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Structured spontaneity: building circuits in the human prenatal brain

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Abstract

Early brain activity is crucial for neurogenesis and the development of brain networks. It has been challenging however to localize regions in the developing human brain contributing to spontaneous waves of neuronal activity. Recently, Arichi and colleagues reported that the temporal and heteromodal insular cortices play a central role in propagating these neural instructional signals.

Main text

Organization of mammalian neuronal circuitry emerges in the womb. Patterning of this circuitry begins at early stages in development, before many of the sensory organs are functional, and is guided by genetically programmed events as well as spontaneous neural activity that reverberates through circuits in the form of propagating waves. These spontaneous waves are thought to reinforce appropriate connections and also trigger essential activity-dependent signaling processes. While animal studies provide important clues about how these spontaneous events may be coordinated among brain regions, the large-scale constituents of these spontaneous waves of activity in the developing human fetal brain are largely unknown.

The emergence of spontaneous activity in neural circuits *ex vivo* had been observed long ago. Given the opportunity, neuronal populations cultured in media begin within days to produce spontaneous action potentials and calcium transients at irregular intervals [1]. With time, these cells become more integrated, more connected, and begin generating bursts of synchronized discharges that travel over larger territories of the culture. Eventually, a complex functional structure emerges through spontaneous interactive processes. In this

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structure, “hub” neurons that have high degree of input and output connections seem to fulfill a central role in coordinating the network’s activity. Thus, even in a dish, intrinsic cellular properties drive spontaneous activity that is instructive in the establishment of complex neuronal connectivity patterns.

Much of the current understanding about the roles of spontaneous neural activity in influencing maturation of neocortical networks comes from studies in animal model systems. These studies reveal a rich repertoire of spontaneous activity patterns that are present during distinct phases of late prenatal and early postnatal development. This activity is instrumental in neurogenesis and the formation of neural circuits (for a review, see [2]). Notably, these patterns evolve across development, with early network oscillations giving way to more complex activity motifs with age.

Electroencephalography (EEG) studies in preterm born neonates confirm that endogenously driven spontaneous activity is a fundamental process also in human brain development. Preterm newborns exhibit very slow (up to 5 seconds) spontaneous activity transients (SATs) that cover large spatial extents. Faster EEG activity is “nested” within these slow oscillations, implying that the majority of spontaneous brain activity in the immature neocortex is framed within these developmentally programmed SATs.

In human development, one of the most common SATs is the delta brush waveform, characterized by a slow delta wave (0.3–1.5 Hz) with superimposed fast alpha-beta spindles (8–25 Hz). Delta brushes emerge at the beginning of the third trimester; their incidence peaks at approximately 34 weeks; and they cease by term age. Importantly, delta brushes observed in preterm neonates seem to correlate, for reasons that are not yet understood, with measures of brain development. Specifically, occurrence of delta brushes predicts more favorable outcomes, and new research suggests that incidence of these in preterm early postnatal days positively predicts subsequent brain growth [3]. These discoveries compel interest in understanding the origin and function of these SATs. The timing of these events coincides with emergence of whole brain functional neural networks [4], but due to the limited penetrance and spatial resolution of EEG, the basis of these signals in the spatial domain is poorly understood.

A recent paper by Arichi et al. [5] addressed the question of SATs localization by performing the first simultaneous EEG and functional magnetic resonance imaging (fMRI) assessment of delta brushes in the neonate preterm human brain. This group measured multi-modal EEG-fMRI brain activity during 7.5 minutes (median) of natural sleep in 10 infants (5 female) in the late preterm period, 32–36 weeks. All cases yielded robust posterior-temporal delta brush EEG activity, which fits with expectations for this developmental time frame. fMRI data revealed for the first time that these posterior temporal delta brushes are associated with hemodynamic activity localized in insular and temporal cortices.

The involvement of insular cortices in developmental delta brushes, as identified by Arichi et al., is compatible with known aspects of this highly connected, functionally versatile portion of the cortex. In primates and rodents, insular cortices are documented “hubs” of the neural connectome, with dense connections to almost all other regions of the brain. This property

emerges early in development, is apparent already in infancy [see Figure 1; 6], and positions these regions well to serve as a form of ‘switch operators’, signaling transitions between shifting dominance of competing large-scale neural networks [7]. The insular cortices receive somatotopic afferent signals from all areas of the body, and perform essential homeostatic functions through regulation of the autonomic nervous system (both sympathetic and parasympathetic). The findings by Arichi et al. expand the concept of the insula as a hub region by underscoring a role for the insula during maturation of the early human brain.

In addition to the discovery of insular cortices as a major location of spontaneous activity events in early human life, Arichi’s group also observed activity patterns in the temporal pole, superior temporal sulcus, and parietal operculum that were correlated with posterior-temporal delta brush events. These are regions that are highly connected to limbic and paralimbic regions, including the insula, that are in turn important later in life for emotion, language, and sensory processing. In the context of spontaneous activity generation, the temporal lobes also stand out as the most common origin of localized seizures, i.e. those seen in temporal lobe epilepsies. It is noteworthy that seizure disorders are 2–5 times more prevalent in individuals born preterm [8]. It is possible that early birth interferes with instructive spontaneous activity transients that are particularly relevant to temporal and insular maturation, as these are areas that are frequently altered in individuals born preterm [9].

In conclusion, through multi-modal imaging in preterm neonates, the study by Arichi et al. offered insight into the brain regions that are likely involved in generating waves of spontaneous activity across neural systems before birth and before functional circuitry are fully in place. Notably, the areas identified are heteromodal and involved in an array of higher order cognitive functions. The areas isolated are also highly connected, and some of them have been characterized as hubs in the eventual, mature connectional architecture of the brain. Over the years, much attention has been given to sensory and motor systems as among the first to emerge, perhaps in part due to their being more amenable to experimental testing in young animal preparations. The small but growing number of studies in humans seems to point at important roles for higher order and highly-connected cortices in the organization of the developing brain. Data from our group in human fetuses, for instance, depicts an important role for the posterior cingulate cortex (PCC, see [10]), another major hub of neuronal connectivity. Perhaps, when it comes to the development of large-scale brain systems, it is the connectional position, rather than overt function, that dictates how instrumental a given region will be in programming development of large-scale neural systems. Here, it seems, the insula, a hub of global brain connectivity, and other widely connected regions of the temporal lobes, are positioned well to play a major role in governing activity-dependent brain maturational processes.

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Figure 1.

Regions that are hubs of global brain connectivity in neonates and infants. Functional MRI data were obtained in a healthy pediatric sample of 51 neonates (panel A), 50 1-year-olds (panel B), and 46 2-year-olds (data not shown) during natural sleep. Colors on brain surfaces are used to visualize mean regional 'betweenness centrality' (BC) values. BC is a quantitative graph-theoretical measure that represents how connected a given region is to all other regions. Regions with the highest BC values included regions of bilateral insular cortices and temporal lobes, which based on new results by Arichi and colleagues [5] are regions involved in propagation of spontaneous activity transients that are important for network development in the antenatal period. Figure modified from Gao et al. [6].