Developmental Changes in Neuronal Oscillations and Synchrony: Evidence for a Late Critical Period

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The role of synchronized oscillations

Synchronised neural oscillations in low- (delta, theta and alpha) and high- (beta and gamma) frequency bands are a fundamental mechanism for enabling coordinated activity during normal brain functioning [Buzsaki & Draguhn, 2004; Fries, 2009]. A large body of evidence from invasive electrophysiology in non-human primates and electro- and magnetoencephalographic- (EEG/MEG) recordings in humans that have tested the amplitude and synchrony of neural oscillations have demonstrated close relations between synchronous oscillatory activity and a variety of cognitive and perceptual functions. An important link between oscillations and cortical computations was the discovery of the role of oscillatory rhythms in the beta/gamma range (20-80 Hz) in establishing precise synchronization of distributed neural responses. Gray and colleagues [Gray *et al.*, 1989] showed that action potentials generated by cortical cells align with the oscillatory rhythm in the beta and gamma range, which has the consequence that neurons participating in the same oscillatory rhythm synchronize their discharges with high precision. Thus, it is a central role of cortical oscillations in the beta/gamma range to enable neuronal synchronization and by virtue of establishing systematic phase lags, to define precise temporal relations between the discharges of distributed neurons [Womelsdorf *et al.*, 2007].

Self-generated oscillations and synchronization are highly dynamic phenomena and depend on numerous conditions, such as central states [Herculano *et al.*, 1999], stimulus configuration [Gray and Singer, 1989; Gray *et al.*, 1989] or attention [Fries *et al.*, 2001]. The strength of synchrony is closely correlated

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with perceptual processes such as feature binding, subsystem integration, brightness perception and interocular rivalry [for a recent review see Uhlhaas *et al.*, 2009a]. In addition, the strength of synchronization predicts whether an animal will give a correct response in an upcoming trial of a perceptual decision task, [Kreiter and Singer, 1996] suggesting its important functional role.

In addition to the high frequency oscillations in the beta- and gamma-band, oscillatory rhythms in the theta- and alpha-band also play an important role in cortical computations. Alpha activity (8-12 Hz) has been associated with inhibitory functions [Klimesch *et al.*, 2007] but also with the long-distance coordination of gamma-oscillations [Palva and Palva, 2007] and theta activity has been proposed to support large-scale integration of subsystems serving the formation and recall of memories [Buzsaki, 2005]. In general, there is a correlation between the distance over which synchronization is observed and the frequency of the synchronized oscillations. Short distance synchronization tends to preferentially occur at higher frequencies (gamma-band) than long-distance synchronization, which often manifests itself in the beta- but also in the theta- (4–8 Hz) and alpha- (8–12 Hz) frequency range [Kopell *et al.*, 2000; von Stein *et al.*, 2000].

While the relationship between neural synchrony and cognitive and perceptual processes has received widespread attention, a less explored aspect is the possible role of neural synchrony in the development of cortical networks. Oscillations and the generation of synchronized neuronal activity play a crucial role in the activity dependent self-organisation of developing networks [Ben-Ari, 2001; Hebb, 1949; Khazipov and Luhmann, 2006; Singer, 1995] (Figure 1, p. 260). The development and maturation of cortical networks critically depends on neuronal activity, whereby synchronized oscillations play an important role in the stabilization and pruning of connections [Hebb, 1949]. For example, in spike-timing dependent plasticity, pre- and post-synaptic spiking within a critical window of tens of milliseconds has profound functional implications [Markram *et al.*, 1997]. Stimulation at the depolarizing peak of the theta cycle in the hippocampus favours long-term potentiation (LTP), whereas stimulation in the trough causes depotentiation (LTD) [Huerta and Lisman, 1993]. The same relationship holds for oscillations in the beta- and gamma-frequency range [Wespatat *et al.*, 2004], indicating that oscillations provide a temporal time structure that allows for precise alignment of the amplitude and temporal relations of presynaptic and postsynaptic activation that determine the polarity (strengthening or weakening) of synaptic changes. Accordingly, the extensive modifications of synaptic connections during the development of cortical networks are critically dependent upon precise timing of neural activity.

