality. Brain activity can be studied at different levels, from individual ion channels to complex measures of behavior. One of the greatest challenges in neuroscience is to understand the neuronal mechanisms that link these levels of analyses. Translation across species, or between preclinical and clinical work, is relatively easy at levels where methodology is essentially similar. Early neonatal neurophysiological research used to be heavily translational, including routine species comparisons (Ellingson, 1972; Pampiglione, 1977), while further technological developments in cellular and molecular neuroscience split the field into more distinct preclinical and clinical research. Translational gaps arise rapidly when the levels of inspection are not matched, which is a major bottleneck in bridging the latest advances between preclinical and clinical developmental neuroscience. With rapidly advancing development of neurobiological knowledge and complexity in experimental setups in each subfield, we are witnessing more divergence and widening of translational gaps, even within fields of preclinical or clinical research. For instance, work using in vitro versus in vivo preparations may grow apart, similar to research on neonatal neurological care departing far from the concurrent studies of basic neonatal neurophysiology. Here we aim to bridge this growing divide and define a middle ground where further research should occur and could directly inform clinical practice.

INSERT FIGURE 1 HERE

2. Monitoring and analyzing activity in the immature brain

Brain activity can be recorded at multiple levels, ranging from the level of subcellular compartments (e.g. dendritic spine) to the systems level, including behavioral measures (Fig. 2). The challenge for translational work comes from bridging across species, which may be about using comparable measurements, signal analyses, or mechanistic framework in interpreting the results. Increasingly sophisticated and invasive methods used in animals provide deep insights but also produce data unavailable and mostly unobtainable in humans. Translational bridging should be based on a known or assumed neuronal mechanism. Notably, a graphological resemblance in e.g. signal waveforms should not be taken as evidence of common mechanistic underpinnings. The best match between experimental and clinical measurements is achieved by using a combination of comparable recording settings and signal analysis paradigms. The key questions are (i) what can be measured in clinical settings versus

animal experiments and (ii) how do these relate to milestones in morphological and physiological development? Furthermore, every translational research setting is constrained by practical and ethical realities, leading to methodological compromises. The cost-benefit of this balance between ideal and pragmatic can only be assessed by combining all prior neurophysiological knowledge to the given research aims. In the next section, we describe methods for direct measurement of neuronal activity, for indirect measurement of neuronal activity, and for measurement of other body functions that can be used as indicators for early brain activity.

2.1. Direct measurement of neuronal activity

Invasive, intracranial recordings

Placing electrodes into extracellular or intracellular space of brain parenchyma allows recording of neuronal population or single-cell activity, respectively. This gives a very high spatial and temporal resolution, allowing for detailed studies of cellular level correlates in neuronal activity, including assessment of transmitters and ion channels. While in vitro intracellular (e.g. single-cell patch-clamp) recordings are common place in animal research, only few comparable pilot studies have been performed using human fetal or neonatal brain tissue (Moore *et al.*, 2011; Moore *et al.*, 2014). In vivo recordings can be done with high density arrays directly at the cortical surface (epicortical) (Khodagholy *et al.*, 2015; Zhao *et al.*, 2021) or within brain parenchyma (for review (Buzsáki, 2004; Steinmetz *et al.*, 2018) to allow detailed assessment of wider network interactions (Gelbard-Sagiv *et al.*, 2018). Translational bridging at this level is impeded by the lack of clinical justification for invasive recordings in a human infant, hence such measurements are only possible in animal models.

Non-invasive, extracranial recordings

EEG electrodes can be placed extracranially, either on the scalp or subdermally, in both human newborns and in animal models. These recordings would include a few or more (up to >100) electrodes that are typically placed on well-defined positions on the scalp (Seeck *et al.*, 2017). This recording modality allows for the technically closest correlates between species. The overall signal properties are mostly comparable between newborn human and all other species reported so far (newborn rodents, dog pups, kittens, ferrets, lambs, piglets) (Luhmann and Khazipov, 2018; Ohshiro and Weliky, 2006; Pampiglione, 1977; Wess *et al.*, 2017). Comparability across studies and species is sometimes challenged by the fairly fixed traditions in the clinical and laboratory practice with respect to channel count and electrode placements (especially the reference channel), recording montages, electrode material, sampling rates,

and amplifier characteristics. Recent evidence clearly shows that key mechanisms in a newborn brain are readily ignored by current recording settings (Vanhatalo and Palva, 2018). In particular, the newborn brain exhibits robust infraslow signals with maximal spectral power well below the traditional filter cutoff at 0.5 Hz (Vanhatalo and Palva, 2018). Furthermore, many cortically recorded activities involve brain-wide structures, which can only be seen with sufficient electrode coverage (Odabaee *et al.*, 2013). Hence, an ideal newborn recording would have (i) Full-band (FbEEG) amplifier and DC-coupled electrodes to allow recordings of all physiological frequencies, and (ii) a sufficient number of appropriately placed electrodes to capture the spatial features of interest. Infraslow cortical oscillations in the range of 0.02 Hz (~1/min) have been observed in mammalian species from mice to humans during sleep, but neither the underlying mechanisms of this activity pattern nor its function is currently known (for review (Fernandez and Lüthi, 2020; Vanhatalo and Palva, 2018; Watson, 2018). Notably, technical difficulties in performing ideal FbEEG recordings from the human newborn infants (Stjerna *et al.*, 2012) may sometimes support compromising particular details (e.g. infraslow frequency range or spatial sampling) in the interest of better access to unique patient material. Such compromise should obviously be considered in the analysis and conclusions of the study. Slow activity transients resembling the activity recorded in preterm human babies have been also demonstrated with DC recordings in the visual cortex of unanesthetized rats before eye opening (Colonnese and Khazipov, 2010). A detailed species comparison is also challenged by anatomical differences between species. Besides evolutionary differences, for instance, the low positioning of the brain inside the skull makes it notably difficult in many animal species to access functionally important cortical regions (frontal, temporal, occipital) using scalp-attached electrodes. Therefore, it may be useful to compare epicortical recordings in animal models to scalp recordings in human infants (Ellingson, 1972; Pampiglione, 1977). This leap is justified also by recent studies that suggest a high resemblance between cortical and scalp signals, mainly due to only little spatial smearing at the well-conducting non-ossified cranium (Gargiulo *et al.*, 2015; Odabaee *et al.*, 2013).

Magnetoencephalography (MEG) is an alternative, non-invasive way to measure cortical activity, which provides many advantages for an accurate source localization in newborn infants (Nevalainen *et al.*, 2014) and even allows recording of fetal brain activity (Kiefer-Schmidt *et al.*, 2013). While MEG's use in animal models has been sparse, compared to EEG, MEG has not proven to provide enough additional information value to balance its many technical and logistic challenges (for review (da Silva, 2013)

INSERT FIGURE 2 HERE

2.2. Indirect measures of neuronal activity

Besides direct recordings, neural activity can be detected using indirect measures. Intrinsic optical signal (IOS) imaging (for review (Zepeda *et al.*, 2004), voltage-sensitive dye imaging (VSDI) (Higashi *et al.*, 2005; Higashi *et al.*, 2002) (for review (Luhmann, 2017), and fluorescence imaging with dyes or genetically encoded indicators (Meng *et al.*, 2021; Mukherjee *et al.*, 2021) (for review (Yang and Yuste, 2017) are powerful techniques to monitor activity from subcellular compartments (e.g. a dendritic spine) to across the entire cortex (for review (Barson *et al.*, 2020; Cardin *et al.*, 2020). Implanting a cranial window or imaging through the (removed, thinned or cleared) skull (Holtmaat *et al.*, 2009; Steinzeig *et al.*, 2017; Zhao *et al.*, 2018) allows for imaging of small cortical regions over several days and weeks using 2- or 3-photon imaging (for review (Grienberger and Konnerth, 2012; Wang *et al.*, 2018). The recently developed deep three-photon imaging technique allows in vivo imaging of small neuronal networks to single cells of a depth of over 1 mm below the cortical surface (Horton *et al.*, 2013; Takasaki *et al.*, 2019; Wang *et al.*, 2018). However, to date these powerful techniques are limited to animal models as no medical indication would justify the use of these techniques in human infants since it requires invasive thinning or opening of the skull, and the injection of dyes into the brain or its transfection with viruses.

Reflections of neuronal activity can also be estimated invasively or non-invasively from measuring changes in brain blood flow or oxygenation, via neurovascular coupling. Such invasive measurements of IOS performed through cranial windows provide information on activity-dependent changes in neurovascular coupling (Sirotin *et al.*, 2009). Optical recordings of neurovascular coupling combined with wide-field imaging of a genetically encoded calcium indicator have been performed in developing mouse cortex (Kozberg *et al.*, 2016) and longitudinally over an eight weeks period (Gu *et al.*, 2018). In humans, non-invasive techniques are used. The most studied indirect measures of brain activity are near infrared spectroscopy (NIRS) (Hu *et al.*, 2020) and BOLD/fMRI (Doria *et al.*, 2010; Fransson *et al.*, 2007), which can both be used in the animal and human contexts. NIRS has been successfully applied to recordings from newborns for decades and is a routine diagnostic imaging tool in many neonatal intensive care units. NIRS has been used to monitor brain blood perfusion to optimize cardio-respiratory care (Hyttel-Sorensen *et al.*, 2017; Mintzer and Moore, 2019), rather than monitoring brain activity per se and relatively little is known about the relationships between brain activity and NIRS signals, apart from the extreme pathophysiological conditions (Hendrikx *et al.*, 2019) or simple task-related conditions (Kotilahti *et al.*, 2010). There is also a larger number of studies on human infants using fMRI, providing evidence of spontaneous and task-related fluctuations in the BOLD signal (Doria *et al.*, 2010; Fransson *et al.*, 2007; Verriotis *et al.*, 2016).

A decade ago, functional ultrasound imaging (fUS) based on ultrafast Doppler measurements of cerebral blood flow volume changes was introduced in imaging sensory-evoked thalamic and cortical responses in the rat brain (Macé *et al.*, 2011). More recently, fUS was used to demonstrate e.g. 3D tonotopic maps in the auditory pathway of awake ferrets (Bimbard *et al.*, 2018). The first pilot studies have demonstrated that it might be used clinically to measure vascular changes during brain activation in newborn infants (Demene *et al.*, 2017) and recently fUS was introduced as bedside functional monitoring of very preterm neonates and term newborns (Baranger *et al.*, 2021).

