Zárójelentés

Újszülött csecsemők hangfeldolgozási képességei (K 101060)

A projekt során a kommunikációt megalapozó hallási feldolgozási folyamatokat vizsgáltunk egészséges, időre született újszülötteken, eseményfüggő agyi potenciálok (EAP) segítségével. Az eredményeket az egyes kérdések bontásában írjuk le.

I) Befolyásolja-e a hangkörnyezet az újszülött hallási EAP-k morfológiáját?

Megállapítottuk, hogy a hasonló eseményfüggő agy potenciál (EAP) morfológia mögött eltérő folyamatok húzódnak meg két széles spektrumú hang (fehér zaj és környezeti hangok) feldolgozásánál. Amíg a fehér zajra adott EAP válasz nem függött attól, hogy a hangot önmagában vagy egy összetett szinuszos hangokból álló hangsor részeként mutattuk-e be, a környezeti hangokra adott EAP választ szignifikánsan változtatta a hangsorbeli környezet.

Az eredményekről készült beszámolónk megjelent:

Háden, G.P., Németh, R., Török, M., Drávucz, S., & Winkler, I. (2013). Context effects on processing widely deviant sounds in newborn infants. Frontiers in Psychology, 4:674.

II) Magyarázható-e az újszülöttek EAP válasza deviáns ingerekre refraktórikussággal?

Megállapítottuk, hogy az újszülötteknél mérhető eltérési válasz nem magyarázható pusztán neuronális refraktórikussággal. A ritka deviáns ingereket egy olyan kontroll válasszal hasonlítottuk össze, amelyet a deviáns ingerrel azonos valószínűségi és azonos akusztikus paraméterekkel rendelkező hangok váltottak ki, melyek azonban a saját hangsorukban nem sértettek meg semmilyen szabályosságot. Az így kapott különbségi válasz ezért az emlékezeti összemérés EAP hatásának egy viszonylag tiszta becslése. Ez a kísérlet helyettesíti az eredeti terv II. kísérletét, melyet közben más kutatók már elvégeztek.

Az eredményekről készült beszámolónk megjelent:

Háden, G.P., Németh, R., Török, M., & Winkler, I. (2016). Mismatch response (MMR) in neonates: beyond refractoriness. Biological Psychology, 117, 26–31.

III) Az újszülött csecsemők felbontják-e a hangokat egymástól független ingertulajdonságokra?

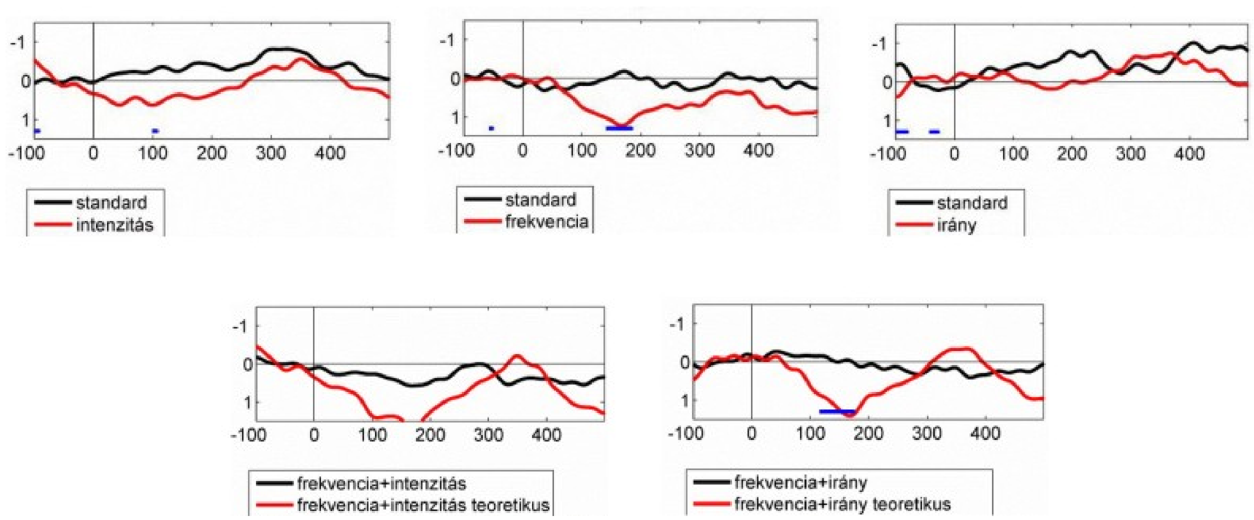
Ennek a kérdésnek a megválaszolásához először bizonyítani kellett, hogy az újszülöttek érzékenyek egy korábban nem vizsgált hang-tulajdonságra, a hangforrás helyére. Megállapítottuk, hogy az újszülött csecsemők feldolgozzák a horizontális irányú hangforrás lokalizáció két legfontosabb jelzőmozzanatát, a fülek között idő és hangerősség különbséget. Azonban, a jelzőmozzanatok szenzoros felbontása jelentősen alacsonyabb a felnőttekhez képest. Újszülöttek a hangforrások irányának eltérést csak redundáns jelzőmozzanatok (egyik vs. másik fül, vagy valódi térben elhelyezett hangforrások) esetén detektálják megbízhatóan.

Az eredményekről készült beszámolónk megjelent:

Németh, R., Háden, G.P., Török, M., & Winkler, I. (2015). Processing of horizontal sound localization cues in newborn infants. Ear and Hearing, 36(5), 550-556.

A következő lépésben a hangmagasság és a) a hangerősség illetve b) a hangforrás helye tulajdonságok független reprezentációját vizsgáltuk meg oly módon, hogy összehasonlítottuk a ritka, mindkét tulajdonságban a gyakori ingertől eltérő hangokra adott választ a két külön-külön megjelenő eltérésre adott válaszok összegével. Az összeadott (elméleti) és a valós válaszok egyenlősége a két tulajdonság függetlenségére utal. Felnőtt adatok alapján, a hangmagasság és a hangerő között összefüggést, a hangmagasság és a hangforrás helye között függetlenséget vártunk.

Az eredmények mindkét esetben jelentős eltérést mutattak az elméleti és a valós válaszok között (1. ábra). Ez arra utal, hogy az újszülöttek nem bontják fel a hangokat független hangtulajdonságok mentén. Az eredmények értékelése még folyamatban van. A későbbiekben ezekről cikkben kívánunk beszámolni.



1. ábra. Felső sor: A gyakori hangingerektől különböző tulajdonságokban (intenzitás: bal oldal; hangmagasság: közép; hangforrás helye: jobb oldal) eltérő ritka hangokra adott átlagolt EAP válaszok újszülött csecsemőknél (n=22). A gyakori ingert fekete, a ritka ingert piros vonallal ábrázoltuk. Alsó sor: Az egy tulajdonságban eltérő ritka hangingerekre adott válaszok összegének és az egyszerre két tulajdonságban eltérő ritka hangokra adott EAP válaszok összehasonlítása. Az ingerre adott választ fekete, a két egy-egy tulajdonságban eltérő ingerre adott válasz összegét piros vonallal ábrázoltuk.

IV) Érzékenyek-e az újszülött csecsemők a párhuzamosan működő hangforrások szétválasztásának azonnali jelzőmozzanataira?

Megállapítottuk, hogy újszülött csecsemők érzékenyek a hallási láncra bontás két azonnali jelzőmozzanatára, az elhangolt harmonikusra és az eltérő hangkezdetre. Amennyiben összetett szinuszos hangok valamelyik harmonikusát elhangoljuk, vagy a többihez képest késleltetjük, akkor az EAP-ben megjelenik egy olyan eltérés, amely analógiába hozható, a felnőtteknél talált tárgyhoz kötött negatívitás (TKN) komponenssel.

Az eredményekről készült beszámolónk megjelent:

Bendixen, A., Háden, G.P., Németh, R., Farkas, D., Török, M., & Winkler, I. (2015). Newborn infants detect cues of concurrent sound segregation. Developmental Neuroscience, 37(2), 172-181.

V) Reprezentálják-e az újszülöttek a hangmagasság változások trendjét?

Megállapítottuk, hogy újszülött csecsemők detektálják hangmagasság trendek megtörését. Monoton csökkenő hangmagasságú hangokból álló hangsorba ritkán beiktatott hangismétlések kiváltják a várható hangtól való eltérést jelző eltérési negatívitással (EN) analóg EAP komponenst. Az eredmények azt is megmutatták, hogy az újszülöttek a változás detektált iránya alapján előrejelzéseket tesznek a következő hang várható magasságára.

Az eredményekről készült beszámolónk megjelent:

Háden, G.P., Németh, R., Török, M., & Winkler, I. (2015). Predictive processing of pitch trends in newborn infants. Brain Research, 1626, 14-20.

