childhood language development. These techniques focus more on structural and functional definition of alterations in brain development that may underpin the adverse neurodevelopmental consequences of preterm birth.

In summary, one can rationally consider which technique moving from the more conventional "tool approach" to the more holistic "concept approach" as demonstrated in Table 1A and 1B. To understand which technique must be considered for monitoring the newborn brain, one must assess three key elements - what, why and the nature of the abnormality that you may wish to monitor?

TERRIE INDER
Chair, Department of Pediatric Newborn Medicine, Brigham and Womens Hospital
Mary Ellen Avery Professor in Pediatrics, Harvard Medical School, Boston, MA

TOOL	STRUCTURE	FUNCTION
Cranial Ultrasound	2D and 3D renderings	Doppler CUS
Magnetic Resonance Imaging	Conventional injury Brain volumes Diffusion Microstructure	Functional MRI Resting State fMRI MR Spectroscopy
EEG/aEEG	Localize injury/anomaly	Background activity Abnormal activity
Near Infrared Spectroscopy	NA	Cerebral Blood Flow CMRO2
Magneto-encephalography	Abnormal structures e.g. focal epilepsy	Magnetic Field from Cerebral activity
Functional and Neurological Examination	NA	HHNE, Thomson, NNNS, APIB, Prechtl. Family evals. Infant/Child Outcomes

	CONCEPT	METHOD	MEASURE
STRUCTURE	Injury Regional & total volume Micro- and chemical structure	MRI	T1, T2 conventional DTI – Microstructure H-MRS – Chemical Cartography – maps
STRUCTURE	Injury and Structure	Cranial US	2D, 3D
FUNCTION	Baseline cerebral blood flow	Cranial US NIRS rsfcMRI	CUS Doppler CBF Synchronous networks
FUNCTION	Activated or functional cerebral blood flow	fMRI Diffuse Optical Tomography	Regional activation
FUNCTION	Cerebral activity	EEG aEEG	Background Abnormality
FUNCTION	Cerebral Metabolism	NIRS P_MRS	CMRO2 ATP
FUNCTION	Neurological Function	HNNE, NNNS etc.	Outcomes/Function

Table 1: A) The Tool Approach and B) Concept Approach to monitoring the Newborn Brain.

RELATION BETWEEN FUNCTIONAL AND STRUCTURAL BRAIN DEVELOPMENT IN EXTREMELY PRETERM BORN INFANTS

■ For neonates born extremely preterm, there is an important overlap of brain development – which normally occurs in the third trimester of pregnancy – with the Neonatal Intensive Care admission. Over the last decades major steps have been taken by studies evaluating developmental changes using neuromonitoring (functional brain development) and neuroimaging ((micro)structural brain development).

Amplitude-integrated electroencephalography (aEEG) – using the filtered and time compressed raw EEG – is widely accepted as a useful tool for continuous bedside neuromonitoring[1,2]. In extremely preterms, the (a)EEG background pattern and spontaneous activity transients (SATs or bursts) in early life are found to correlate to long-term neurodevelopment[3]. The aEEG background can be influenced by brain injury, drugs – for example morphine – and overall illness[4]. Magnetic resonance imaging (MRI) is the most advanced tool to examine (micro-)structural brain maturation. In the last trimester of gestation immense volume expansion and gyrification of the cortical gray matter take place[5,6] while at the same time the aEEG background pattern is maturing from a broad amplitude to a smaller bandwidth with increase of sleep-wake cycling (figure1). This suggests the maturation of the cerebral cortex to be reflected by changes in aEEG amplitude and background pattern.

One of the most critical events for brain development occurring in the late fetal phase is the growth of thalamocortical connections. The afferent neurons grow from the thalamus into the subplate where a waiting period takes place and the neurons synapse to the subplate neurons[7]. After 24 weeks of gestation fibers start to migrate from the subplate into the cortical plate to form synapses there. From the 29th week onwards cortical organisation is initiated with the formation of cortico-cortical connections[8,9]. As soon as synapses are formed they will start to generate transient electrical signals, which correspond with SATs on the aEEG. The frequency and amplitude of SATs will decrease with increase of gestation, and are normally not found after term equivalent age[10]. Biagioni et al.[11] showed that EEG in the first week of life is correlated to structural cortical gray matter development on MRI around the same time.