Conversely, synchronisation of oscillatory activity is an important index of the maturity of cortical networks. Neural oscillations depend on anatomical and physiological parameters that undergo significant changes during development [Buzsaki and Draguhn, 2004]. Thus, synchronisation of oscillatory activity in the beta– and gamma–frequency range is dependent upon cortico–cortical connections that reciprocally link cells within the same cortical area, across different areas or even across the two hemispheres [Engel *et al.*, 1991; Löwel and Singer, 1992]. Furthermore, GABAergic interneurons play a pivotal role in establishing neural synchrony in local circuits, as indicated by the fact that a single GABAergic neuron may be sufficient to synchronise the firing of a large population of pyramidal neurons [Cobb *et al.*, 1995] and that the duration of the inhibitory post–synaptic potential (IPSP) can determine the dominant frequency of oscillations within a network [Wang and Buzsaki, 1996].

Postnatally, changes occur in both GABAergic neurotransmission [Doischer *et al.*, 2008; Hashimoto *et al.*, 2009] and the myelination of long axonal tracts [Ashtari *et al.*, 2007; Perrin *et al.*, 2009]. Thus, changes can be expected in the frequency and synchronisation (amplitude) of oscillation as well as in the precision with which rhythmic activity can be synchronised over longer distances at different developmental stages.

In the following we will provide evidence for important changes in parameters of neural synchrony during childhood and adolescence. While high-frequency activity emerges during early development, we will show that cortical networks fully sustain precise synchrony only during the transition from adolescence to adulthood, which is compatible with concurrent changes in anatomy and physiology.

Resting-state oscillations

Developmental changes in the frequency spectrum of the EEG were first described by Berger and subsequent studies have confirmed pronounced changes in the amplitude and distribution of oscillations in different frequency bands [for a review see Niedermeyer, 2005]. In adults, resting-state activity is characterised by prominent alpha–oscillations over occipital electrodes while low (delta, theta) and high (beta, gamma) frequencies are attenuated. During childhood and adolescence, however, there is a reduction in the amplitude of oscillations over a wide frequency range that is particularly pronounced for delta– and theta–activity [Whitford *et al.*, 2007]. These development changes occur more rapidly in posterior than in frontal regions [Niedermeyer, 2005] and follow a linear trajectory until age 30 [Whitford *et al.*, 2007]. When the relative magnitude is taken into ac-

count, oscillations in the alpha- and beta-range increase whereas activity in lower frequency bands decreases with age.

Changes in resting-state activity during adolescence can also be observed during sleep. Campbell and Feinberg [2009] analysed delta- and theta-activity during non-rapid eye movement sleep (non-REM) in a cohort of 9- and 12-year-old children twice yearly over a 5-year period and observed profound changes in slow-frequency oscillations. The power of delta-oscillations did not change between 9-11 years but then showed a reduction by over 60% until 16.5 years. Similar results were obtained for oscillations in the theta-band. According to the authors, the decrease in the power of low-frequency oscillations reflects synaptic pruning and is independent of pubertal stages.

In contrast to the reduction of slow-wave activity, resting-state gamma-band oscillations increase during development. They can be detected around 16 months and continue to increase in amplitude until age 5 [Takano and Ogawa, 1998]. Correlations between the amplitude over frontal electrodes and the development of language and cognitive skills suggest a functional role of early gamma-band activity in the maturation of cognitive functions [Benasich et al., 2008].