VI) Detektálják-e az újszülöttek a hangsorok kezdetét, végét és a hangsor ütemének változását?

Megállapítottuk, hogy újszülött csecsemők detektálják rövid hangsorok kezdetét, belső ütemváltozását és befejezését. Az eredmény azt mutatja, hogy már újszülöttek is rendelkeznek a "turn-taking" és a beszéd-ütem adaptációhoz szükséges hallási perceptuális képességekkel.

Az eredményekről készült beszámolóink megjelentek:

Háden, G.P., Honing, H., Török, M., & Winkler, I. (2015). Detecting the temporal structure of sound sequences in newborn infants. International Journal of Psychophysiology, 96(1), 23-28.

Háden, G.P., Honing, H., & Winkler, I. (2012). Newborn infants are sensitive to sound timing. In E. Cambouropoulos, C. Tsourgas, P. Mavromatis and K. Pastiadis (Eds.), Proceedings of the 12th International Conference on Music Perception and Cognition and the 8th Triennial Conference of the European Society for Cognitive Sciences of Music (pp. 378-379), July 23-28, 2012, Thessaloniki, Greece.

A hangok időzítésére való érzékenység fejlődésének vizsgálata során megállapítottuk, hogy két és négy hónapos csecsemők reprezentálják a hangsorok bemutatási ütemét: az ingerek közötti idő ritkán történő lerövidítése kiváltja az automatikus előrejelzések megsértésének megfelelő EAP-ket. Az EAP-k morfológiájában két és négy hónapos kor között található különbségek jelzik a feldolgozási folyamatok fejlődését.

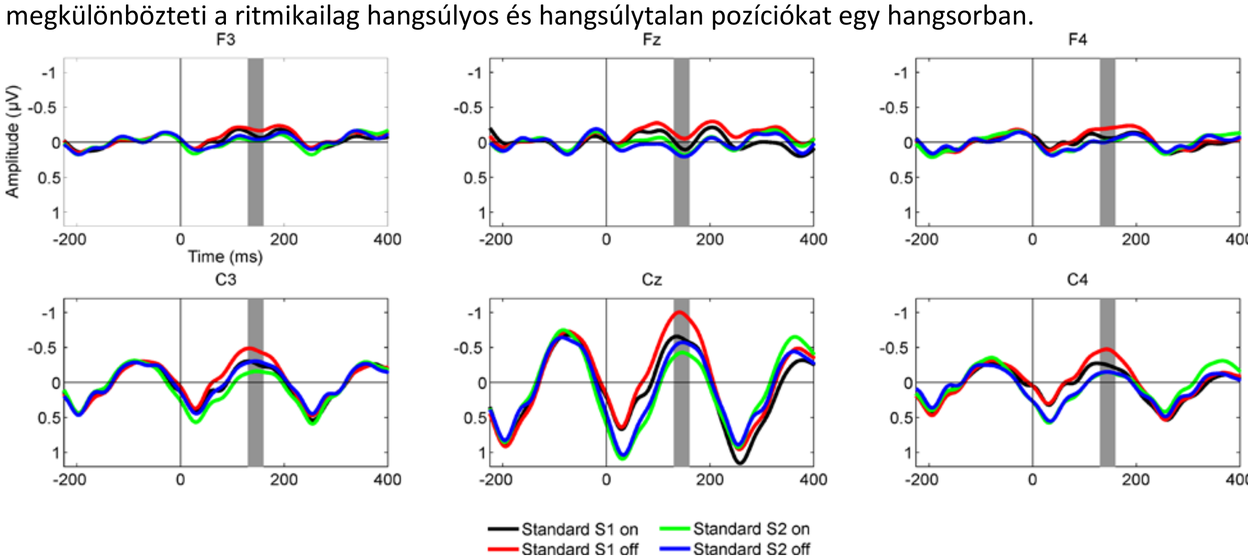
Az eredményekről készült beszámolónk megjelent:

Otte, R.A., Winkler, I., Braeken, M.A.K.A., Stekelenburg, J.J., van der Stelt, O., & Van den Bergh, B.R.H. (2013). Detecting violations of temporal regularities in waking and sleeping two-month-old infants. Biological Psychology, 92(2), 315-322.

van den Heuvel, M.I., Otte, R.A., Braeken, M.A.K.A., Winkler, I., Kushnerenko, E., & Van den Bergh, B.R.H. (2015). Differences between human auditory event-related potentials (AERP) measured at 2 and 4 months after birth. International Journal of Psychophysiology, 97(1), 75–83.

VII) Ritmikailag hangsúlyos és hangsúlytalan hangok feldolgozása újszülött csecsemőknél

Kidolgoztunk egy olyan ingerparadigmát, amellyel egy ingersorban a ritmikailag hangsúlyos és hangsúlytalan pozíciókban kiváltott agyi válaszok hasonlíthatóak össze, akusztikailag jól kontrolált környezetben. Az elrendezésben zongora és csembaló hangok felváltva követik egymást és a sorozat kezdő hangja határozza meg, hogy a kettő közül melyik hangot észleljük hangsúlyosnak. Eredményeink (lásd 2. ábra) alapján az újszülött hallórendszer e minimális kontextuális információ alapján is megkülönbözteti a ritmikailag hangsúlyos és hangsúlytalan pozíciókat egy hangsorban.



2. ábra. Átlagolt (n=24) EAP-k újszülött csecsemőknél hangsúlyos (on) és hangsúlytalan (off) pozícióban megjelenő zongora (S1) és csembaló (S2) hangokra. A szürke sáv az EAP amplitúdó mérési ablakát jelzi.

Az eredményekről beszámoló cikk megírását megkezdtük. Egy előadást már tartottunk az eredményekről:

Háden, G.P., Simon, J., Winkler, I.: Rhythmic context affects deviant processing in newborn infants. BACN, The British Association for Cognitive Neuroscience (BACN) annual meeting, September 12-14, 2016, Budapest Hungary.

VIII) Születési és anyai változók hatása csecsemők agyi aktivitására

A fogantatástól a megszületésig eltelt idő befolyásolja az újszülöttek EEG-ből számított nyugalmi funkcionális hálózatának struktúráját. Az elemzéshez elsőként alkalmaztuk újszülötteknél a minimális feszítő fák módszerét. A módszer lehetővé tette számunkra a hálózatok globális tulajdonságainak vizsgálatát. A frontális és parietális hálózatok topológiai tulajdonságai összefüggést mutattak a terhesség hosszával. Ez alapján arra következtethetünk, hogy az agyi funkcionális hálózatok változása összefügg az agy érésével: a centralizált hálózatok decentralizáltabb hálózatoknak adják át a helyüket.

Az eredményekről készült cikk jelenleg revízió alatt áll (lásd a csatolt kéziratot):

Tóth, B., Háden, G.P., Urbán, G., Molnár M., Török, M., Stam, C.J., & Winkler, I. (under revision). Resting-state EEG functional connectivity in newborn infants. Human Brain Mapping.

Az anyai gondosság és szorongás hatással vannak a bejósolhatatlan hang-változások által kiváltott EAP válaszokra 9 hónapos csecsemőknél. Megállapítottuk, hogy az anyai gondosság csökkenti, a szorongás növeli az ilyen válaszokat. Ezt úgy értelmeztük, hogy az anyai gondoskodás hatással van arra, hogy a váratlan események milyen mértékű figyelmi elterelődést váltanak ki a csecsemőben.

Az eredményekről készült beszámolónk megjelent:

van den Heuvel, M.I., Donkers, F.C.L., Winkler, I., Otte, R.A., & Van den Bergh, B.R.H. (2015). Maternal mindfulness and anxiety during pregnancy affect infants' neural responses to sounds. Social Cognitive and Affective Neuroscience, 10(3), 453-460.

IX) Elméleti összefoglalók

Összefoglaló elemzést közöltünk arról, hogyan válik szét az akusztikus eltérés és az újdonság feldolgozása az élet első évében.

Kushnerenko, E.V., Van den Bergh, B.R.H., & Winkler, I. (2013). Separating acoustic deviance from novelty during the first year of life: A review of event-related potential evidence. Frontiers in Psychology, 4:595.

Elemeztük az újszülött csecsemők hallási képességeinek mintázatát. Arra a következtetésre jutottunk, hogy e képességek jelentős része a hangokkal történő kommunikáció, azon belül is a dialógusok felépítésének és fenntartásának szolgálatában áll.

Winkler, I. (2015). Előbb az összetett, később az egyszerű: Csecsemők magasabb szintű hangfeldolgozási képességei a beszédértés előtti időszakban. Magyar Pszichológiai Szemle, 70(4), 675-721.