Despite the visually appealing results in NIRS and fMRI research, the mechanistic interpretations of all blood flow-dependent measures in the infant are challenged by the absence of a predictable neurovascular coupling in spontaneous fluctuations of neuronal activity (Kozberg and Hillman, 2016). Conversely, spontaneous bursts may associate with about any kind of change in cerebral circulation (Nourhashemi *et al.*, 2020), indicating task-related changes in cortical blood flow in newborn infants (Allievi *et al.*, 2016) and developing rats (Colonnese *et al.*, 2008; Zehendner *et al.*, 2013b). Importantly, those studies have demonstrated that, compared to adults, newborn blood flow reaction to an increase in neuronal activity is both very slow and of low amplitude, which greatly challenges the use of blood flow-dependent measures in newborn brains. Furthermore, during early postnatal development, both, rats (Kozberg *et al.*, 2013) and mice (Zehendner *et al.*, 2013b) show a decline in regional cerebral blood flow to stimulation (negative BOLD) whereas adults reveal an increase. Of note, there is also a genuine conceptual, hence mechanistic mismatch in the way how "neurovascular coupling" is commonly defined by the neuroscience field in general vs research on neonatal intensive monitoring; the latter literature mostly ignores the multi-second scale coupling, and instead uses the term neurovascular coupling (NVC) to mean longer time scale (minutes to hours) correlation between brain circulation and changes in brain/vigilance states (i.e. brain activity level) (Das *et al.*, 2020; Hendrikx *et al.*, 2019).

2.3. Other readouts of brain activity

Beside monitoring neuronal activity directly and indirectly with a variety of non-invasive (and in animals with invasive) techniques, other measures of brain activity are also relevant for both clinical and preclinical studies. These methods have become widely used after recent emergence of novel sensor technology as well as automated analyses of physiological signals and video recordings.

Spontaneous movements

For clinical assessment of a newborn infant, spontaneous behaviour is the most important neurological readout, and spontaneous movements comprise most of the observable neurological performance in a newborn infant (Einspieler and Prechtl, 2005; Novak *et al.*, 2017). Spontaneous movements in awake infants can be observed early in development, including age-specific movement repertoire assessed in the framework of general movements (Einspieler and Prechtl, 2005; Novak *et al.*, 2017), as well as twitches observed in the body, limbs and facial area during infant's sleep (Sokoloff *et al.*, 2021; Sokoloff *et al.*, 2020). Animal studies have shown that these twitches are coordinated by central pattern generators in the spinal cord, brainstem, and motor cortex (An *et al.*, 2014; Khazipov *et al.*, 2004; Tiriac *et al.*, 2014b) (for review (Luhmann *et al.*, 2016) and subsequently cause a prominent activation of the somatosensory system, including the cortex. Spontaneous twitches likely play important roles in the self-organization of developing spinal and supraspinal sensorimotor networks (for review (Blumberg *et al.*, 2013; Khazipov and Milh, 2018). Their developmental change was also recently described in human infants (Sokoloff *et al.*, 2021; Sokoloff *et al.*, 2020). In humans, twitches and general movements can be easily measured and quantified via movement detectors, EMG electrodes, or even automated video analysis (Irshad *et al.*, 2020; Marchi *et al.*, 2019), while the resulting cortical responses can be monitored with EEG over the somatosensory cortex (Milh *et al.*, 2007; Whitehead *et al.*, 2017). Recently, skin-based wireless biosensors were introduced to monitor movements, body orientation, cardiac activity, blood pressure and also vocalization and crying in pre-/newborns (Chung *et al.*, 2020). It remains to be investigated in more detail, whether myoclonic twitches and other spontaneous movements represent valuable readouts for functional maturation of the brain and in this way could serve as early functional biomarkers. To further develop this, longitudinal animal studies are required using similar recording techniques as in infants and experimentally-controlled pathophysiological conditions (e.g. different levels of hypoxia) or pathology (e.g. IVH, infection, inflammation, fever).

Sleep behavior, and vigilance state cycle

The analysis of the sleep-wake cycle and the neuronal activity pattern during sleep in the immature brain recently became a focus in experimental research (for review (Cirelli and Tononi, 2015). the differentiation between sleep (states) and wakefulness is rather challenging, both in newborn rodents and preterm infants (Cirelli and Tononi, 2015). Therefore, clinical studies identifying biomarkers of physiological sleep and sleep-wake cycle in infants and animal studies (Sokoloff *et al.*, 2021; Tiriac *et al.*, 2012), and the ways in which these patterns are disturbed under and following pathophysiological conditions during early stages of development remain to be done.

2.4. Signal analysis as the translational bridge

The above considerations identify EEG and behavioral measures as modalities that allow direct translation. However, translation also requires that acquired signals are analyzed and interpreted in a uniform framework. Many recent advances in computational methods, ranging from mathematical developments to improved computational power, have improved extraction of details in mechanisms of neuronal activity with high precision and statistical reliability. These computational signal analysis methods are particularly interesting in the translational context because they hold promise for rendering analyses objective, and are able to bridge across species, or even across different recording constellations. Most of the analytic algorithms can be directly applied on EEG recordings from different species as long as the recording constellation is sufficiently comparable. In the following, signal analytical approaches are organized into entities according to their interpretation at neuronal activity mechanisms.

Spontaneous versus evoked activity

Much of neurophysiological literature is focused on temporally defined transient activity, such as epileptic spikes, bursts, sleep events, or cortical responses after sensory stimulation. Recent progress in computational paradigms has improved analyses of spontaneous, a.k.a. ongoing brain activity, which in many ways holds promise for higher functional relevance compared to transient activities. In the clinical context, spontaneous activity is often described as EEG background, which gives the basis in all neonatal EEG assessment. However, EEG background is mostly a clinical concept, with only gradually emerging understanding about its neurophysiological or mathematical characterization. A translational bridge across species can be made directly by applying the same analytical algorithms on both human and animal EEG datasets (for review (Aru *et al.*, 2015), an approach that is as yet only applied in a very limited number of studies (Colonnese *et al.*, 2010; Ranasinghe *et al.*, 2015; Tucker *et al.*, 2009). A particular challenge in the cross-species comparison is introduced by the graphological terminology used in the clinical reading of EEG waveforms. A variable number of visually identified graphoelements are reported in the clinical practice, referring to waveforms that are seen with a particular recording setting (e.g. number of electrodes and their placement, filtering, montages), in certain behavioural contexts (sleep, wake, stimulation), or at specific conceptional ages (Vanhatalo and Kaila, 2010). Some of these graphoelements may have comparable appearance in the animal recordings (Colonnese *et al.*, 2010), but there is also some graphological mismatch between species (e.g. temporal theta is only reported in the human EEG). It remains to be shown, however, how much of that mismatch can be assigned

to genuine species differences rather than the above listed, physical factors in the recording methodology (Vanhatalo and Kaila, 2010).

Event-based measures

Analysis of identified brain events gives a complementary view on neuronal activity compared to assessing background activity that focuses on general signal properties over longer time spans. In the neonatal EEG context, the early bursting activity is a prime example of a clearly identifiable and mechanistically distinct form of brain activity. Several methods have been developed for its detection in both human (O'Toole *et al.*, 2017; Roberts *et al.*, 2014) and animal (Cichon *et al.*, 2014) datasets. Burst detection opens a new level of analytic approaches where one can analyze mere burst occurrence (burst percentage) (Palmu *et al.*, 2013), interburst intervals (Wikstrom *et al.*, 2012), its fluctuation as an index of sleep state (Palmu *et al.*, 2013), the internal structures of the burst such as frequency content or waveform shape (Iyer *et al.*, 2015a). These will also allow performing for model-based studies, and they also provide perhaps the best translational benchmarking across different settings ranging from in vitro preparations to clinical studies. However, it is always important to note that a single analytical comparison at the event level is hardly sufficient to establish a mechanistic similarity between different levels of inspection.

Local vs network activity

Signal properties can be analyzed at the level of a single signal, or brain area, or at the level of neuronal networks. Analysis of single signals is typically focused on estimating amplitude, frequency spectrum, or nonlinear measures, which may indirectly reflect behavior of neuronal networks. With the growth of modern network neuroscience (Bassett and Sporns, 2017), it has become increasingly popular to assess interactions between brain areas using neurophysiological recordings where one can estimate correlations in the signal's oscillation phase, amplitude (Tokariev *et al.*, 2019a; Tokariev *et al.*, 2019b), or other larger-scale measures of dependency, such as avalanches of neuronal activity (Jannesari *et al.*, 2020; Seshadri *et al.*, 2018). These analytic paradigms (Seshadri *et al.*, 2018; Shriki *et al.*, 2013) can be readily applied in both animal and human EEG data to build direct translational bridges.

Network interactions

Neuronal interactions in the EEG signal can be studied by estimating well-defined mathematical relationships between two or more signals, such as phase synchrony and amplitude correlations, also referred to as intrinsic coupling mode (Engel *et al.*, 2013). These coupling modes take place within or between oscillatory frequencies across brain-wide networks. It is now well established that several networks may co-exist (Siebenhühner *et al.*,

2020) to give rise to various higher brain functions (Singer, 2018, 2021), while each network reveals also a highly dynamic changing pattern over different time scales. In the context of early development, a particularly interesting mode of network function is phase-amplitude coupling (a.k.a. nestedness) (Vanhatalo *et al.*, 2005), which implies correlation between higher frequency amplitude and lower frequency phase. This mode of cross-frequency coupling is very strong in the early networks where nearly all activity is characterized by such multifrequency bursts (Vanhatalo *et al.*, 2005). It is shown to co-vary with sleep states as well as be affected by *in utero* drug exposures (Tokariev *et al.*, 2016; Videman *et al.*, 2017). Recent animal experimental (Bitzenhofer *et al.*, 2017) and modeling studies (Aru *et al.*, 2015) have suggested the cellular level mechanisms of nestedness, pointing to the intrinsic cortical circuitry. Hence, analysis of nestedness from epicortical recordings may offer a way to probe the development of intracortical circuit function in both animal and human measures.