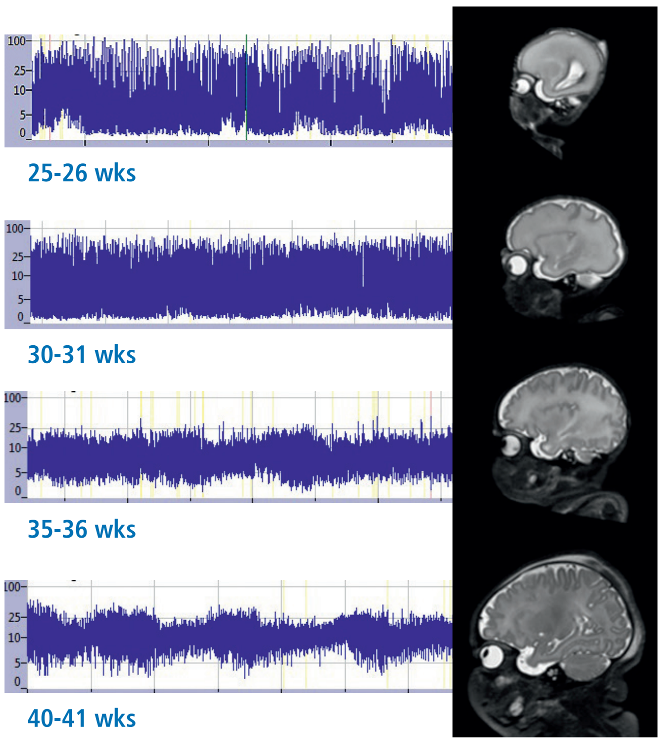

Figure 1: aEEG background pattern at four different time points showing the maturation over time, where the background patterns goes from a broad amplitude to a smaller bandwidth with sleep-wake cycling. The corresponding T2 weighted MRI images in the sagittal view are showing a near smooth brain at 25 weeks, with a brain folded similar to the adult brain at term age.

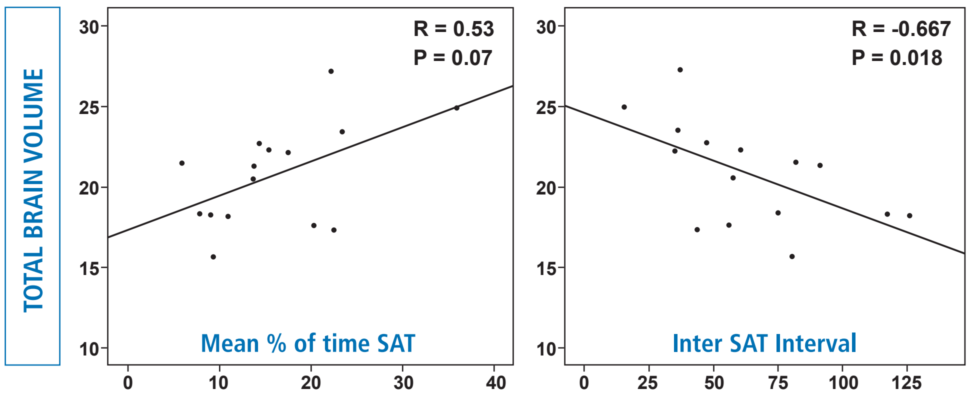

Figure 2: Image adapted from a paper by Benders et al. in Cerebral Cortex (13). A higher % of time detected as SAT was correlated to a higher total brain volume (in ml), where larger periods of intervals between SATs were negatively correlated.

The question remains whether there is a correlation between early brain activity (in the first days of life) and structural brain development over time. Natalucci et al.[12] found in extremely preterms a correlation between aEEG maturity in the first days of life and MRI brain maturation at term equivalent age. In our study published in 2014[13] we found similar results. The total brain volume increased faster between 30 and 40 weeks of gestation in preterms showing more SAT events and/or less quiet intervals in the first days of life (figure 2). The same could be found for subcortical gray matter volume (basal ganglia and thalamus) and cortical surface.

aEEG can be used to monitor early brain function, and SATs are mirroring the development of thalamocortical connections, but also seem to be predictive of structural brain development over time. This is consistent with the idea that increased levels of early brain network activity are associated with better brain growth, showing the intimate relation between brain structure and function during brain development.

MANON JNL BENDERS, MD PhD., NATHALIE HP CLAESSENS, MD
Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

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