Összefoglalás

A pályázat megvalósítása során haladást értünk el az újszülött csecsemők hallási képességeinek feltérképezésében. Ezekre, és korábbi vizsgálatokra támaszkodva előre léptünk e képességek funkcionális értelmezésében is.

Egy eltéréssel, amelyet a szakirodalom menet közbeni fejlődése indokolt, megvalósítottuk a tervezett kísérleteket. Az eredmények többségét a pályázati időszakban publikáltuk; a fennmaradó vizsgálatok eredményeinek publikációja pedig folyamatban van. Néhány területen, nemzetközi együttműködés segítségével túlteljesítettük a pályázatban vállalt feladatokat.

Melléklet:

Tóth, B., Háden, G.P., Urbán, G., Molnár M., Török, M., Stam, C.J., & Winkler, I. (under revision). Resting-state EEG functional connectivity in newborn infants. Kézirat.

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Large-scale network organization of EEG functional connectivity in newborn infants

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Keywords:	Electroencephalography, neonate, functional connectivity, network analysis, graph theory, Minimum Spanning Tree

Full title: Large-scale network organization of EEG functional connectivity in newborn infants

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Short title: Functional connectivity in the newborn brain

Keywords: Electroencephalography, neonate, functional connectivity, network analysis, graph theory, Minimum Spanning Tree

Abstract

The organization of functional brain networks changes across human lifespan. The present study analyzed functional brain networks in healthy full-term infants (N = 139) within 1-6 days from birth by measuring neural synchrony in EEG recordings during quiet sleep. Large-scale phase synchronization was measured in six frequency bands with the Phase Lag Index. Macroscopic network organization characteristics were quantified by constructing unweighted minimum spanning tree graphs. The cortical networks in early infancy were found to be significantly more hierarchical and had a more cost-efficient organization compared to MST of random control networks, more so in the theta and alpha than in other frequency bands. Frontal and parietal sites acted as the main hubs of these networks, the topological characteristics of which were associated with gestation age (GA). This suggests that individual differences in network topology are related to cortical maturation during the prenatal period, when functional networks shift from strictly centralized toward segregated configurations.

1. Introduction

Efficient communication between brain regions in both micro- and macroscopic scales is essential for healthy cognitive functioning [Bassett et al., 2009; van den Heuvel et al., 2009; Varela et al., 2001; Uhlhaas and Singer, 2010]. The establishment of synaptic connections between cortical neurons forming highly organized cortical networks has been suggested as a hallmark of neuronal maturation [Boersma et al., 2011]. Previous infant studies found that genetic factors and sensory input are both crucial for the development of cortical networks [for a review, see Khazipov and Luhmann, 2006]. Neuronal communication between brain areas, the temporal coupling/dependency between spatially remote neuronal assemblies (termed "functional connectivity"; FC), has been shown to develop throughout the human lifespan [Fransson et al., 2007, Uhlhaas et al., 2009; Uhlhaas et al., 2010]. Therefore, it is important to determine its characteristics at birth, the point at which the environmental stimulation radically changes from that of the preceding fetal period. The aim of the present study was to track the organization of large-scale functional brain networks in newborn infants during quiet sleep and explore its relationship with gestational age (index of prenatal maturation) and variables characterizing possible prenatal influences on brain maturation, including some general clinical risk factors of the mother and the offspring.

EEG amplitude coherence and phase synchronization of neural rhythms are the most widely used methods for determining the strength of FC in spontaneous brain activity during rest or sleep. The large majority of studies investigating the development of FC in infancy have assessed either 1) FC differences between preterm or extremely low birth-weight infants and full-term newborns (Pereda et al., 2006, Gonzalez et al., 2011, Meijer et al., 2014, Grieve et al, 2008, Omidvarnia et al. 2014) or 2) longitudinal changes in FC following preterm birth (Jennekens et al., 2012, Myers et al., 2012). One important result of these studies is the observations of rapid increase in fronto-parietal connectivity in preterm population from day one to three (Schumacher et al., 2015) and stronger connectivity in healthy relative to extremely low birth-weight newborns (Grieve et al, 2008). Although these and similar results clearly demonstrate that FC patterns are potential indicators of cortical immaturity, yet little is known about the effects of prenatal development on FC in healthy newborn infants.

Functional brain networks can be described as graphs, an abstract mathematical description of the network's elements and their interactions [for a review, see Stam, 2014; Stam and van Straaten, 2012]. Graph theoretical modelling has been useful for investigating the organizational principles of brain networks (for a review, see Varela et al., 2001). In healthy adults, in rest or no-task condition, EEG/MEG functional networks take the form of the cost-efficient "small-world" organization, which produces optimal ratio of direct communication between closely spaced and separated brain areas [Stam and van Straaten, 2012]. The small-world network organization combines the high-level clustering of ordered regular networks (which enable fast information flow within local subnetworks) with the short path length of random networks (which enable efficient large-scale integration of subnetworks). These neuronal networks also display hierarchical topology (see de Haan et al., 2012; van den Heuvel and Pol, 2010) and include densely connected 'hub' regions, which can serve as coordination centers [Achard et al., 2006].

So far, only few studies assessed the early development EEG brain networks in healthy newborns (Tokariev et al., 2015, Omidvarnia et al. 2014). During the first ca. 2 weeks after birth an increase in interhemispheric phase synchrony was observed together with a concurrent decrease in the ratio of intra-/interhemispheric connections in the low delta range (Tokariev et al., 2015). Another study (Omidvarnia et al. 2014) showed that the FC network organization during late gestation exhibits salient, spatially selective developmental trajectories: subnetwork clustering increases in anterior and decreases in posterior cortical areas, evidenced both at lower (3–8 Hz) and even stronger at the higher frequencies (5–18 Hz). These results represent network reorganization resulting from maturation or the change in external stimulation. Subnetworks further develop later during infancy and they are gradually differentiated during childhood, suggesting a relationship with the development of cognitive abilities [Ferreira and Busatto, 2013; van den Heuvel and Pol, 2010]. From a graph-theoretical perspective, FC between 5 and 7 years of age already exhibits the economical trade-off between high level clustering and short path length [Boersma et al., 2011; Fair et al., 2008; Micheloyannis et al., 2006; Power et al., 2010; Supekar et al., 2009, Smit et al., 2012, Bathelt et al., 2013]. fMRI studies of structural and functional connectivity in typically developing infants and children consistently observed that 1) after birth, the infant brain first develops strong local connectivity; 2) later, the focus shifts gradually toward stronger long-distance connectivity by strengthening the distant and weakening the local connections [Barry et al., 2004; Gong et al., 2009; Thatcher, 1992; Thatcher et al., 2008, Fair et al., 2008; Lebel et al., 2008; Power et al., 2010; Supekar et al., 2009; Yap et al., 2011].

In the present study, EEG has been recorded during quiet sleep [Prechtl, 1974] in healthy newborn infants born to term. The most frequent quiet sleep state was chosen because it is easily identifiable and it is the dominant vigilance state of the newborns; further, it has been associated with postmenstrual age (Duffy et al. 2003; Dulce et al., 2007). The characteristic features of FC have been extracted from EEG by calculating phase synchronization (measured as phase lag index, PLI; [Stam et al., 2007]) and represented using the graph-theoretical measures of minimum spanning tree (MST) topologies [Boersma et al., 2013, Stam and van Straaten, 2012]. The PLI measure reduces the effects of volume conduction (the effects of common sources on the EEG signal) and it is (largely) independent of the reference electrode [Martin and Chao, 2001]. PLI has been previously employed in measuring newborn infants' EEG-based FC (Gonzalez et al., 2011). Medical/biological data about the gestation age, the mother, and the infant were collected and their relationship with the characteristics of the functional networks was determined for assessing their possible association with brain maturation. In particular, we expected that 1) the topology of neuronal FCs will differ as a function of the underlying oscillatory frequencies and 2) longer gestation age, higher birth-weight, and optimal cardiovascular measures of the mother will result in more mature FC topologies (closer to the organization that combines the optimal ratio between functionally integrated and segregated FCs) in the infants.

2. Materials and methods

2.1. Participants

EEG was recorded in 164 healthy, full-term (gestation age (GA) 36 weeks and above) newborn infants (90 male) during day 1-6 postpartum. Data of 25 infants were excluded based on the criterion of retaining overall 140 seconds of EEG signal after artifact rejection (at least 35 epochs of 4096 ms duration). Thus, 139 healthy, full-term new-born infants (76 male) were included in the final sample. Table 1 summarizes descriptive statistics of medical/biological measures, whereas Supplementary table 1 shows the distribution of categorical data in our sample.