Changes in the amplitude of oscillations are accompanied by developmental trends in the synchrony of oscillations. Thatcher et al. [2008] tested the hypothesis that white matter maturation involves the differential development of short- and long-range fibre connections and is reflected in changes in the coherence of beta-oscillations. EEG coherence between 2 months and 16 years of age was characterised by an increase in coherence at shorter distances (< 6 cm) while long-range coherence (> 24 cm) did not vary with age. Pronounced increases in long-range coherence in the alpha-band were reported by Srinivasan et al. [1999]. The authors tested EEG-coherence in 20 children (6-11 years) and 23 adults (18-23 years). Reduced power over anterior electrodes in children was accompanied by reduced coherence between anterior and posterior electrodes. These findings suggest that in addition to an increase in fast rhythmic activity, the maturation of oscillations during childhood and adolescence is accompanied by an increase in precision with which oscillations are synchronised suggesting a continued maturation in the spatial and functional organisation of cortical networks.

Maturation of steady-state responses

Steady-State Responses (SSR) represent a basic neural response to a temporally modulated stimulus to which it is synchronized in frequency

and phase. Thus, steady-state paradigms are ideally suited to probe the ability of neuronal networks to generate and maintain oscillatory activity in different frequency bands. Previous research had shown that the power of the auditory SSR is largest in the 40 Hz range [Galambos *et al.*, 1981], suggesting a natural resonance frequency of cortical networks.

Developmental studies have so far focused on the auditory SSR (ASSR). Rojas *et al.* [2006] examined the 40 Hz ASSR in MEG data in 69 participants in the age range from 5-52 years. Regression analyses showed a significant effect for age indicating that the amplitude of the 40 Hz ASSR between 200-500 ms increased significantly during development. Specifically, a marked increase in 40 Hz power was observed during childhood and adolescence and appeared to reach a plateau during early adulthood.

The protracted maturation of the auditory SSR was confirmed in a recent study by Poulsen *et al.* [2009]. Sixty-five participants aged 10 were tested with EEG in a longitudinal study that involved a follow up after 18 months. Comparison with an adult group revealed a marked reduction of the 40 Hz ASSR in children relative to adult participants. In addition to an overall reduction of the amplitude of the ASSR, adults were also characterised by a reduced variability and higher peak frequencies than children. Similar differences were also found between 10 and 11.5 year old children. Analyses of developmental changes of the source waveforms indicated that adults had significantly higher source power in the left temporal cortex whereas no difference was found for activity in the right temporal source nor in the brainstem.

Development of task-related oscillations

Csibra *et al.* [2000] measured gamma-band responses in EEG data in 6- and 8-month-old infants during the perception of Kanisza squares that require the binding of contour elements into a coherent object representation. Based on prior behavioural studies that showed that infants up to 6 months of age are unable to perceive Kanisza figures, the authors hypothesized that perceptual binding in 8-month-old infants is related to the emergence of gamma-band oscillations. This was supported by an induced oscillatory response between 240-320 ms over frontal electrodes that was not present in the younger group, suggesting that the emergence of gamma-band oscillations during infancy is correlated with the maturation of perceptual functions.

Further studies have demonstrated continued maturation of neural synchrony during visual processing until adulthood. Werkle-Bergner *et al.* [2009] tested the amplitude and phase-stability of evoked gamma-band os-

cillations during the perception of squares and circles in children (10-12 years), young adults (20-26 years) and older adults (70-76 years). Evoked oscillations in children were significantly reduced between 30-148 Hz over occipital electrodes relative to adults. In addition, gamma-band activity in children was not modulated by the size of the stimulus as in adult and older participants. Participants in the 70-76 years age range, while displaying a similar degree of phase-locking, were characterised by reduced amplitudes of gamma-band oscillations relative to younger adults during the perception of large stimuli.