Network neuroscience

Analysis of functional networks is commonly performed by first estimating the bivariate neuronal interactions such as pairwise correlations or Granger-causal interactions (see above). This yields representation of the network (adjacency matrix), where recorded (or modelled) signals are taken to represent neuronal sources (nodes), that connect via a given interaction mechanism (edges). The ensuing dimension-rich network is then characterized by applying compressive measures, such as plain statistical descriptors or graph theoretical measures (Bassett and Sporns, 2017; Vecchio *et al.*, 2017). Networks may be analyzed further using paradigms designed to allow testing generative network models (Bassett *et al.*, 2018), or correlation with clinical phenotypes (Fornito and Bullmore, 2015; Tokariev *et al.*, 2019a). These analyses will typically consider each oscillatory frequency and interaction measures independently, however recent studies have emphasized the rich interactions across frequency bands, between coupling modes, and over time, hence introducing network dynamics as a new level of analysis. Due to the physiologically and analytically complex nature of associated phenomena, it is understandable that correlating neurophysiological network analyses with other behavioral phenotypes remains a poorly resolved challenge. Conversely, there are currently no analytic paradigms that would allow direct translation across different recording settings or between species.

Machine learning

Recent developments of machine learning methods have boosted the development of a large variety of novel analysis algorithms for EEG signals or kinematic data (Mathis *et al.*, 2018). The application of these methods can be broadly divided to (i) classifiers that aim to recognize distinct classes of signal (e.g. sleep state or clinical diagnosis) (Ansari *et al.*, 2020; Koolen *et*

al., 2017; Moghadam *et al.*, 2021), and (ii) detectors that aim to recognize specific physiological (e.g. burst) (O'Toole *et al.*, 2017) or pathological features in the signal (e.g. epileptic seizures) (Ansari *et al.*, 2019; O'Shea *et al.*, 2020; Stevenson *et al.*, 2019). While these approaches have proven to provide fundamental changes in many EEG analytics, their translational application is more challenging due to the need to train the algorithms with exactly matching datasets and hardware demands. Here cloud computing strategies could be useful.

3. Comparative electrophysiology and anatomy of the developing cortex

Continuous and evoked activity

The distinction between evoked and continuous ("spontaneous") activity may be attractive experimentally, but artificial physiologically. For example, continuous activity recorded in the cortex may have its origin in the sensory periphery (e.g. retina, cochlea) or in other neuronal structures (e.g. spinal cord, brain stem) or caused by self-generated motion (Penn *et al.*, 1998; Stellwagen and Shatz, 2002; Sun *et al.*, 2018; Tritsch *et al.*, 2007; Wong *et al.*, 1993) (for review (Luhmann and Khazipov, 2018; Luhmann *et al.*, 2016; Vanhatalo and Kaila, 2010). The cellular mechanisms underlying the various activity patterns differ and change profoundly during specific stages of early development. Since peripherally generated activity propagates through ascending circuits the spectral signature of the activity will be transformed. For example, high frequency components in firing patterns are likely being attenuated due to immature and depressing synapses.

Thus, at the cortical level these various forms of activity intermingle, and their electrical signatures are diverse. Centrally and peripherally generated events show different temporal signatures, likely due to transmission losses in subcortical pathways. Thus, it is possible to start separating some of these components. Such separation requires the acquisition of signals with sufficient spatial and temporal resolution. Work in rodents has revealed that centrally generated events show higher synchronization and larger amplitude than peripherally generated events (Leighton and Lohmann, 2016). One hallmark of cortical spontaneous activity is its oscillatory nature (Fig. 3A). The frequency content of the oscillations changes with development (Luhmann and Khazipov, 2018), thus source separations will have to take these changes into account (Fig. 3B). The signals elicited from thalamic stimulation shows considerable changes in spatio-temporal patterns (Higashi *et al.*, 2005; Higashi *et al.*, 2002) indicating different column learning rules in the cortex.

INSERT FIGURE 3 HERE

Although the developing brain shows age-dependent patterns of continuous EEG activity (Wallois *et al.*, 2020) and elaborate EEG classification schemes for preterm and full-term infants exist (for review (André *et al.*, 2010), animal studies suggest that the subdivision of the various activity patterns into distinct events can be questioned (for review (Colonnese and Khazipov, 2012). Also, in clinical settings it seems to be more appropriate to see the ongoing activity patterns of the immature brain as a singular class of discrete events termed "spontaneous activity transients" (SATs) (for review (Vanhatalo and Kaila, 2006). Furthermore, the temporal structure of certain events is generally far more complex as the superficial "by eye analysis" may indicate (see section on Signal Analysis). The amplitude of high-frequency activity may be coupled to the phase of a slower oscillation (phase-amplitude coupling or nested oscillation). Spindle bursts and delta brushes are examples of such nested oscillations in the EEG and can be easily identified (Fig. 3C, D). However, the situation becomes more complex when the slow rhythm is of very low frequency (as in infraslow activity) or when the high-frequency component exceeds 30 Hz.

Evoked neuronal activity can be evoked endogenously by continuous activity in other brain structures or sensory organs, can be triggered non-invasively by an external sensory, magnetic or electrical stimulus (TMS, DCS, ACS; both in animal and human studies) or invasively by a direct electrical (deep brain) or optogenetic stimulation of defined nervous structures. The evoked effect is a motor response or a change in the EEG potential, which is so small that its recognition requires averaging over a larger number of events. In the early brain, a single sensory stimulation is also known to cause larger scale population events that are readily visible in the human (Hrbek *et al.*, 1968; Leikos *et al.*, 2020; Milh *et al.*, 2007) and animal recordings (for review (Luhmann and Khazipov, 2018). It is now known that these events are strongly modulated by the temporal context, or other ongoing cortical activity (Leikos *et al.*, 2020; Nevalainen *et al.*, 2012). It is also notable that local evoked activity often triggers network-wide reactions (Ahtola *et al.*, 2020; Barson *et al.*, 2020; Yang *et al.*, 2013), known to underlie higher cognitive functions in the older subjects (Hirvonen *et al.*, 2018). Their analyses require more elaborated methods that account for oscillatory activities, and various cross-frequency and network interactions (Hirvonen *et al.*, 2018).

Circuit topology of the developing cortex

Within the cortex, ascending thalamic activity is relayed and amplified by intrinsic cortical circuits. These circuits are comprised of early maturing subplate neurons and developing cortical plate neurons (Molnár *et al.*, 2020). During development, thalamic projections accumulate closer to the cortex and this crucial developmental period is marked by highly dynamic, transient, and essential interactions between thalamus and cortex and the largely transient subplate neurons (Friauf and Shatz, 1991a; Higashi *et al.*, 2002; Luskin and Shatz,

1985b; Wess *et al.*, 2017; Zhao *et al.*, 2009a) (Fig. 4A). Subplate neurons are among the first excitatory cortical neurons to mature and are the first cortical neurons to receive thalamic inputs, long before thalamic inputs innervate their eventual target cortical layer (L) 4 (Chun and Shatz, 1989; Friauf and Shatz, 1991b; Hanganu *et al.*, 2002; Kostovic and Rakic, 1990; Luskin and Shatz, 1985a; Molliver, 1967; Molliver and Van der Loos, 1970; Molnar *et al.*, 2003; Zhao *et al.*, 2009b). Subplate neurons can respond to sensory stimuli before L4 neurons (Wess *et al.*, 2017) and an early sensory topography exists in subplate (Molnár *et al.*, 1998). This early developmental time window marks a "proto-organizational" period. Early sensory experience can already at this age shape the circuits impinging on subplate neurons (Meng *et al.*, 2021; Mukherjee *et al.*, 2021).

Subplate neurons themselves form a heterogeneous population of neurons based on their molecular profile as well as local and long-distance connectivity (Hoerder-Suabedissen *et al.*, 2018; Hoerder-Suabedissen and Molnar, 2013; Meng *et al.*, 2014; Viswanathan *et al.*, 2012; Viswanathan *et al.*, 2017). Excitatory subplate neurons provide input to L4 and other cortical layers including L1 (Deng *et al.*, 2017; Viswanathan *et al.*, 2017; Xue *et al.*, 2022; Zhao *et al.*, 2009b), and thus form an early relay of thalamic information to future thalamo-recipient layers before the ingrowth and synapse formation of thalamic terminals on target neurons. GABAergic subplate neurons innervate Cajal-Retzius (CR) neurons in the marginal zone/L1 (Myakhar *et al.*, 2011).

Subplate neurons are thought to play a possibly instructive role on thalamocortical as well as intracortical connectivity (Ghosh and Shatz, 1992a; Kanold *et al.*, 2019; Kanold *et al.*, 2003; Kanold and Luhmann, 2010; Tolner *et al.*, 2012). Subplate neurons also pioneer corticothalamic (McConnell *et al.*, 1989) and thalamocortical (Molnár *et al.*, 1998) projections and subsets of subplate neurons survive to adulthood and target higher order thalamic nuclei (Hoerder-Suabedissen *et al.*, 2018; Viswanathan *et al.*, 2017). Due to their specific receptor expression these neurons could orchestrate cortical state transitions in the adult (Horvath *et al.*, 2022).

Subplate neurons are crucial for oscillatory activity based on the observation that subplate ablation abolishes oscillatory activity (Dupont *et al.*, 2006; Tolner *et al.*, 2012). Synchronized network activity can be triggered by cholinergic suprathreshold activation of GABAergic subplate neurons, which are coupled to neighboring subplate neurons via gap junctions, and ambient level of extracellular GABA boosts this network to generate oscillatory activity (Hanganu *et al.*, 2009). However, subplate neurons do not oscillate by themselves at the observed frequencies (Sun *et al.*, 2012), indicating that oscillations are likely generated via circuit mechanisms. Subplate neurons receive glutamatergic and GABAergic input (Ghezzi *et al.*, 2021; Hanganu *et al.*, 2002; Meng *et al.*, 2014; Viswanathan *et al.*, 2012) and excitatory subplate neurons are embedded in a mutually excitatory loop with cortical plate neurons,

sending excitatory projections to and receiving input from layers 4-6 whose synaptic nature changes with development (Ghezzi *et al.*, 2021; Kanold *et al.*, 2019; Meng *et al.*, 2014; Viswanathan *et al.*, 2012). During development, many glutamatergic synapses contain only NMDA, but no AMPA receptors (Hanse *et al.*, 2013; Kanold *et al.*, 2019), thus, at a "typical" resting potential these synapses are functionally "silent". At young ages, subplate neurons receive inputs from L4 via NMDA receptor only connections (Kanold *et al.*, 2019; Meng *et al.*, 2014; Viswanathan *et al.*, 2012) while intra-subplate and thalamocortical synapses on subplate neurons are not silent (Hirsch and Luhmann, 2008). Given these profound synaptic changes in thalamocortical and intracortical circuits, it is important to note that the occurrence of "spontaneous" cortical events can have a major impact on the processing of later ascending peripherally-generated spontaneous or sensory evoked events. For example, centrally-generated events will render cortical circuits depolarized and thereby increasse inactivation of sodium channels and thus reducing excitability. Moreover, developing synapses depress easily, thus centrally generated events have the potential to depress synapses and reducing the probability of peripheral activity being able to drive central activity.