2.2. Procedure, Electroencephalographic recording

EEG was recorded in a dedicated experimental room at the Department of Obstetrics-Gynecology and Perinatal Intensive Care Unit, Military Hospital, Budapest. Informed consent was obtained from one or both parents. The mother of the infant could opt to be present during the recording. The study was conducted in full accordance with the World Medical Association Helsinki Declaration and all applicable national laws; it was approved by the relevant ethics committee: Medical Research Council – Committee of Scientific and Research Ethics (ETT-TUKEB), Hungary. The infants in our sample participated in one or more other EEG studies on sound processing within the same session. The EEG data reported here was always recorded first within the session.

Five minutes of spontaneous EEG was recorded during quiet sleep with Ag/AgCl electrodes attached to the scalp at the Fp1, Fp2, Fz, F3, F4, F7, F8, T3, T4, Cz, C3, C4, Pz, P3, P4 locations according to the International 10-20 system. The reference electrode was placed on the tip of the nose and the ground electrode on the forehead. Eye movements were monitored with two bipolarly connected electrodes: one placed lateral to the outer canthus of left eye and the other above the left eye. EEG was digitized with 24 bit resolution at a sampling rate of 1 kHz by a direct-coupled amplifier (V-Amp, Brain Products GmbH). The signals were on-line low-pass filtered at 110 Hz. The impedance of the electrodes was kept below 20 kΩ. Infants' sleep state was determined based on behavior criteria according to Anders et al. (1971). Only infants that were in quiet sleep for the whole 5 minute duration were included in the study. In addition to the behavioral criteria employed, the EEG signal was visually inspected. If movement related artefacts were present, the data was rejected from the further analysis (ensuring that muscle tension was tonic, respiration regular, and eyes movements absent).

2.3. EEG data analysis

EEG signals were off-line filtered (band-bass, Hamming windowed Fast Fourier Transform) in the 0.5-45 Hz frequency range. EEG data was analyzed by extracting 4096 ms long epochs (minimum of 35 epochs per participant; average number of epochs/participant: 55.54, SD = 14.88). The strength of FC was quantified by measuring phase synchronization between EEG channels in five frequency bands (delta: 0.5-4 Hz; theta: 4-8 Hz, lower alpha: 8-10 Hz, upper alpha: 10-12 Hz, beta: 13-30 Hz, gamma 30-45 Hz), separately for each epoch. The level of FC between any two signals is defined as the phase lag synchronization strength measured by the phase lag index (PLI). PLI reflects the consistency by which one signal is phase leading or lagging with respect to another signal [a detailed mathematical description can be found in Stam et al., 2007]. PLI is expressed as a value between 0 (random phase difference: minimum strength of functional connectivity) and 1 (constant phase difference: maximum strength of functional connectivity). PLI was calculated by using the BrainWave software version 0.9.151.5 [available at http://home.kpn.nl/stam7883/brainwave.html]. Graph construction was based on the full connectivity matrix constructed from the PLI values obtained for each pair of electrodes.

2.4. Graph-theoretical analysis

In order to investigate the global topological organizational of infant functional brain networks, the graph theoretical representation of the functional connectivity matrix was created by the MST approach [Boersma et al., 2013, Stam and van Straaten, 2012]. The MST graph of a connectivity matrix is a graph in which all nodes (electrodes) are connected using the strongest available connections and without forming loops. As a consequence, only one path connects any pair of nodes. MST graphs were generated separately for each infant, epoch and frequency band. Graph metrics computed from MSTs are strongly related to those computed from the original network as characterized by weighted connections between each pair of nodes [Tewarie et al., 2015]. The characteristics extracted from the graphs derived by the MST approach have been successfully employed for describing FC network properties (e.g. hierarchical structure, degree distribution etc.) of healthy adults and patient groups with neurodegenerative disorders, such as epilepsy and multiple sclerosis (for review, see Stam et al., 2014). For the current analysis, MST connectivity networks were derived by the Kruskal's algorithm [Kruskal, 1956]. Following the construction of MSTs, global and node-specific network characteristics (see Figure 1) were quantified based on the measures described by Stam et al. (2014). “Degree Centrality” (DEG) is the number of edges connected to a node. “Betweenness Centrality” (BC) is a measure of the node’s ‘hubness’ within the network. It is defined as the normalized fraction of all shortest paths connecting two nodes that pass through the particular node [for detailed mathematical description see Newman and Girvan, 2010; Stam et al., 2014]. The

DEG and BC measures were calculated for each node separately and the maximum values within each MST were included in the statistical analyses as global characteristics of the MST (MaxDEG and MaxBC, respectively). “Leaf Fraction” (LF) is the number of nodes with only 1 connected edge divided by the total number of nodes in the MST. “Diameter” (DIAM) is the largest distance between any two nodes within the MST, where distance refers to the minimum number of edges required to proceed from one node to another (the shortest path). “Tree Hierarchy” (TH) assesses how hierarchical a given network is compared to the so called ‘star-like network organization’. The calculation of TH is based on the values of maximum BC and Leaf Fraction [for a detailed mathematical description, see Boersma et al., 2013, and Tewarie et al., 2015]. TH ranges from 0 (indicating a line-like topology) to 1; for the star-like topology, TH approaches 0.5. The optimal TH is somewhere between a path and a star like topology; the higher the TH, the better the tradeoff between integration and differentiation in an MST. MST network characteristics values were normalized by dividing them by the number of EEG channels. The global MST network characteristics were averaged across epochs, separately for each infant and frequency band.

PLEASE INSERT FIGURE 1 HERE

For assessing whether the graph-theory based descriptions of the FCs represent common tendencies for the current group of infants, brain network characteristics were compared with those of referential random networks. Random-network characteristics were calculated by randomly permuting the PLI values within the connectivity matrix, separately for each epoch, infant, and frequency band. Random-network MST graphs were quantified the same way as was described above for the actual EEG data.

MST graphs may also carry information regarding the topography of FCs common within the group of infants. Therefore, we assessed the distribution of the node characteristics Betweenness Centrality and Degree Centrality over the scalp. Commonalities between the MSTs should result in non-uniform scalp distributions of these node characteristics. For each node (electrode), infant, and frequency band, the average DEG and BC values were computed and their scalp distributions were then calculated.

2.5. Statistical analysis

Statistical analysis was performed with the SPSS software package [version 20.0; IBM Corp., 2011]. For testing whether the observed functional networks represent characteristics of the infant brain, repeated-measures Analyses of Variance (ANOVA) were used to compare the characteristics of random network and the infant FC networks, separately for each frequency band (NETWORK TYPE × BAND) and each MST network characteristic (MaxDEG, MaxBC, LF, DIAM, and TH). Greenhouse-Geisser correction was employed to correct for sphericity violations. In this case, Mauchly’s W (ε) and the significance value of the sphericity test (p_ε) are given. Effect sizes (partial eta squared, η^2) are also shown. For testing the scalp distribution of node indices of the infant brain networks, one-way ANOVAs were used to compare the spatial characteristics of these node measures (NODE LOCATION), separately for each frequency band and network characteristic (MaxDEG, MaxBC).

By following a data-driven Forward algorithm[1], linear regression models [Pearson, 1895] were constructed for assessing the relationship between medical/biological data and functional network characteristics (DEGMax, BCMax, LF, DIAM, and TH), separately for each frequency band. To avoid distorted results we controlled the skewness value of variables with the “rule of thumb” threshold of -1.0 1.0 [Pearson, 1895]. This type of filtering allowed us to enter into these analyses the following variables: “gestation age” (GA), “infant’s birth weight” (BW), “infant’s age at the time of the recording” (IA), “mother’s age” (MA), “mother’s postpartum weight” (MW), and “mother’s height” (MH). Because linear regression models are not sensitive to multiple comparisons, the emerging patterns of relationships between the medical/biological and network-describing variables do not run the danger of producing false positive results due to multiple probabilistic tests [Gelman, Hill, and Yajima, 2012].

3. Results

To illustrate the general FC network topologies, a group-averaged connectivity matrix was constructed for each frequency band. The visualized MSTs of these mean matrices are shown in Figure 2. Note that the topology of the EEG networks varies across frequency bands (see detailed statistical results below). In the delta, theta and alpha frequency bands, fronto-central nodes (Fz and Cz) showed the highest centrality values and strongest functional connections. In the faster frequency bands, the nodes of the temporal lobe displayed the highest centrality values and strongest functional connectivity. The infant FC networks are quite hierarchical in all frequency bands (see detailed statistical analysis below): they are generally organized into 3-4 hierarchical layers (see Figure 2.) with most of the nodes being functionally linked to only one of the nodes in the first layer. Therefore the functional connections of infant brain networks appear to be organized in a highly centralized manner.