The development of induced oscillations and their synchronisation was examined in a study by Uhlhaas *et al*. [2009b] who investigated children, adolescent participants and young adults during the perception of Mooney faces (see Figure 1, p. 260). In adult participants, perceptual organisation of upright Mooney faces was associated with prominent gamma-band oscillations over parietal electrodes as well as long-range synchronisation in the theta- and beta-band. During development, profound changes in these parameters occurred that correlated with improved detection rates and reaction times. In particular, neural synchrony in the beta- and gamma-band increased until early adolescence (12-14 years) that was followed by a *reduction* in phase-synchronization and amplitude of high-frequency oscillations during late adolescence (15-17 years). In 18-21 year olds, high-frequency oscillations showed a significant increase relative to late adolescent participants that was accompanied by a reorganisation in the topography of phase-synchrony patterns in the beta-band as well as by an increase in theta phase-synchrony between frontal and parietal electrodes. Accordingly, the development of induced oscillations and their synchronisation from late adolescence to early adulthood reflect a critical developmental period that is associated with a rearrangement of functional networks and with an increase of the temporal precision and spatial focusing of neuronal interactions.

Changes in neural synchrony have also been demonstrated in auditory processing during development. Müller *et al*. [2009] assessed differences in oscillatory activity between 0-12 Hz in young children (age: 9-11 years), older children (age: 11-13 years), young adults (age: 18-25 years) and older adults (age: 64-75 years) during an auditory oddball task. Differences in the synchronisation and amplitude of oscillations in EEG-data were most prominent for comparisons between children and young adults and for the processing of attended and deviant stimuli. Children were characterised by reduced synchronisation in local circuits over fronto-central electrodes at delta- and theta-frequencies as well as by reduced long-range synchronisation. Reduced local and long-range synchronisation was accompanied,

however, by a relative increase in the power of evoked and induced oscillations in children in the same frequencies, suggesting that, as development progresses, low-frequency activity is characterised by a shift to more precisely synchronised oscillations during adolescence. Similar results were reported by Yordanova *et al.* in the alpha-band [1996].

Changes in neural synchrony during development are also present in the motor system in which beta-band oscillations are associated with the preparation and execution of motor commands [Kilner *et al.*, 2000]. Synchrony of spinal inputs to motorneurons can be investigated by measuring the covariation of signals from electromygraphic (EMG) recordings over abductor muscles. Farmer *et al.* [2007] analysed the coherence of EMG-signals in the 1-45 Hz frequency range during development in a sample of 50 participants (age range: 4-59 years). Pronounced developmental changes in beta-band coherence were found between 7-9 and 12-14 years, with adolescent participants showing elevated levels of beta-band coherence relative to children.

Relations to anatomical and physiological changes

Following the emergence of gamma-band oscillations during infancy [Benasich *et al.*, 2008; Takano and Ogawa, 1998] oscillations shift to higher frequencies and synchronisation becomes more precise [James *et al.*, 2008; Müller *et al.*, 2009; Poulsen *et al.*, 2009; Rojas *et al.*, 2006; Uhlhaas *et al.*, 2009b]. This development is not complete until early adulthood and neural synchrony continues to mature throughout the adolescent period, which represents a critical phase of brain maturation.

The maturation of neural synchrony during adolescence is compatible with the development of cognitive functions during this period that depend on neural synchrony, such as working memory and executive processes [Luna *et al.*, 2004] as well as with concurrent changes in anatomy and physiology [Toga *et al.*, 2006]. Specifically, late development of gamma-band oscillations is compatible with recent data suggesting important changes in GABAergic neurotransmission during adolescence. Hashimoto *et al.* [2009] showed a predominance of GABA α_2 subunits in the monkey dorsolateral prefrontal cortex (DLPFC) during early development, whereas in adult animals α_1 subunits are more expressed. This switch was accompanied by marked changes in the kinetics of GABA transmission, including a significant reduction in the duration of miniature IPSPs in pyramidal neurons. The shift in α subunit expression could provide a direct correlate of the observed increase in both amplitude and frequency of gamma-band oscillations during adolescence as α_1 subunits predominate at synapses of parvalbumin (PV)-positive basket cells

(BCs) [Klausberger *et al.*, 2002] that are crucially involved in the generation of gamma-band oscillations [Sohal *et al.*, 2009].

The decrease in the slow-wave oscillations (delta, theta) has been related to synaptic pruning [Feinberg and Campbell, 2010]. According to this view, the higher number of synapses during childhood could explain the excess of delta- and theta-oscillations as well as the initially high metabolic rate that becomes reduced during adolescence leading to reduced slow-wave activity and decreased energy consumption.