Beside subplate neurons, early generated CR neurons also initially participate in transient cortical circuits before they are almost completely eliminated by programmed cell death (for review (Causeret *et al.*, 2021; Kirischuk *et al.*, 2014). While subplate and CR neurons are transient elements in the developing thalamocortical and intracortical circuit, other cells in the cortex make transient connections during development and could also contribute to changes in the intrinsic capability of cortical circuits to oscillate. For example, inhibitory somatostatin interneurons in L5 receive thalamic input and project transiently to L4 (Marques-Smith *et al.*, 2016; Tuncdemir *et al.*, 2016) and cells in L1 and L2/3 receive largely transient inputs from L5/6 in the critical period (Meng *et al.*, 2021; Xue *et al.*, 2022).

While the functional circuitry of the developing cortex is being unraveled in animals, only few functional synaptic/circuit level studies have been performed in developing human tissue (Moore *et al.*, 2011; Moore *et al.*, 2014) and many human studies have used post-mortem tissue (Kostovic, 2020). Given the diversity of subplate neurons in animals (Montiel *et al.*, 2011; Wang *et al.*, 2010) and that the human subplate is highly overexpanded compared to rodents and carnivores, detailed functional studies of human subplate circuits are major gap (Mólnar *et al.*, 2019). Moreover, the above discussion centers on the columnar level and might be picked up between EEG recording sites as differences between electrodes are larger. To date, we have little information about the organization of functional circuits at a macro-scale.

INSERT FIGURE 4 HERE

4. Pathology and pathophysiology of the developing cortex

Early neurodevelopment forms a cascade where deviance in an earlier phase will have an impact on all later phases of development. Due to the robustness and resilience of many neurodevelopmental processes (Davis, 2013; Innocenti and Price, 2005), the impact of an early adversity on the ultimate neurodevelopmental outcome, or disorder manifestation, maybe significantly tapered during later life. The cascades of neurodevelopment imply that the "neurological landscapes" are changing over time; conversely, the clinical symptoms or any measures thereof will also change over lifetime. A common clinical practice is to divide the etiologies to inherited and acquired disorders, the latter of which refers to disorders caused by an external adversity, such as infection, brain lesion, or malnutrition. The emergence of molecular medicine has boosted the interest in studying inherited pathophysiologies, such as metabolic or migration disorders (Adle-Biassette *et al.*, 2017); however, the acquired disorders are much more common and potentially preventable, and hence have far higher clinical and societal impact. Both inherited and acquired disorders may have clinical onset at any age of life, and their effects on neurodevelopment is best understood in the context of how they interfere with neurodevelopmental cascades. It is therefore fruitful to examine the key mechanisms that form common pathways for many pathophysiologies. The most common causes of early brain dysfunction include asphyxia, vascular lesion by intracerebral hemorrhage or stroke, as well as early prematurity with host of ensuing mechanisms (Millar *et al.*, 2017b; Mwaniki *et al.*, 2012). While they all will affect spontaneous cortical activity, they may also damage many subcortical structures, such as subplate or thalamocortical tracts (Fig. 4B). As described below, the subcortical lesions and their functions can be indirectly assessed using scalp EEG.

Neurophysiology as the window to the newborn brain

A key challenge in the clinical examination of newborn neurology is the paucity of neurological signs or neuronal measures that could be reliably studied (Hawes *et al.*, 2020). Clinical neurological assessment is primarily about observing behavior, motor functions, and the reactivity of newborns to handling. Consequently, neurophysiological methods are often the means of acquiring more detailed information about brain function in a newborn infant. A clinical neurophysiological study is always interpreted in the context of clinical condition, and it aims to answer three key questions: First, what is the type of spontaneous cortical activity in different vigilance states, and are there sleep wake cycles or epileptic seizures? Second, is the cortical activity reaching sufficient maturity for the known conception age (time after conception)? Developmental maturity of the EEG signal is a key benchmark, and many clinical

issues are expected to reflect on the EEG as developmental delays ("dysmature") (Watanabe *et al.*, 1999). Third, how has brain activity recovered after a known challenge or insult?

Cortical bursting as a measure of newborn brain function

Early brain activity is characterized by intermittent bursting, which supports a host of developmentally crucial downstream events, including neuronal survival and spatial coding of emerging brain networks (Luhmann *et al.*, 2016). Through allostatic mechanisms, this early activity may be resilient to longer term (hours to weeks) environmental challenges, however it is yet sensitive to many acute (seconds to hours) disturbances. The most typical clinical finding is, that different kinds of structural damage of the brain (Hellstrom-Westas *et al.*, 2001; Iyer *et al.*, 2015b; Omidvarnia *et al.*, 2015), pharmacological interventions (Nguyen The Tich *et al.*, 2003) or pathophysiological compromise (Olischar *et al.*, 2004; Wikstrom *et al.*, 2011) may acutely affect the early bursting activity. Long-term follow-up studies have shown further that the frequency (Benders *et al.*, 2015; Klebermass *et al.*, 2011; Tataranno *et al.*, 2018; Wikstrom *et al.*, 2018; Wikstrom *et al.*, 2012) and the structure of early bursting (Iyer *et al.*, 2015a) correlates with brain growth and neurodevelopmental outcomes. Cortical bursts recorded with EEG in infants surviving perinatal hypoxia-ischemia and receiving 72 h of therapeutic hypothermia predicted cognitive and language outcomes independent of structural MRI findings (Koskela *et al.*, 2021); Moreover, scaling characteristics of the burst waveforms are also predictive of outcome suggesting that clinically valuable, directly translatable information may be extracted from studying cortical mass behaviour in an injured neonatal brain (Iyer *et al.*, 2014).

A particular research challenge comes from the changing neurological landscapes, where neurodevelopmental impact of the same adversity will change over time both qualitatively and quantitatively. This is partially due to the different maturational time courses of different brain areas as connections, between them. These constitute high-dimensional, poorly understood interactions that greatly complicate clinical follow-up studies. Their fully resolved studies are not possible in the fragile human infants where data collection is limited by acute care settings. For instance, serial EEG recordings have indicated that intraventricular hemorrhage (IVH) in an early preterm infant would cause an acutely aberrant bursting (acute stage abnormalities), which is replaced by a graphologically different type of bursting (chronic stage abnormalities) (Hayakawa *et al.*, 1999), during the upcoming weeks. Conversely, studies have indicated a change in burst structure (Iyer *et al.*, 2015b) or its frequency (Hellstrom-Westas *et al.*, 2001; Olischar *et al.*, 2007) preempting a clinical occurrence of cerebral bleeding.

Analysis of cortical bursting as bedside testing of subplate function

A particular type of cortical bursting in an early preterm infant is readily seen in the EEG signal after somatosensory (Fabrizi *et al.*, 2011; Leikos *et al.*, 2020; Milh *et al.*, 2007), visual (Colonnese *et al.*, 2010) or auditory stimulation (Chipaux *et al.*, 2013; Kaminska *et al.*, 2018), which all result in a largescale complex event near the corresponding sensory cortices. These events interact with the cortical bursts that occur without external sensory stimulation, and recent animal work suggests that the subplate is centrally involved (Tolner *et al.*, 2012). Such functional bedside testing of subplate-cortex networks in the neonatal intensive care unit (NICU) is particularly important due to the key roles that subplate plays in many phases of normal and abnormal brain development (Molnár *et al.*, 2020). A study on human infants showed that those responses may integrate bi-hemispheric cortico-cortical networks, the development of which is affected by early IVH (Leikos *et al.*, 2020), however their predictive value for later neurodevelopment remains to be established. Likewise, somatosensory activation in a full-term infant is shown to be the most accurate predictor of later evolving cerebral palsy (Nevalainen *et al.*, 2021), presumably due to its ability to measure function of thalamocortical networks.

Analysis of cortical correlations as bedside assessment of newborn cortico-cortical networks

Recent work shows further that long-range cortico-cortical correlations in brain activity arise primarily via bursting activity in the preterm brain (Omidvarnia *et al.*, 2014), and these correlations are disrupted by IVH lesions independent of the level of activity *per se* (Omidvarnia *et al.*, 2015). While the correlated bursting or its deviance cannot be observed later in development, it is straightforward to assume that early disruption in such network activity would underlie many neurodevelopmental disorders associated with early IVH (Omidvarnia *et al.*, 2015).

Episodic behaviors are frequent in all newborn infants that require medical attention

Perhaps the most common reason for neurophysiological monitoring is suspicion of epileptic seizures, which can be reliably detected only from the scalp EEG. The majority of newborn seizures manifest as reactions to a known medical cause, such as asphyxia, stroke or infection (Nunes *et al.*, 2019). They are shown to have a variable time course with rapid onset and almost always a spontaneous resolution within hours or days, which makes their treatment trials particularly challenging (Stevenson and Vanhatalo, 2018).

All these findings together suggest that EEG monitoring may provide crucial insights to a clinical course as well as to research on pathophysiology. Due to changing landscapes, however, the EEG information is exquisitely time sensitive, and its full interpretation is only possible with significantly more insight from animal work about underlying network

mechanisms. Correlating the wealth of detailed circuit measures, for example gained by in vivo imaging, in animals with EEG signatures is thus of high importance. The fundamental questions for experimental animal work include the exact neuronal mechanisms as well as all dose-response relationships that associate early adversity to neurodevelopmental outcomes.