PLEASE INSERT FIGURE 2 HERE

3.1. Comparing network characteristics between infant FC networks and corresponding random networks

[1] The Forward algorithm adds independent variables into the model as long as it significantly changes the value of explained variance. In the current analysis, other linear regression methods (Backward, Stepwise, etc.) yielded the same results. Therefore, we do not mention these alternatives.

Maximal Degree. The MaxDEG values were significantly higher for the infant FC networks then for the random networks (main effect of NETWORK TYPE: see Table 2). The BAND×NETWORK TYPE interaction was significant, because unlike for random networks, MaxDEG significantly varied across frequency bands for the infant FC networks ($p < .001$ in all pairwise comparisons between the gamma and any other band as well as between the delta/beta and the theta/lower-alpha/higher-alpha comparisons).

Maximal Betweenness Centrality. The MaxBC values were significantly higher for the infant FC networks then for the random networks. The BAND×NETWORK TYPE interaction was significant, because unlike for random networks, MaxBC significantly varied across frequency bands for the infant FC networks ($p < .001$ in all pairwise comparisons between the gamma and any other band as well as between the delta/beta and the theta/lower-alpha/higher-alpha comparisons, except for the comparison between the delta and the upper alpha band, which yielded a p value of .002).

Leaf Fraction. The LF values were significantly higher for the infant FC networks then for the random networks. The BAND×NETWORK TYPE interaction was significant, because unlike for random networks, LF significantly varied across frequency bands for the infant FC networks ($p < .001$ in all pairwise comparisons between the gamma and any other band as well as between the delta/beta and the theta/lower-alpha/higher-alpha comparisons).

Diameter. The DIAM values were significantly lower for the infant FC networks then for the random networks. The BAND×NETWORK TYPE interaction was significant, because unlike for random networks, DIAM significantly varied across frequency bands for the infant FC networks ($p < .001$ in all pairwise comparisons between the gamma and any other band as well as between the delta/beta and the theta/lower-alpha/higher-alpha comparisons, except for the comparison between the delta and the beta band, which yielded a p value of .1).

Tree Hierarchy. The TH values were significantly higher for the infant FC networks then for the random networks. The BAND×NETWORK TYPE interaction was significant, because unlike for random networks, LF significantly varied across frequency bands for the infant FC networks ($p < .001$ in all pairwise comparisons between the gamma and any other band as well as between the delta and any other band).

Overall, all network characteristics significantly differed from those of the corresponding random networks. Further, in contrast to the random networks, the characteristics of infant FC networks differed across the different frequency bands. These results suggest that the infant FC networks, relative to random control networks, have more integrated/star like structure.

3.2. Scalp distribution of Betweenness Centrality and Degree Centrality

Figure 3 (left panel) shows the scalp distribution of the BC values, separately for the different frequency bands. The main effect of NODE LOCATION was significant for all frequency bands (see detailed results in Table 3). Post-hoc comparisons indicated a parietal maximum in the delta, midline fronto-central maximum in the theta, midline frontal maximum in the lower alpha, centro-temporal maximum in the higher alpha, and lateral fronto-temporal maxima in the beta and gamma bands ($p < .001$ in most comparisons). Figure 3 (right panel) shows the scalp distribution of the DEG values, separately for the different frequency bands. The main effect of NODE LOCATION was significant in all frequency bands (see detailed results in Table 3). Post-hoc comparisons indicated temporo-parietal maximum in the delta, midline fronto-central maximum in the theta, midline fronto-central and temporo-parietal maxima in the lower and upper alpha, and lateral fronto-temporal maxima in the beta and gamma bands ($p < .001$ in most comparisons, see Table 3).

PLEASE INSERT FIGURE 3 HERE

3.3. Relationship between network characteristics and medical/biological measures

Table 4 and Figure 4 summarize the significant results yielded by the linear regression models. For the delta band we have found only one significant regression model, with GA explaining R^2 = 3% of the variance accounted for MaxBC. For the beta, and gamma bands no significant linear regression models were obtained.

Linear regression models for the theta (4.0-8.0 Hz) frequency band. In the theta frequency band, MaxDeg had R^2 = 6%, LF had R^2 = 5%, and DIAM had R^2 = 4% of the variance accounted for by Gestation Age length (GA). TH had R^2 = 8% of the variance explained by GA and Mother's height (MH). Thus, MST network characteristics in the theta band were mainly associated with GA.

Linear regression models for the lower alpha (8.0-10.0 Hz) frequency band. In the lower alpha frequency band, LF had R^2 = 5% and TH had R^2 = 4% of the variance accounted for by GA. DIAM had R^2 = 3% of the variance explained by GA. Thus, similarly to theta frequency band, MST network characteristics in the lower alpha band were mainly associated with GA.

Linear regression models for the upper alpha (10.0-13.0 Hz) frequency band. In the upper alpha frequency band, MaxDeg had R^2 = 5%, LF had R^2 = 8%, and TH had R^2 = 7% of the variance accounted for by GA. MaxBC had R^2 = 7% while DIAM had R^2 = 12% of the variance explained by GA and Mother's age (MA). Thus again, MST network characteristics in the upper alpha band were mainly associated with GA, while MA has also appeared in two models.

Overall, these results suggest that GA affects the properties of neonatal infant FC networks in the theta, lower and upper alpha bands (see Figure 4). Colinearity measures showed no significant collinearity when two medical/biological variables appeared in the same model: tolerance, which is the percent of variance in independent variables not explained by other independent variables, was always greater than 1-R^2, suggesting that our predictors were not redundant.

PLEASE INSERT FIGURE 4 HERE

Discussion

The aim of the present study was to characterize the topological organization of the human large-scale EEG-based FC in a large sample of healthy full-term neonates. By comparing the brain FC network topology with referential random networks, the presence of an early cost-efficient organization and hierarchical architecture has been demonstrated in all EEG frequency bands. The results also suggested that the FC networks of theta and alpha oscillations are characterized by a more optimal ratio between functionally segregated and integrated neuronal communication than those appearing in the other frequency bands. We found that fronto-central and parieto-central sites appear to be the main hubs of these networks. Furthermore, some characteristics of the theta- and alpha-band FC network topologies were found to be associated with gestational age. This suggests that individual differences in the functional network organization are related to the level of cortical maturity at birth. Results are discussed in detail in the following sections.

Topology of functional networks in newborn infants

FC networks extracted from the EEG of newborn infants in quiet sleep were compared to referential random networks (constructed by randomly rewiring graphs connections). In all studied EEG frequency bands (delta, theta, lower and higher alpha, beta and gamma), the empirically obtained FC networks exhibited significantly higher maximal degree (MAXDEG) and betweenness centrality (MAXBC), tree hierarchy (TH), and leaf fraction (LF) together with lower diameter (DIAM) relative to random networks. These results suggest that the organization of the neuronal communication follows a hierarchical pattern (high TH) composed of some densely connected nodes (high MAXBC and MAXDEG) with the majority of nodes serving as periphery within the network (high LF). Low path length promote long range connections optimized for maximal processing speed, while high clustering support high level of local connectivity optimized for minimal wiring cost and resilience [Watts and Strogatz, 1998]. MST diameter positively correlates with the path length and with the clustering coefficients while the leaf fraction is negatively associated with path length and positively with clustering [Tewarie et al., 2015]. Random networks have low clustering and a short average path length while networks in a regular, lattice-like configuration are characterized by high clustering and a long average path length [Stam et al., 2014; Bullmore and Sporns, 2009]. Finally, scale free networks with star like topology combine the lower path length compared to regular or random networks but lower clustering than regular. Scale-free networks are characterized by the relative commonness of nodes with a degree that greatly exceeds the average [so-called hub nodes; Barabasi and Albert, 1999]. Our findings suggest that the neonatal FC networks show scale free network organizational principles, which are thus likely to be present from an early stage of the cortical connectome. In line with our findings, a similar study in 5- 7 years old children showed that their FC networks display a star-like centralized topology which shifts toward more ordered configuration by development [Boersma et al., 2013]. The current results of the early architecture of the functional connectome is consistent with studies reporting small-world modular topological properties in infants, children, and adults [Otte et al., 2015; Omidvarnia et al. 2014; Boersma et al., 2011; Boersma et al., 2013; Fair et al., 2008; Power et al., 2010; Supekar et al., 2009; Bassett and Bullmore, 2006; Bathelt et al., 2013; Hagmann et al., 2010; Bullmore and Sporns, 2009; Tymofiyeva et al., 2013].