In addition to the changes in the amplitude of oscillations, changes in the precision of synchrony have been observed that can be related to anatomical changes. The development of white matter that continues until early adulthood [Ashtari *et al.*, 2007; Salami *et al.*, 2003] probably contributes to the maturation of long-range synchronisation between cortical regions by increasing the precision and frequency with which neural oscillations can be propagated. This is supported by several studies showing that the myelination of long axonal fibres increases during adolescence and results in enhanced long-range connectivity.

The data on the development of high-frequency oscillations and their synchronisation during adolescence are furthermore consistent with and extend findings on age-related changes in fMRI-activity patterns in a variety of cognitive tasks [Casey *et al.*, 2008] and during the resting-state [Supekar *et al.*, 2009]. These studies revealed a developmental pattern whereby brain areas critical for task performance become increasingly activated [Durston *et al.*, 2006]. Activation of frontal and parietal regions was found to be more prominent and focused in adult participants than in children and adolescents during tasks involving working memory, executive controls and visual processing [Crone *et al.*, 2006; Golarai *et al.*, 2007; Rubia *et al.*, 2007]. As the amplitude of the BOLD-signal is closely and positively correlated with the entrainment of neurons into synchronized gamma-band oscillations [Niessing *et al.*, 2005], the fMRI data are fully compatible with the notion that the ability of cortical networks to engage in precisely synchronized high-frequency oscillations increases during development and is a hallmark of maturity.

Implications for psychopathology and education

In addition to the role of neural synchrony during normal brain maturation, the reviewed data have also important implications for the understanding of neuropsychiatric disorders, such as Autism Spectrum Disorders (ASDs) and Schizophrenia, which are associated with abnormal neural synchrony and aberrant neurodevelopment [Uhlhaas and Singer, 2010, 2007].

Considering the important role of neural synchrony in the shaping of cortical circuits at different developmental periods, we hypothesize that in ASDs abnormal brain maturation during early pre–natal and post–natal periods results in cortical circuits which are unable to support the expression of high-frequency oscillations during infancy. These impaired oscillations may in turn reduce the temporal precision of coordinated firing patterns and thereby disturb activity dependent circuit selection during further development. In schizophrenia, on the other hand, clinical symptoms typically manifest themselves during the transition from late adolescence to adulthood. As high-frequency oscillations and their synchronisation increase strongly during late adolescence and are associated with a reorganisation of cortical networks, we propose that in schizophrenia cortical circuits are unable to support the neural coding regime that emerges during late adolescence and relies on temporally more precise and spatially more focused synchronisation patterns.

With respect to educational considerations the data recording a marked reorganisation of cortical networks during late adolescence may be of particular relevance. They suggest a transition from a more diffuse protonetwork towards more focused, presumably more specialized subnetworks, and a late but substantial increase in the temporal precision of phase locking across cortical areas. These changes suggest the existence of a critical period of brain development during late adolescence. The neuronal underpinnings of this developmental phase are less well studied than those underlying the critical periods in early life, during which brain architectures are subject to extensive epigenetic shaping by experience dependent processes. The reason is that, until recently, postpubertal brain development was mainly considered as a consolidation process associated with the final stage of myelination and not with major reorganisation of functional networks. In the light of the new evidence it appears necessary to explore in greater depth not only the neurobiological changes underlying this late reorganisation but also the possible windows of opportunity that this developmental phase may provide for epigenetic, in particular educational influences. If the mechanisms supporting these late developmental changes share features with those acting during the early critical periods, one should expect enhanced susceptibility to use dependent modifications, i.e. to epigenetic shaping. This may shed new light on Freud's view that late adolescence provides a 'second chance'.