In utero assessment of fetal brain function

Some recent works have developed methods to assess brain activity in utero, based on MEG or fMRI recordings (Vasung *et al.*, 2019). While the idea of measuring brain function in an unborn child is intriguing, these studies have so far been focused on proving their ability to measure brain activities that were already known before. Indeed, it is unclear to what degree such methods are able to genuinely advance the understanding of brain development in health or disease. While MEG is greatly compromised by the physiological noise, especially maternal cardiac signals, interpretation of the fetal fMRI data is even more challenged by the proven lack of correlation between neuronal activity and fMRI signal in that age group. Finally, there is an abundant resource of generally healthy preterm infants in the intensive care units, providing much easier access to studying early brain development in a clinically meaningful context.

For the bedside clinician, the most important decision is to choose individually optimized treatment protocols in a rapidly changing clinical scene. This calls for a better means to reliably recognize the infants who would benefit from rapid interventions, as well as the infants who will recover better without additional intervention. The time scales in early brain monitoring may vary from hours (e.g. neonatal seizures or birth asphyxia) to months (e.g. cerebral palsy), however clinical inspection and/or other medical testing of the given infants is significantly hindered by the lack of direct measures of brain function, the ultimate target of therapeutic actions. For instance, an optimal neurorehabilitation for cerebral palsy should start within the first few months of life (Novak *et al.*, 2017), while the current clinical practice would identify these infants up to one year later. Moreover, there is an imminent need for early readout measures, a.k.a. functional biomarkers, to benchmark the treatment effects in a dynamic fashion. Such proximal outcome measures hold promise for significantly expediting the study cycles in clinical trials, as well as allowing for better individualized medical care.

5. Animal models and translational challenges

Choice of model species

Rodent studies have become most popular in biomedical research because they allow transgenic manipulation and validated behavioral tests but they cannot provide insights into aspects that are uniquely human (for review (Chini and Hanganu-Opatz, 2021; Luhmann and

Fukuda, 2020). Nevertheless, rodent models were invaluable for establishing hypothermia as a therapy for neonatal hypoxia-ischemia before it was taken into larger animal models and further to become widely used in clinical settings (Aquilina *et al.*, 2007; Davidson *et al.*, 2018; McQuillen *et al.*, 2003; Millar *et al.*, 2017a; Sheikh *et al.*, 2021; Sheikh *et al.*, 2019). In its structural and functional properties, the mouse brain, here generally the cerebral cortex, may roughly resemble human infants, however recent studies have highlighted fundamental species differences in many key aspects of cerebral networks (Horvat *et al.*, 2016) and genetics (Cardoso-Moreira *et al.*, 2020; Zhang *et al.*, 2010). Therefore, the choice of model species should be based on a multi-faceted cost-benefit analysis that leads to different choices with e.g. studies on molecular and cellular mechanisms compared to studies replicating clinical therapeutic approaches (Aquilina *et al.*, 2007; Davidson *et al.*, 2018).

Age calibration

There are no universal age-calibrations available to translate neurodevelopmental age between human and animal models. Individual structures and functions can be compared between human infants and a larger number of mammalian species (Clancy *et al.*, 2007; Workman *et al.*, 2013), but these calibration tables need to be considered with caution. The age calibration across species is highly multidimensional, where each brain structure, its function, and even gene expression patterns have their unique translational timeline. Different parts of the central nervous system have differential velocity of maturation, thus translating one part of the brain might not fit for others. For example, there are differences in neurogenesis, laminar positioning, and thalamic innervation between sensory cortices (Chang *et al.*, 2018; Ghosh and Shatz, 1992b; Ignacio *et al.*, 1995; McConnell *et al.*, 1989, 1994; Noctor *et al.*, 1997; Sanderson and Aitkin, 1990). There are also other qualitative differences between species, such as the protracted development of human subplate and frontal cortex co-existence of fetal transient and later permanent neuronal networks (Kostovic, 2020), or marked differences in the ultimate cortico-cortical network structure (Horvat *et al.*, 2016). Nevertheless, it is widely assumed that the cerebral cortex of a P0 mouse can be compared to the human cortex during the third trimester, and functional studies in P0 to P10 mice would cover the clinically relevant period from early prematurity to about term equivalent age. However, this age calibration does not account for the relative time of birth. For example, mice spend their first postnatal days in their normal, ex-utero environment, while the human developmentally comparable human infants should still be in utero instead of an artificial NICU environment. Importantly, there are no comparative studies available for most neurophysiological phenomena or mechanisms. The preclinical developmental work has been heavily focused on mechanisms related to sensory cortices or midbrain structures, while the human level of neurophysiological inspection is more based on EEG, hence corticocentric, with less

orientation to any particular brain area. Therefore, in order for there to be better translation of research, both animal and human studies need to converge on similar areas and in particular the development of non-sensory areas in animal models needs to be elucidated.

Requirements for animal models

The value of a translational animal model depends on its accuracy in recapitulating the physiological state, and pathophysiological mechanisms of the human infant and also allow for similar measurements and treatments. In an optimal situation, for instance, the animals should not be restrained and/or anesthetized, since anesthetics influence brain function and may cause massive morphological and functional changes (Colonnese *et al.*, 2010; Gao *et al.*, 2017; Kelz and Mashour, 2019; Paasonen *et al.*, 2018). Studying unrestrained mice is difficult because a number of invasive techniques such as intracortical multi-electrode array (MEA) recordings, widefield, or 2-photon imaging require a careful head-fixation to obtain stable recording conditions (Meng *et al.*, 2021; Meng *et al.*, 2020a; Mukherjee *et al.*, 2021; Yang *et al.*, 2013). However, awake newborn mice recordings are possible with head-fixation if appropriately nursed. Movement restriction can also be overcome by using miniature imaging devices (de Groot *et al.*, 2020) or telemetric electrophysiological recording systems (Fan *et al.*, 2011) that offer monitoring of optical or electrophysiological activity in awake, non-restrained mouse pups but chronic monitoring is challenging due to rapid head growth and maternal grooming. Deep brain recordings, e.g. in the thalamus, may be desirable (Yang *et al.*, 2013), as well as larger array EEG recordings to detect widespread brain activity during ongoing (spontaneous) and sensory evoked activity, such as visual, auditory and somatosensory evoked potentials. Long periods of ongoing activity lasting at least 1 hour should be recorded and animals should be simultaneously video-monitored. Combination of electrophysiological (EEG or ECoG) recordings with intracortical 2-photon, intracranial MEA recordings or measuring blood oxygenation with e.g. near-infrared imaging spectroscopy may offer clinically relevant, complementary readouts in brain monitoring. In addition to these measures of neuronal function, it is also possible to assess brain function indirectly from polygraphic measures, such as muscle tone using electromyography (EMG), eye movements with electrooculography, or variations in heart rate and respiration, which can be easily and non-invasively monitored online in neonatal rodents with piezoelectric transducer elements (Zehendner *et al.*, 2013a). If possible, blood gas analyses should be performed to determine the pH and CO_2 tension at critical time points of the experiments (Zehendner *et al.*, 2013a). Behavioral correlates can be assessed by monitoring spontaneous movements of the whole body or the limbs (a.k.a. twitches) (Glanz *et al.*, 2021), as well as motor responses to sensory stimuli (Inacio *et al.*, 2016), all of which can be measured using piezoelectric elements and/or (3D) video monitoring (Gomez *et al.*, 2021; Mathis *et al.*, 2018). Notably, some of these non-

invasive monitoring techniques may be challenging in individual newborn rodents that move freely with their mother and littermates. Finally, the EEG / ECoG recordings and the monitoring of movements can be used to identify the sleep state and pattern, both in animals (Tiriac *et al.*, 2014b) and human infants (Sokoloff *et al.*, 2021). If possible successive recordings over at least 1 hour should be performed over the first postnatal days to cover a longer developmental period. ECoG, EEG, intracranial tetrodes and the miniscope allow such recordings over several days in rodents (Fig. 2A). Finally, in animal models investigating the long-term consequences of pre-/neonatal pathophysiological insults, chronic recordings (e.g. via tetrodes) or successive monitoring sessions (e.g. imaging via cranial window or through thinned skull) allow functional analyses of the same neuronal network over days to a few weeks.

Replication of clinical pathophysiology

A disease model needs to replicate the physiological state, pathophysiological mechanisms, and the actual clinical treatment used for a human newborn infant. Preferentially, the situation should be identical to what is seen in the clinical setting, which is often challenging as animal models would rarely, if ever, naturally exhibit those conditions. Moreover, the size of smaller animals does not allow for fully replicating physical care procedures. Many animal models are just primarily mimicking some phenomenological aspects of the clinical phenotype rather than replicating the underlying pathophysiology. For instance, the widely used model of perinatal hypoxic-ischemic encephalopathy is made by carotid artery ligation (Domnick *et al.*, 2015; McQuillen *et al.*, 2003; Millar *et al.*, 2017a; Okusa *et al.*, 2014; Sheikh *et al.*, 2021; Sheikh *et al.*, 2019) coupled to hypoxia exposure, neither of which occurs in the human birth asphyxia that is characterized by a variable and always unknown combination of genuine ischemia, leading to a cascade of systemic hypoxia, hypercapnia, acidosis, and multiorgan effects. Therefore, a more pathophysiologically valid model should be based on replicating these at a systemic level (Helmy *et al.*, 2011), which was recently shown to replicate many aspects of clinical hypoxic-ischemic encephalopathy (HIE) presentation (Pospelov *et al.*, 2020) as well as allow mechanism-driven development of novel therapeutic approaches (Helmy *et al.*, 2012). "Double hit" models like combination of mild systemic inflammation and moderate hypoxia may also become valid models (Mordel *et al.*, 2016). Likewise, there is a need for systematic testing of novel therapeutic regimes in a clinically relevant manner (Davidson *et al.*, 2018). Such work would need to include all the complexity of a clinical care protocol, such as hypothermia coupled to sedative and anti-seizure medications as well as cardiorespiratory medication and respiratory support (Zhou *et al.*, 2020). The complex interactions in such clinical circumstances (Ophelders *et al.*, 2020) are impossible to predict from the well-controlled laboratory conditions without full replication of the entire clinical scenario (Dhillon *et al.*, 2020; Wassink *et al.*, 2020).