We also found that the topology of the FC networks obtained for the theta and alpha frequency bands characteristically differed from those of the other frequency bands suggesting the emergence of distinct FCs already at birth. The networks in theta and alpha rhythms displayed lower level of MAXBC, TH, and LF with higher DIAM relative to the gamma-, beta-, and delta-band networks. These results indicate that theta- and alpha-band FC networks are shifted towards the regular network topology with more ordered chain-like configuration and higher level clustering. This topology favors the segregation of subnetworks. Therefore these functional networks are better suited for local processes versus the networks working in the other bands. Concordant to our results, Omidvarnia and collages [2014] obtained evidence supporting a similar frequency-specific network organization. Specifically, they found that for theta and alpha oscillations, the level of clustering in the precentral regions and general modularity were higher in full-term relative to preterm newborns, suggesting developmental changes during late gestation at these frequency bands. Oscillations in different frequency bands are often linked to different physiological mechanisms: slower oscillations associated with variation in large-scale excitability (probably through neuromodulation, Miller, 2009), while higher-frequency oscillations were reported to correspond to local field potentials [Buzsáki and Draguhn, 2004]. It has been proposed that the emergence of discrete bands in infancy and childhood may reflect the maturation of distinct cortical generators producing the observed rhythms [Bollimunta et al., 2011] and the processes of synaptogenesis and pruning [Tarokh et al., 2010; Tarokh et al., 2011; Kurth et al., 2010, for review see Uhlhaas et al., 2009].

Topography of functional networks in newborn infancy

The observed high nodal centrality (MAXBC and MAXDEG) of the newborn brain networks indicates that most information is routed via a few central nodes. These hub nodes serve the integration of the functional networks. Figure 3 shows that midline frontal, central and posterior electrodes displayed the highest BC and DEG values in the lower frequency-band (delta to low alpha) MSTs. Lateral temporal electrodes were most likely to serve as hubs in the MSTs for faster bands (beta and gamma bands) with the high-alpha band BC and DEG showing an intermediate scalp distribution pattern. It is important to note that although spatial resolution of the present EEG recording was limited, clear spatial specificity of hub nodes in low versus high frequency oscillations was demonstrated. Analysis of MST graphs on a large sample of EEG data (N=227) recorded from 5-7 years old children showed similar fronto-parietal dominance of BC and DEG, and the connectivity strength further increased between these hub nodes during development [Boersma, 2013]. The hub regions observed here also overlap with both structural and functional hub regions as reported for the adult brain [Hagmann et al., 2008; Hoff et al., 2013; Bulmore and Sporns, 2009]. This suggests an early presence of connectivity hubs in the human brain. Our results are compatible with evidence about the topography of FC in pre- and full-term newborns (Omidvarnia et al. 2014). These authors showed that the anterior region exhibits the strongest clustering and DEG in the theta and low alpha frequency bands. From an anatomical perspective, despite the methodological differences, the midline frontal and posterior hubs of the delta-, theta- and alpha-band networks identified in the present study are consistent with the main hubs regions described in the fMRI literature. Under rest/no-task conditions, the functional brain network comprises the strongly interconnected medial prefrontal cortex, the posterior cingulate, the inferior parietal lobe, and the lateral temporal cortices [Fox and Raichle, 2007; Fox et al., 2005; Power et al., 2010; Bathelt et al., 2013]. It has been suggested that the alpha band resting state EEG network is the one most likely to be associated with the default mode network [Chen et al., 2008; Knyazev et al., 2015] and the frontal–parietal attention networks [Sadaghiani et al., 2012]. The crucial role of these hub nodes in development is supported by findings showing that frontal and parietal areas might be affected in neurodevelopmental disorders, such as autism [Courchesne and Pierce, 2005; Just et al., 2012] and attention deficit/hyperactivity disorder [Tomasi and Volkow, 2011 for reviews see Uhlhaas et al., 2009; Uhlhaas et al., 2010].

Developmental changes of functional networks topology

From the investigated variables of prenatal influences and general clinical risk factors, only GA was found to be consistently associated with the FC network characteristics, mainly in the theta and alpha bands. Linear regression analysis showed that functional networks of more mature infants (longer prenatal development, as measured by GA) were less centralized (lower leaf number, MAXDEG, and MAXBC) and less hierarchical (longer DIAM) than for infants with shorter prenatal development. Larger diameter and lower leaf number both point to a more chainlike, elongated shape of the MSTs. In other words more mature infants are ahead in terms of resting state network topology, having more decentralized network organization than infants with shorter prenatal development time. Thus it appears that the human connectome is mainly star-like during the late prenatal development. Possibly at about the time of birth, its functional specialization increases through increased effectiveness of information transfer between neighboring nodes. These connectivity changes may reflect intermediate cost efficient topology that optimizes communication without overloading central nodes by segregation of sub-networks that subserve different functions and integration of areas involved in the same function. The observed early architecture of the functional connectome is consistent with recent studies showing a small-world organization of the infant functional brain networks as derived from EEG recordings [Omidvarnia et al. 2014, Fair et al., 2008; Power et al., 2010; Supekar et al., 2009, Bassett and Bullmore 2006; Hagmann et al. 2008; Bullmore and Sporns 2009; Tymofiyeva et al. 2013]. Thus the current findings suggest that developmental changes of FC occur as early as the third trimester of gestation (36-41 week).

The maturation of body systems of the human fetus including the brain's connectome genesis during the last trimester of gestation are regarded as a critical period of prenatal ontogenesis [see Fransson et al. 2007; Uhlhaas et al. 2010]. Our conclusion regarding the early development of FC network topology during this period may thus reflect, to some extent, anatomical maturation processes, which could include ongoing growth in axonal count of the cortical and thalamo-cortical pathways by white matter myelination and synaptic pruning [Volpe, 1995, Hermoye et al., 2006; Huttenlocher and Dabholkar, 1997]. Myelination is one of the core developmental events in the late prenatal period by which maturation of the neuronal fibers in the neuronal feedback loops are realized and the signal transmission speed increases [Cayre et al., 2009; Goldman et al., 1997, Bollimunta et al., 2011]. The current most widely accepted theory suggests that neuronal feedback loops, comprising thalamic, cortical and thalamo-cortical relay cells and GABAergic interneurons play an important role in the generation and synchronization of brain oscillations [for review see Uhlhaas et al. 2010, Fritschy, 2008; Le Magueresse and Monyer, 2013]. Thus, one may hypothesize that structural and functional connectivity between regions develops similarly with the maturation of the neuronal fibers in these areas.

Previous cross-sectional studies investigating the strength of cortical coupling in relation to prenatal development reported stronger FC in fronto-central and temporal regions in the delta and theta bands [González et al., 2011; Dulce et al., 2007, Omidvarnia et al. 2014] in full-term compared to preterm infants. Further, weaker coupling of the posterior areas in the delta band and lower intra-hemispheric FC in the theta and alpha bands were observed in full-term than in preterm neonates [Batuev et al., 2008]. However the few existing longitudinal studies measuring FC topology in full term healthy newborns showed somewhat different associations with gestational age. For instance, alpha-band FC was found to be weakening over time between frontal and parieto-temporal electrode locations, while increases in fronto-occipital FC strength was associated with low medical risk and optimal neurobehavioral measures [Duffy, Als and McAnulty, 2003]. Consistently, a follow-up study of preterm infants reported weakening functional coupling in the theta and delta bands with gestation age and postnatal maturation while more mature infants displayed stronger coupling at higher frequencies at occipital recording sites (Meijer et al., 2014). These discrepancies between the findings of cross-sectional and longitudinal studies could be explained by the assumption of Thatcher [Thatcher et al., 2008; Thatcher, 1992], who suggested that development in children is programmed in cycles with periods of increasing and decreasing coherence which have different on- and offsets in different regions. The current results are compatible with this hypothesis.

We speculate that the gradual decentralization of the neuronal networks with maturation may be related to the partial switching from thalamo-cortical to cortico-cortical dominance of neuronal network, which leads to the emergence of higher FC strength in function-differentiated cortical areas (such as the primary sensory cortical areas). This would appear in the EEG measures as a weakening of the strong FC connectivity of the most overloaded hub regions in the midline fronto-posterior areas (indexed by decreasing BC and DEG) after prenatal development, in line with the previously observed weakening of both long-range and local posterior connectivity [Duffy, Als and McAnulty, 2003; Meijer et al., 2014; Batuev et al. 2008]. Pruning or elimination of some non-optimal connections of the thalamo-cortical networks may underlie this developmental change. This idea also is compatible with the suggestion by Thatcher who argued that development involves local excessive production of synaptic connections followed by pruning of the unused connections [Thatcher et al., 2009; Thatcher, 1992].