Acknowledgements

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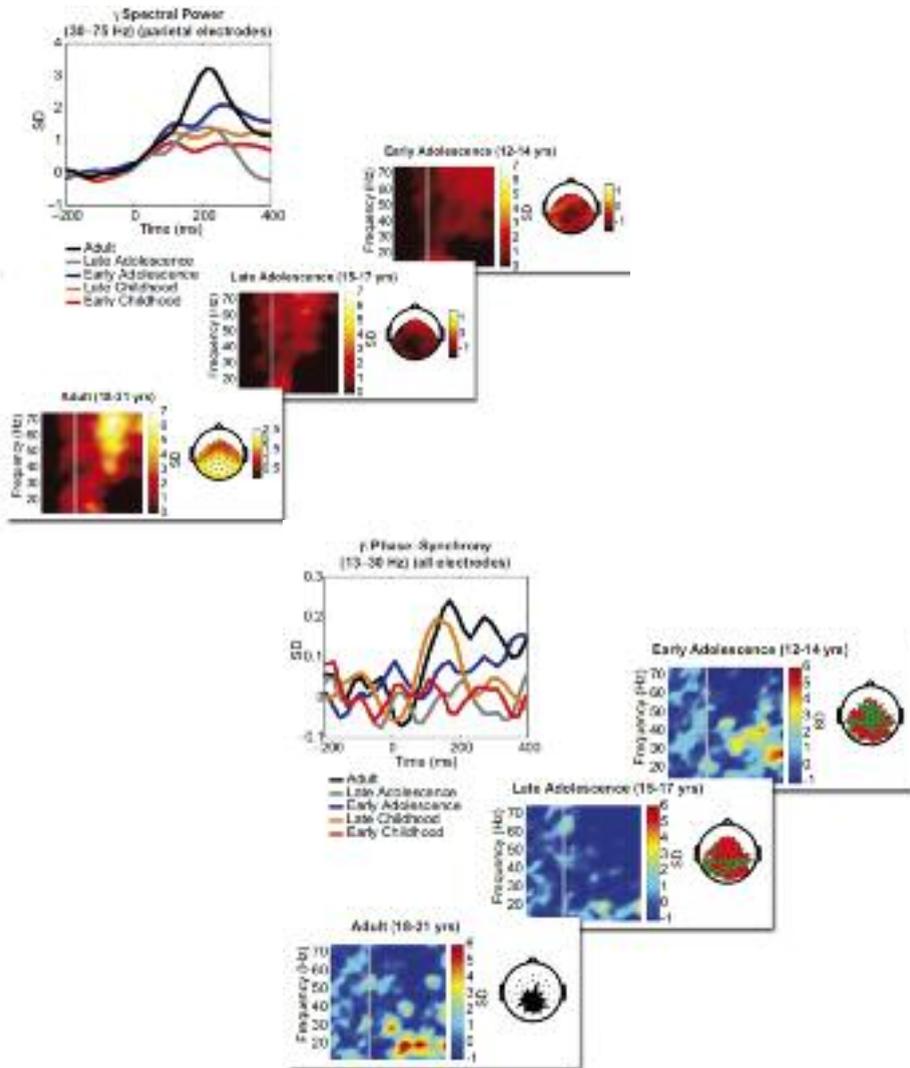
Figure 1. Development of task-related neural synchrony. Left panel: Comparison of spectral power of oscillations in the 30-75 Hz range across all electrodes between 100-300 ms during the presentation of Mooney faces at different ages and time-frequency maps (x-axis: time; y-axis: normalised spectral power in standard deviations (SD)) for early adolescent, late adolescent and adult participants. The data show that gamma-oscillations increase significantly during the transition from adolescence to adulthood. Right panel: Comparison of phase-synchrony in the 13-30 Hz frequency range for all electrode pairs between 100-300 ms at different ages (top left panel) and phase synchrony charts of oscillations in the beta- and gamma-band averaged across all electrodes (x-axis: time; y-axis: normalised phase-synchrony in standard deviations (SD)) for early adolescent, late adolescent and adult participants. Note the drastic reduction in phase locking in the group of late adolescents [adapted from Uhlhaas *et al.*, 2009b].