Choice of disease models with clinical and societal relevance

There has been a dramatic increase in the knowledge of molecular or genetic level mechanisms of rare conditions. However, a much higher clinical, societal, and individual level impact comes from those adversities that are orders of magnitude more prevalent. They include many acquired, systems-level pathologies, such as preterm birth, perinatal asphyxia, sepsis, as well as their many co-morbidities, including intraventricular hemorrhage, stroke, retinopathy of prematurity, cerebral palsy, etc. (Mwaniki *et al.*, 2012). Indeed, researchers in translational neuroscience are at a crossroads in making critical choices between studies on precise molecular mechanisms of rare conditions versus studies on highly prevalent systems-level diseases. These are mutually exclusive in many scientific ways, and the choice between them is easily reinforced by trends and funding policies, which has traditionally favored molecular precision over clinical relevance.

"Cultural challenges" in developing and utilizing functional measures

Clinically used imaging and recording techniques are necessarily compromised when recording live human infants. Their mechanistic interpretation is heavily dependent on the understanding that comes from experimental animal work where underlying neuronal mechanisms can be examined at all possible levels. However, there is a striking paucity of studies that would provide the key to translation, possibly due to the science trends and perceptions that may undervalue such lower resolution studies in animals. Conversely, basic science studies commonly use state of the art cellular imaging or recording techniques to identify circuit abnormalities in disease models, however their translatability to clinically achievable recording scenarios, or to real world human conditions, maybe only speculative.

Another layer of challenge comes from the norms in evidence-based medicine, which have effectively canonized the ways how medical trials should be designed. A major issue in neonatal neurological studies is the perceived need for a long follow-up, which prolongs study cycles to several years as well as compromises the effect size by introducing a myriad of later post-neonatal confounders to the outcome. This leads to a situation where the clinical context may have changed by the time when the scientific evidence is gathered. For instance, long term follow-up of ex-preterm infants may come only decades later, hence the information may be irrelevant for the contemporary early preterm care that has meanwhile continually evolved. This vicious cycle could be broken by orders of magnitude faster study cycles, which are possible (i) by developing very early functional biomarkers for proximal benchmarking of intervention trials and (ii) by implementing dynamic study designs (Balevic and Cohen-Wolkowiez, 2018) that are guided by such proximal readouts.

Box: To do list for …

… the animal experimental scientist:
- Develop non- or minimally invasive recording techniques for newborn animals.
- Generate transgenic mice with embryonic GCaMP expression.
- Combine EEG with calcium imaging and intracranial depth recordings.
- Perform long-term longitudinal studies.
- Study clinically relevant parameters, e.g. EMG, proprioceptive signals, pain, stress, sensory evoked EEG responses.
- Use experimentally controlled pathology (e.g. IVH, hypoxia, infection, inflammation, fever) and perform treatment studies.
- Analyse the development of neurovascular coupling to provide a better mechanistic understanding of age-dependent NIRS measurements.
- Study sex and strain differences.
- Test clinically used drugs (caffeine, fentanyl etc.) experimentally.
- Be open to other (animal) models besides rodents.
- Make dataset publicly available with precise experimental details.

… the translational clinician scientist:
- Provide and standardize EEG parameters.
- Simplify EEG instrumentation (but full-band/DC) and disseminate app-based software and cloud computing resources for standardized quantitative EEG examination including AI.
- Perform longitudinal standardized studies of the same individual and different individuals.
- Map responses to tactile stimulation of different body parts and compare bilateral responses.
- Develop minimal invasive telemetric devices for monitoring.
- Follow some recent low-cost ideas, like exposure to music, soft illumination, sensory (tactile, proprioceptive) enrichment, application of baby massage in NICU.
- Link imaging, clinical, behavioral, and genetic information; understand variabilities in population.
- Link developmental MRI literature to histopathological results and expand repertoire of histopathologists.
- Identify milestones of development, e.g. certain movements, responses to external sensory stimulation, and relate this to specific stages of circuit assembly and other parameters (weight, prematurity, care).
- Identify the cognitive, motor, sensory „catch-up“capabilities (reserves) of preterms later in life.
- Compare epicortical recordings in animal models to scalp recordings in human infants at different developmental stages.
- Relate data to human connectome project and generate a 3D atlas with various imaging (MRI) and histological methods of the infant brain.
- Generate an ultrasound-derived 3D atlas of developing fetal brain.
- Provide novel biomarkers for identification and analysis of therapeutic targets.
- Define the current status and predict developmental outcome of babies.
- Study sex differences.
- Make dataset publicly available with sufficient experimental and clinical details.

6. Challenges of early personalized / precision medicine and Conclusions

Above, we have outlined translational challenges in understanding and diagnosing abnormalities in early brain development. Bridging these gaps is essential in devising effective treatment strategies. On top of these, the neonatal clinical interventions are challenged by using long-term childhood neurodevelopmental outcome as the primary endpoint. This practice prolongs the study cycles typically to over five years, and it also introduces significant confounders that arise from the environmental impacts on child's neurodevelopment (Burnett *et al.*, 2018). To this end, the accurate, objective, and transparent measures of early brain function may hold promise for becoming proximal biomarkers. They could provide immediate feedback on brain development and a functional benchmark on treatment effects. Such measures would allow designing significantly expedited cycles in therapeutic interventions, as well as avoiding the confounders from later environmental effects. Moreover, early functional biomarkers would enable better and considerably earlier therapeutic interventions which are believed to be essential in optimizing patient care of many neurodevelopmental conditions, such as cerebral palsy (Novak *et al.*, 2017).

How can we identify very early neurodevelopmental deviance?

A widely accepted key to an improved neurodevelopmental patient care is early intervention, which should commence before the onset of more severe clinical symptoms (Novak *et al.*, 2017). This calls for new kinds of clinical markers, which can detect early precursors of an upcoming neurodevelopmental deviance in a broad range of clinical settings. It would also be essential to understand the neuronal underpinnings of such biomarkers, which calls for translational research in animal models. Recent studies in neonatal neurology have shown that different measures of spontaneous brain activity may be crucial for such early predictions. For instance, distinct features of cortical activity (Hellstrom-Westas *et al.*, 2001; Iyer *et al.*, 2015a; Iyer *et al.*, 2015b; Klebermass *et al.*, 2011; Lloyd *et al.*, 2021; Wikstrom *et al.*, 2012) or sleep-wake cycle (Hellstrom-Westas *et al.*, 2001; Klebermass *et al.*, 2011; Wikstrom *et al.*, 2012) can predict long-term neurodevelopment during early hours after asphyxia or preterm birth. Likewise, characteristics of spontaneous motility of an awake infant may provide the most sensitive prediction of upcoming cerebral palsy (Einspieler and Prechtl, 2005; Novak *et al.*, 2017). Recent studies have also indicated that in-utero exposure to maternal treatment with anti-depressant (Grieve *et al.*, 2019; Videman *et al.*, 2017) or anti-epileptic drugs (Tokariev *et al.*, 2021; Videman *et al.*, 2016) may affect newborn brain activity. These early biomarkers have so far been developed at the bedside only. However, it would be straightforward to build animal models for these clinical conditions, and the clinically identified EEG markers would provide direct translational bridges where appropriately designed translational research

provides crucial mechanistic insights and suggest improved future therapeutic strategies. For instance, Selective Serotonin Reuptake Inhibitor and opioid exposures in animal models have already been shown to cause long-lasting consequences in sensory processing (Alipio *et al.*, 2020; Alipio *et al.*, 2021). Similarly, infants of mothers exposed to valproate have a higher incidence of autism spectrum disorders and prenatal valproate exposure in animals is associated with altered subplate circuits (Christensen *et al.*, 2013; Nagode *et al.*, 2017).

What treatment strategies are available?

Given the limited specificity of early diagnostics, the optimal early therapeutic strategies are aimed to unselectively restore neurodevelopmental deviance or to limit further harm. Considering the crucial role of neuronal activity in neurodevelopment, it is easy to envisage the key role of activity as the therapeutic target and a key readout measure. A wide range of therapeutic approaches have been developed on the notion that improving the early sensory environment, a.k.a. environmental enrichment, may have a range of positive effects on later neurodevelopment. These enrichment strategies may have arisen from academic schools that count on a special role of some enrichment, such as music, emotions, or touch (Guzzetta *et al.*, 2009; Lordier *et al.*, 2019; Sa de Almeida *et al.*, 2020; Welch *et al.*, 2017). These studies have generally shown mild to moderate improvements in neurodevelopment of the given cohort, typically preterm infants. Due to many logistic and science political issues, however, it has not been possible to compare different enrichment strategies with each other, an approach that would be essential for building evidence-based medical treatments. Some of the underlying key questions, such as treatment comparisons or neuronal effects, could be approached with well-designed translational animal models. Current scientific evidence suggests that the effects of environmental enrichments are likely global and unspecific. Importantly, preclinical evidence has suggested how sensory enrichment could be improved. For example, developing neurons and synapses tend to depress rapidly, thus a continuous stimulation is likely far less effective than a rarely occurring stimulation in driving neural activity. Indeed, such a paradoxical effect is observed after selective subplate lesions combined with monocular deprivation (Kanold and Shatz, 2006). Due to many practical and ethical constraints, it will be impossible to systematically compare sensory enrichment therapies using clinical studies alone. Like pharmaceutical therapies, it would be highly appropriate that the key components of sensory enrichment strategies are developed with preclinical studies prior to progressing into human experiments, and that all approaches are looked at in a similar framework. From the neurobiological perspective, it would be most interesting to implement a combined multisensory approach which “mimics the womb.” This approach is constrained by the little knowledge that we have from the natural fetal sensory environment, which we know to vary dramatically from the environment available inside the NICU.

Furthermore, since childhood socioeconomic status has a strong impact on brain development (for review (Hackman *et al.*, 2010), we need a better understanding how prenatal factors, parent-offspring interactions (Welch and Myers, 2016), environmental enrichments (Beltran *et al.*, 2021), and cognitive stimulation in the home environment may improve cognitive and emotional development. Here, experimental animal studies are challenging and for some questions will be less valuable, but nevertheless may provide important insights into the molecular and cellular mechanisms underlying developmental disturbances during the pre- and early postnatal period.

7. Conclusions and outlook

Here, we summarized the current abilities of measuring early brain activity in developing animals and humans. What can be measured in clinical settings versus animal experiments is vastly different. At the current moment, EEG is the only direct measure of cortical function that is available both at the bedside and in animal models. It may provide powerful early biomarkers, and a strong link between experimental animal models and human studies. However, EEG has limitations due to limited spatial resolution, emphasis on cortical functions, and many computational challenges in signal analytics. Thus, other early biomarkers are needed.