Limitation and future directions

The present study provided data describing the general characteristics and developmental changes in global network integrity of the neonatal brain. Neural network analysis may provide a functional biomarker for monitoring clinical conditions in newborn infants. Further longitudinal studies are needed to establish the relationship between early brain network organization and later neurocognitive development. It is important to note that most studies assessing infant brain activity by electrophysiological means (including the current one) have limited spatial resolution due to practical limitations (Tokariev et al., 2015). Simultaneous fMRI and electrophysiological recoding could potentially improve our understanding of the joint development of structural and functional connectivity the infant brain.

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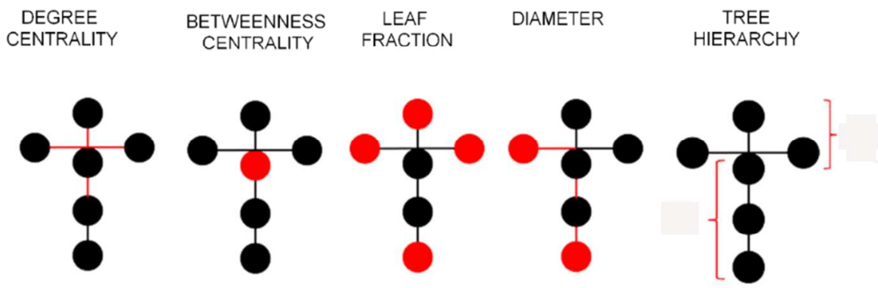
Figure legends

Figure 1. Schematic representation of global and node-specific network characteristics of a simple minimum spanning tree (MST). Circles indicate vertices (nodes), lines edges. Degree Centrality: quantifies the number of edges belonging to a particular node. Betweenness Centrality: fraction of all shortest paths that pass through a particular node. Leaf Fraction: quantifies the number nodes of the MST with degree one. Diameter: the length of the longest “shortest path” of the MST. Tree Hierarchy: quantifies the trade-off between large scale integration in the MST and the overload of central nodes.

Figure 2. Group-average (N = 139) MSTs of newborn infants represented as hierarchical graphs (A) and projected on the scalp (B), separately for each frequency band. The node color refers to the large-scale scalp location (red: frontal nodes; green: central nodes; blue: parietal nodes; yellow: temporal nodes). The edge colors on the head plots show the strength of functional connectivity (PLI) between nodes (see color calibration at the right side).

Figure 3. Scalp distribution of Betweenness Centrality (BC; Panel A) and Degree Centrality (DEG; Panel B), separately for each frequency band (delta: 0.5-4 Hz; theta: 4-8 Hz, lower alpha: 8-10 Hz, upper alpha: 10-12 Hz, beta: 13-30 Hz, gamma 30-45 Hz). Color calibration is shown at the right of each figure. Note that regions with high BC usually also show high DEG values.

Figure 4. Relationship between GA and network characteristics. The network characteristic is marked by the schematic diagram on the left. Diagrams represent the linear relationship between GA (x axis) and the corresponding network characteristics (y axis) shown by different colors for the different frequency bands. Dots correspond to the individual infants’ data.



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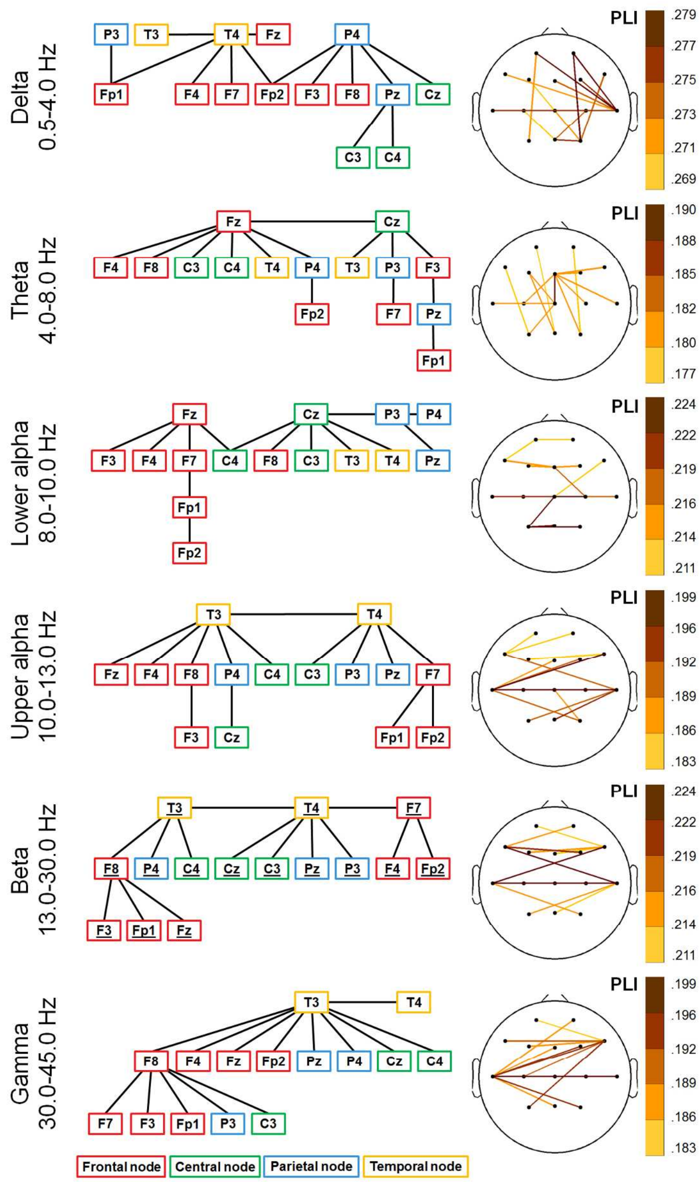

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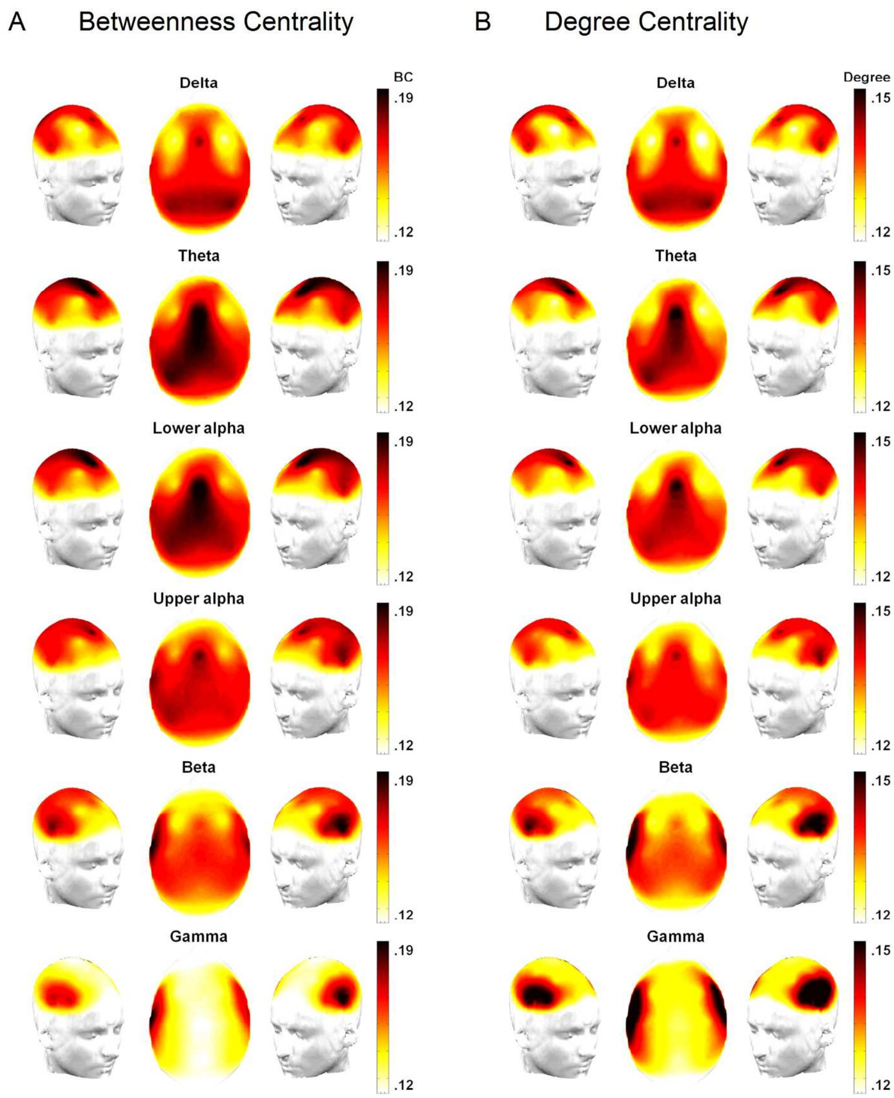

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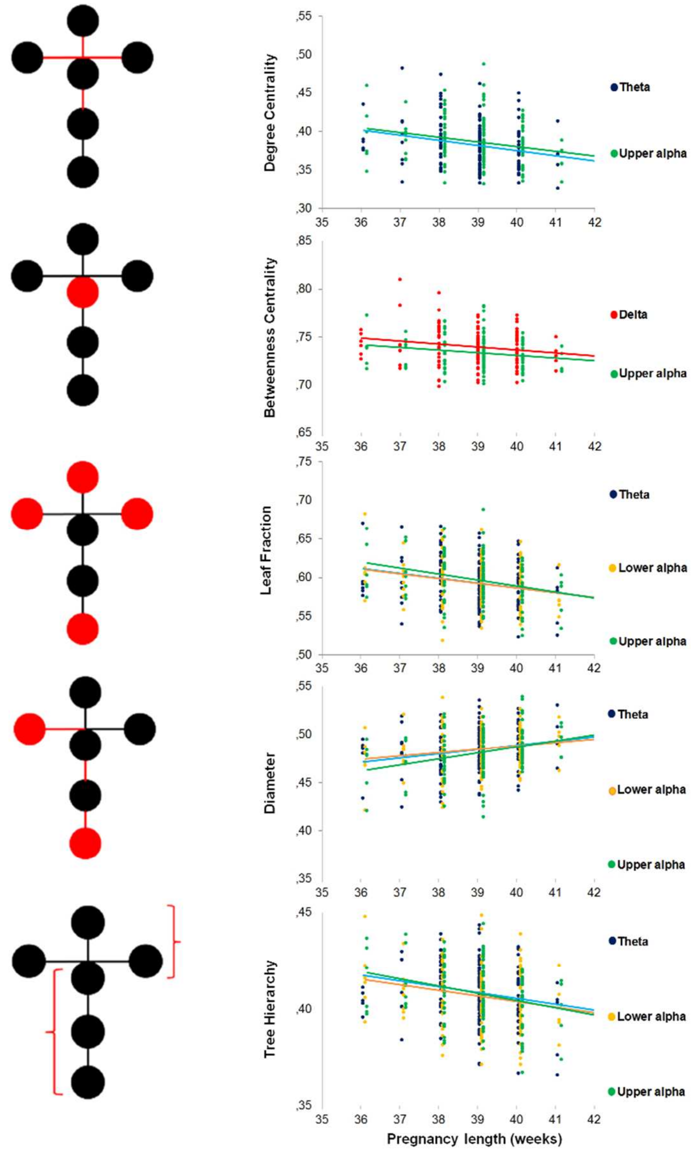

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86x114mm (300 x 300 DPI)

Table 1. Descriptive statistics of the medical/biological measures

	Missing	Mean	SD	Range	Skewness	Kurtosis
Postmenstrual age at birth (weeks)	1	38.84	1.10	36-41	-0.59	0.45
Baby's birth weight (g)	-	3321.69	396.63	2170-4160	-0.25	-0.29
Chronological age at the recording (days)	-	2.39	0.76	1-6	0.64	2.81
Mother's age (years)	1	31.45	4.47	20-43	0.27	-0.12
Mother's pre-pregnancy weight (kg)	2	66.02	12.81	42-124	1.22	2.76
Mother's postpartum weight (kg)	2	78.63	13.92	49-127	0.78	0.83
Mother's height (m)	2	1.66	0.07	1.48-1.84	0.06	0.20
Mother's systolic BP (mmHg)	3	112.63	13.30	70-160	0.42	2.40
Mother's diastolic BP (mmHg)	3	69.63	8.84	50-100	1.19	2.72

Note. The mother's pre-pregnancy weight and the length of the pregnancy were based on self-reports. *BP* = blood pressure.

Table 2. MST network characteristics and their comparison between actual and random functional networs, separately for the different frequency bands.

Descriptives				ANOVA Results					
Variable	Band	Mean	SD	Effect	ε	F	df	p	η^2
MaxDEG	Delta	.4028	.0345	NETWORK TYPE		3209.56	1,138	***	.96
	Theta	.3825	.0311	BAND	.29	117.01	5,690	***	.46
	Lower alpha	.3845	.0283	Interaction	.29	127.77	5,690	***	.48
	Upper alpha	.3869	.0298						
	Beta	.3997	.0383						
	Gamma	.4527	.0473						
MaxBC	Delta	.6874	.0175	NETWORK TYPE		3605.91	1,138	***	.96
	Theta	.6773	.0157	BAND	.73	123.13	5,690	***	.47
	Lower alpha	.6792	.0144	Interaction	.71	128.60	5,690	***	.48
	Upper alpha	.6814	.0149						
	Beta	.6904	.0193						
	Gamma	.7204	.0229						
LF	Delta	.6124	.0316	NETWORK TYPE		4751.59	1,138	***	.97
	Theta	.5941	.0306	BAND	.40	126.10	5,690	***	.48
	Lower alpha	.5933	.0294	Interaction	.43	144.39	5,690	***	.51
	Upper alpha	.5970	.0298						
	Beta	.6086	.0354						
	Gamma	.6622	.0434						
Diam	Delta	.4693	.0240	NETWORK TYPE		5502.26	1,138	***	.98
	Theta	.4838	.0230	BAND	.65	130.50	5,690	***	.49

	Lower alpha	.4844	.0219	Interaction	.68	156.03	5,690	***	.53
	Upper alpha	.4808	.0235						
	Beta	.4679	.0275						
	Gamma	.4217	.0326						
TH	Delta	.4472	.0164	NETWORK TYPE		4946.51	1,138	***	.97
	Theta	.4404	.0171	BAND	.72	40.99	5,690	***	.23
	Lower alpha	.4384	.0171	Interaction	.79	44.26	5,690	***	.24
	Upper alpha	.4397	.0160						
	Beta	.4422	.0170						
	Gamma	.4611	.0192						

Note. The presence of ε indicates the employment of Greenhouse-Geisser correction due to sphericity violation.

*** $p < .001$

Table 3. The effects (ANOVA results) of Node Location on the Betweenness Centrality and Degree Centrality MST network characteristics, separately for the different frequency bands.

	BAND	F	df	p	η^2
Max BC	Delta	21.225	14, 19	***	.133
	Theta	21.663	14, 19	***	.136
	Lower alpha	23.043	14, 19	***	.143
	Upper alpha	15.741	14, 19	***	.111
	Beta	17.250	14, 19	***	.178
	Gamma	29.957	14, 19	***	.188
Max Deg	Delta	21.337	14, 19	***	.134
	Theta	21.462	14, 19	***	.135
	Lower alpha	21.073	14, 19	***	.132
	Upper alpha	14.518	14, 19	***	.095
	Beta	18.997	14, 19	***	.121
	Gamma	32.007	14, 19	***	.188

Table 4. Summary of the linear regression model results.

	MaxDEG	MaxBC	LF	DIAM	TH
			Delta band		
β of Pregnancy length		-.18*			
t, df of Pregnancy length		-2.10 (134)			
R^2		.03			
df, error, df of model		1,133			
F		7.73*			
			Theta band		
β of Pregnancy length	-.24**		-.22*	.21*	-.23*
t, df of Pregnancy length	-2.78 (132)		-2.46 (132)	2.46 (132)	-2.68 (131)
β of Mother's height					.19*
t, df of Mother's height					2.30 (131)
R^2	.06		.05	.04	.08
df, error, df of model	1,132		1,132	1,132	1,131
F	7.73**		6.74*	6.07*	5.75**
			Lower alpha band		
β of Pregnancy length			-.22*	.18*	-.19*
t, df of Pregnancy length			-2.63 (132)	2.10 (134)	-2.26 (132)
R^2			.05	.03	.04
df, error, df of model			1,132	1,133	1,132
F			6.90*	4.39*	5.10*
			Upper alpha band		
β of Pregnancy length	-.23**	-.22*	-.28***	.33***	-.27**
t, df of Pregnancy length	-2.69 (132)	-2.59 (131)	-3.38 (132)	3.94 (131)	-3.23 (132)
β of Mother's age		-.19*		.02*	
t, df of Mother's age		-2.21 (131)		2.35 (131)	

R^2	.05	.07	.08	.12	.07
df, error df of model	1,132	1,131	1,132	1,132	1,132
F	10.42**	5.01**	11.45***	9.31***	10.42**

Note. * p < .05 ** p < .01 *** p < .001. In the F row, the asterisks indicate the level of significance for the final regression model. In the β rows of the biomedical variables, the asterisks indicate the level of significance of the independent predictive power of the variable, separately.