One current bottleneck is how to relate normal and abnormal EEG activity to milestones in morphological and physiological development. This can only be studied using bidirectional translational efforts with invasive animal recordings. A second bottleneck and limitation is a lack of consensus of best practices and the lack of thorough long-term outcome studies. A third bottleneck is the sparsity of analysis tools. Solutions leveraging a ubiquitous cloud computing resources could enable the rapid dissemination of improved algorithms and also allow for the testing of improved analysis.

Translational research could become far more effective by introducing a continuous dialogue between preclinical and clinical research: The scientific questions in preclinical studies could respond to genuine, unmet needs from the clinical field. Such needs are routinely identified in consensus guidelines, the backbone of contemporary evidence-based medicine. It is, unfortunately, less common that these unmet needs migrate to the focal points of competitive funding, or the headlines in leading basic science publication. Yet the change for a better translational neurodevelopmental is possible. Since every translational research setting is constrained by practical and ethical realities, the methodological compromises need to strike a balance between what is ideal and what is pragmatic. Thus, the cost-benefit of such balance can only be assessed by combining all prior clinical and neurophysiological knowledge to the given research aims. While this may seem like a daunting task, the immediate and long-term benefits of evolving translational research efforts will more rapidly and greatly benefit

therapeutic developments for the myriad of diseases, injuries, and disorders that harm patients today.

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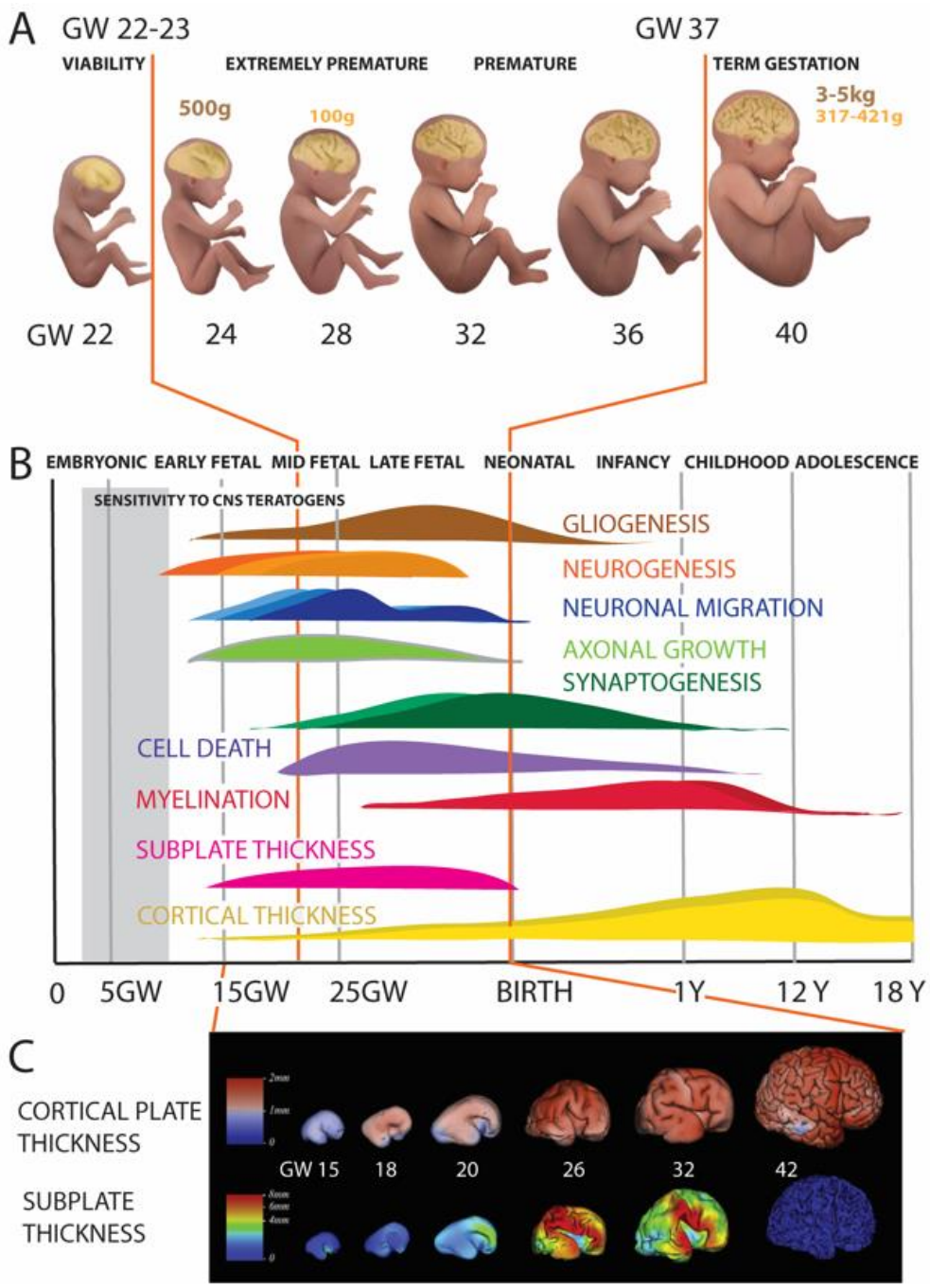

Figure 1 Time frame of the development of the human brain.
A: At term gestation (GW 37) the newborn infant is about 3-5 kg and its brain is around 317-421 g. Premature and extremely premature babies can weigh less than 500 g and their brain is less than 100 g. The viability at extremely premature birth GW22-23 is very low.
B: Relative timing of cortical neurogenesis, gliogenesis, neuronal migration, axonal growth, synaptogenesis, cell death, myelination shows gradient in various cortical areas (indicated in different shades). Myelination can continue in frontal cortical areas unto adolescence. The largely transient subplate peaks mid fetal life and largely removed around birth. Cortical thickness peaks around 12 years of age, although this depends on the exact cortical area, occipital faster, compared to frontal areas.

C: The relative thickness of cortical plate and subplate changes with age during prenatal development. Thickness of cortical plate (upper row) and subplate compartment (bottom row) measured in millimeters (color coded bars on the left, thicker red, thinner blue) at 15, 18, 20, 26, 32, and 42 GW (left to right). (Reproduced with permission from (Vasung *et al.*, 2016).

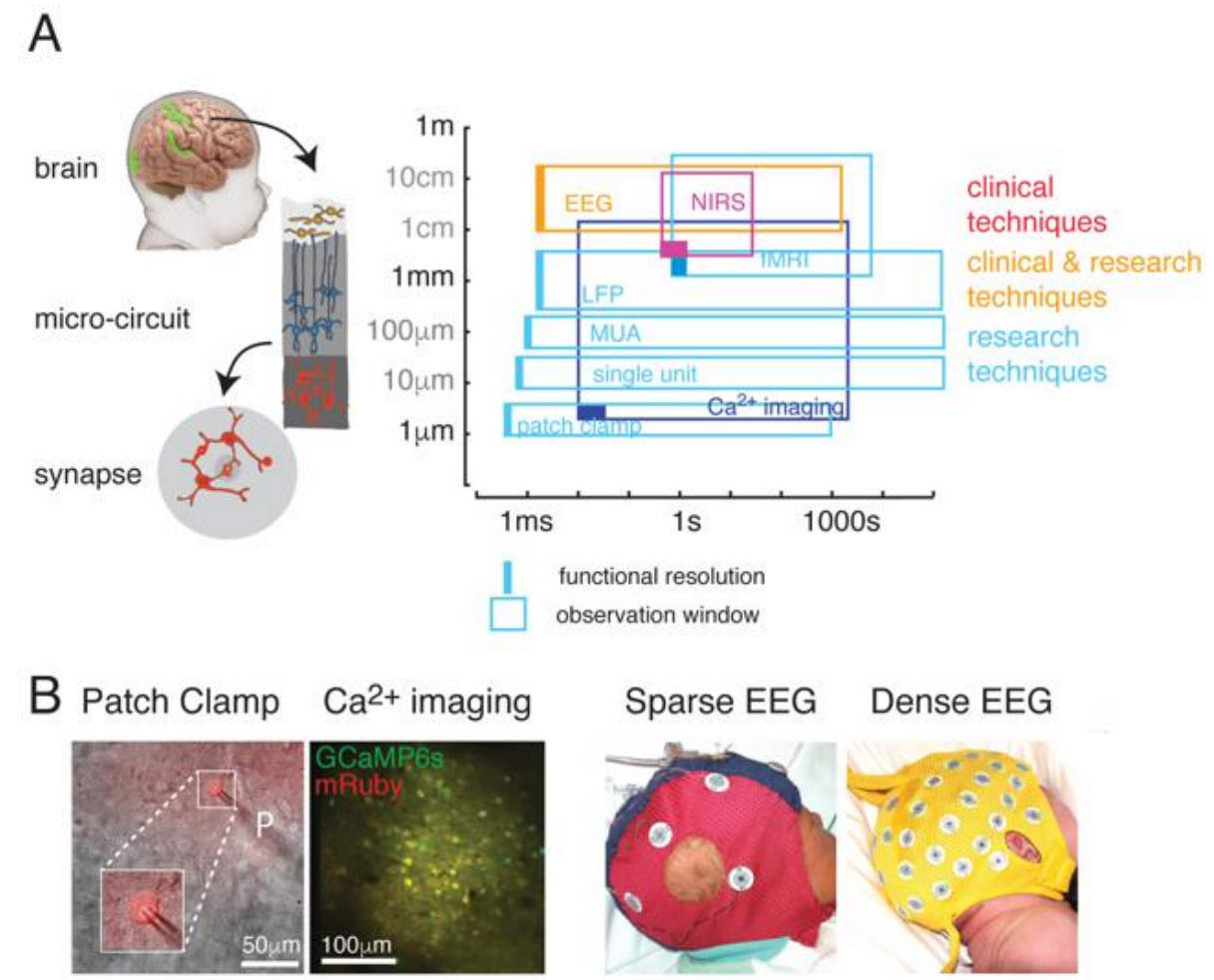

Fig. 2. Spatial and temporal scales of experimental and clinical techniques. **A**, Range of spatial resolution and measurement scale and temporal resolution and observation window for research (blue) and (red) clinical techniques as well as EEG which encompasses both. **B**, Examples of spatial resolution of research techniques such as patch clamp recordings and Ca^{2+} imaging (from (Meng *et al.*, 2017; Meng *et al.*, 2020b)**,** and clinical EEG of a term infant monitoring with sparse electrodes or detailed assessment with a dense EEG array.

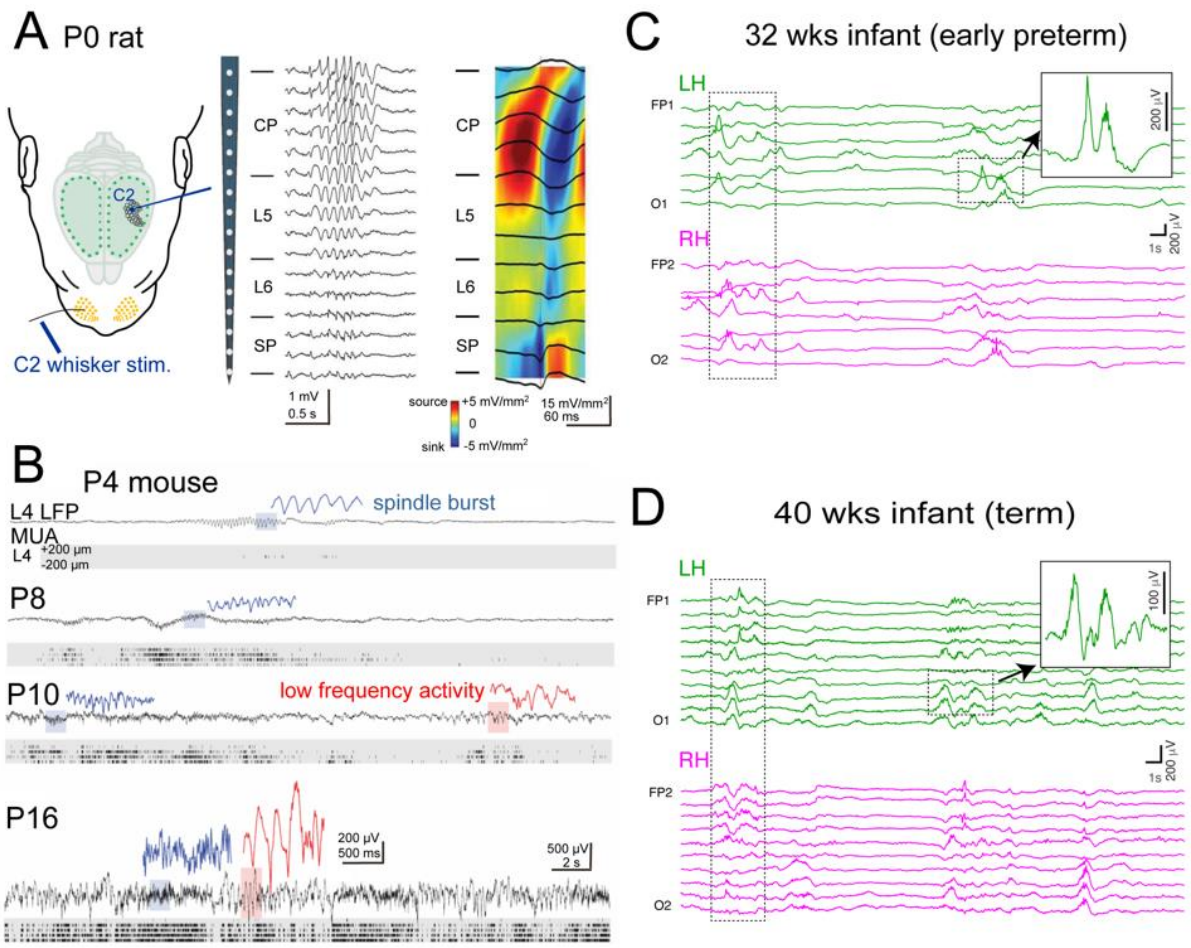

Fig. 3. Development of network activity in rodent and human cerebral cortex. **A**, Depth profile of sensory evoked activity in P0 rat barrel cortex in vivo. Mechanical stimulation of a single whisker evokes spindle burst activity recorded with a 16-channel electrode. The averaged current-source-density plot was calculated from 10 spindle bursts. Note early sink in subplate corresponding to source in cortical plate. From (Yang *et al.*, 2009). **B**, Development of spontaneous network activity in mouse visual cortex in vivo. LFP recorded in L4 and MUA recorded in channels up to 200 µm above and below L4. With maturation spindle bursts (blue traces) and low frequency activity (red traces) show higher frequency and background activity becomes stronger. From (Shen and Colonnese, 2016). **C**, EEG activity during quiet sleep in a preterm infant at 32 weeks of postmenstrual age shows intermittent high amplitude bursts with poor spatial synchrony between cortical sites or left vs right hemispheres (LH and RH, respectively). **D**, Same infant as in figure C recorded two months later at term equivalent age, showing changes in increased number, amplitude and shape of bursts, and enhanced synchronization across cortical areas. Note the larger amplitudes in preterm infant.

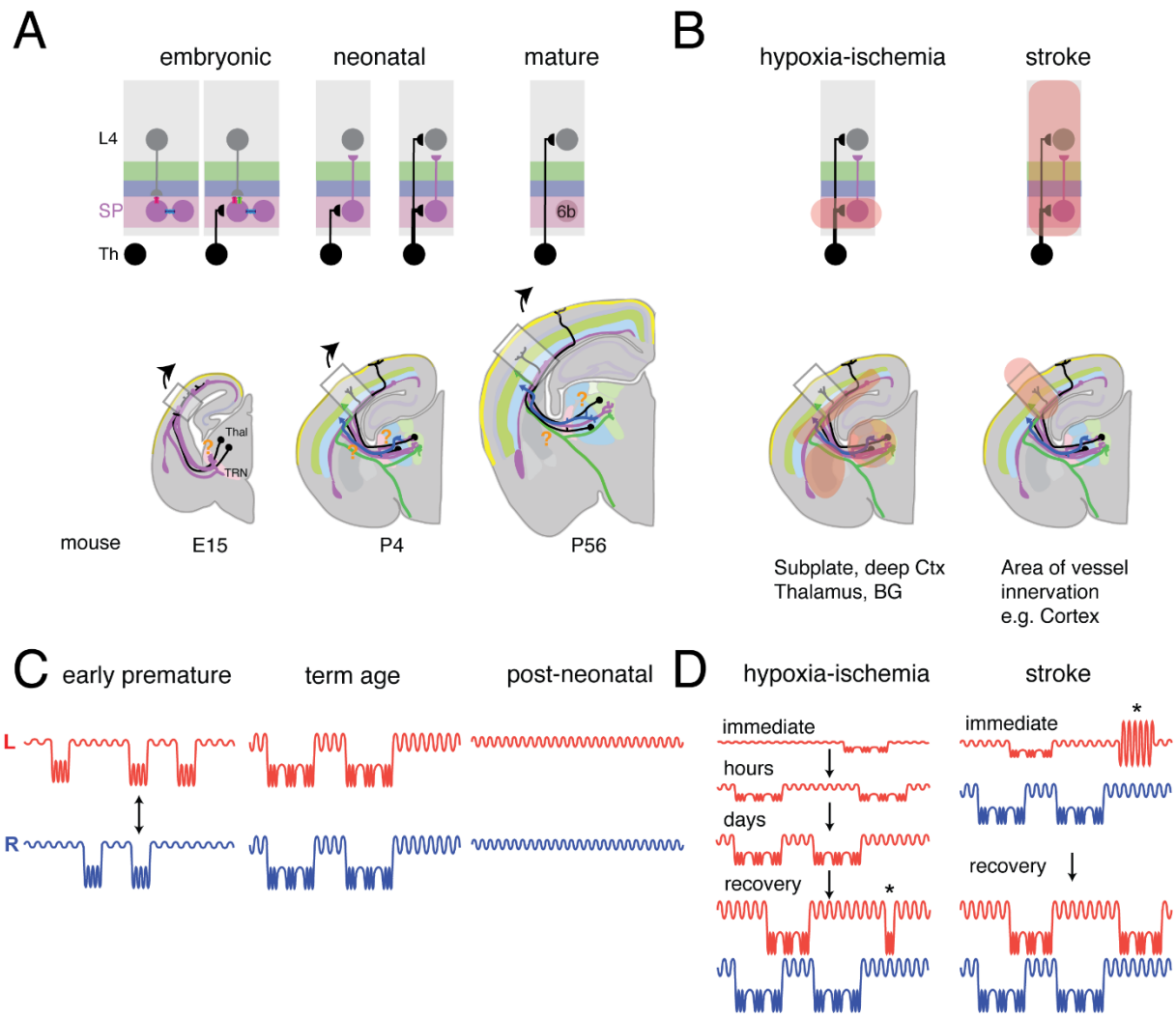

Fig. 4. Changing circuits in the developing thalamocortical system and effects of insults on cortical EEG. **A**, Graphs show connections between thalamus and cortex and within the cortex during development. Subplate neurons are the first targets of developing thalamic projections. **B**, Altered circuits in pathological conditions. **C**, Schematic illustration of the main components and their hemispheric relationships (L, red, left; R, blue, right) in a spontaneous EEG activity during normal human development. In early premature infants, EEG shows very low amplitude continuous activity interrupted by brief high amplitude bursts, spontaneous activity transients (SATs), with nested oscillatory activity at higher frequencies. The SATs are poorly synchronized between hemispheres (arrows). At term age, the continuous EEG activity has become higher amplitude and the SAT events are longer duration, more complex and more synchronized across cortical areas. At post-neonatal age, the EEG activity shows continuous activities at higher frequencies and the intermittent SAT type activities have disappeared. **D**, Hypoxia-ischemia (HI, left) and stroke (right) induced pathophysiological EEG patterns in newborn infants evolve over hours and days after incident. HI induces an immediate decrease in all EEG activity, followed by a gradual and incomplete recovery through burst suppression to continuous EEG over hours or days. Seizures may also occur during this period. After few days at latest, the SATs are still asynchronized between hemispheres and their shape may be altered while intervals maybe increased. A larger stroke induces an immediate suppression of EEG activities near ischemic zone, as well as a frequent occurrence of seizures (asterisk). During recovery, EEG amplitudes would increase to normal level, however the SATs/bursts

remain asynchronous between hemispheres and their shape may be altered. C modified from (Vanhatalo and Kaila, 2006).

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