Review

Neural synchrony and the development of cortical networks

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Recent data indicate that the synchronisation of oscillatory activity is relevant for the development of cortical circuits as demonstrated by the involvement of neural synchrony in synaptic plasticity and changes in the frequency and synchronisation of neural oscillations during development. Analyses of resting-state and task-related neural synchrony indicate that gamma-oscillations emerge during early childhood and precise temporal coordination through neural synchrony continues to mature until early adulthood. The late maturation of neural synchrony is compatible with changes in the myelination of cortico-cortical connections and with late development of GABAergic neurotransmission. These findings highlight the role of neural synchrony for normal brain development as well as its potential importance for understanding neurodevelopmental disorders, such as autism spectrum disorders (ASDs) and schizophrenia.

Function and mechanisms of neural synchrony in cortical networks

Synchronised neural oscillations in the low (delta, theta and alpha) and high (beta and gamma) frequency are a fundamental mechanism for enabling coordinated activity in the normally functioning brain (Box 1) [1,2]. A large body of evidence from invasive electrophysiology in non-human primates and electro- and magnetoencephalographic (EEG/MEG) recordings (see Glossary) 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 (Box 1). Although 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 synchronised neuronal activity play a crucial role in the activity-dependent self-organisation of developing networks [3–6] (Figure 1). The development and maturation of cortical networks critically depends on neuronal activity, whereby synchronised oscillations play an important role in the stabilization and pruning of connections [4]. For example, in spike-timing dependent plasticity, pre- and postsynaptic spiking within a critical window of tens of milliseconds has profound functional implications [7]. 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) [8]. The same relationship holds for oscillations in the beta- and gamma-frequency range [9], indicating that oscillations provide a temporal structure that allows for precise alignment of the amplitude and temporal relations of presynaptic and postsynaptic activation that determine whether a

Glossary

Neural synchrony can be measured non-invasively with **electro- and magnetoencephalography (EEG/MEG)** that sample ongoing electrical brain activity, which oscillates at various frequencies, through electrodes or sensors placed over the whole scalp.

Time-frequency analysis: The first step in order to measure amplitude and synchrony of oscillations in EEG and MEG data is the transformation of the electrophysiological signal into the frequency domain. This can be achieved by several time-frequency techniques [for a review of different methods see 69]. These methods involve Fourier analysis that describes the decomposition of a time series into sinusoidal functions and thereby allows the estimation of the signal at a given frequency.

Evoked vs. induced oscillations: Amplitude measures of oscillations can be further differentiated into evoked and induced components. Evoked oscillations show a constant phase and latency relationship to the onset of an external event and, therefore, can be recovered from the average evoked potentials. Typically, evoked oscillations occur with a latency of 50–150 ms. By contrast, induced oscillations are non time-locked to the onset of a stimulus and occur with a variable delay between trials. For the extraction of induced oscillations, analysis needs to be performed on a single-trial basis because averaging across trials would cancel any oscillatory patterns.

Neural synchrony in EEG/MEG Data: A way to estimate the synchrony of oscillations in EEG/MEG data is the analysis of phase relationships. Phase relationships can be examined by testing the stability of phases across trials (phase-locking) over a single electrode or between pairs of electrodes [70]. These two approaches yield estimates of the precision of local and long-range synchrony, respectively. Importantly, measures of phase-locking provide estimates of synchrony independent of the amplitude of oscillations. This is in contrast to measures of coherence where phase and amplitude are intertwined.

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Box 1. Neural synchrony in cortical networks

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 synchronisation of distributed neural responses. Gray and colleagues [54] 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 synchronise their discharges with high precision. Thus, it is a central role of cortical oscillations in the beta/gamma range to enable neuronal synchronisation and by virtue of establishing systematic phase lags, to define precise temporal relations between the discharges of distributed neurons [55].

Self-generated oscillations and synchronisation are highly dynamic phenomena and depend on numerous conditions, such as central states [56], stimulus configuration [54,57] or attention [58]. The strength of synchrony is closely correlated with perceptual processes such as feature binding, subsystem integration, brightness perception and interocular rivalry [for a recent review see 59]. In addition, the strength of synchronisation predicts whether an animal will give a correct response in an upcoming trial of a perceptual decision task [60] indicating 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 not only with inhibitory functions [61] but also with the long-distance coordination of gamma-oscillations [62], and theta activity has been proposed to support large-scale integration of subsystems serving the formation and recall of memories [63]. In general, there is a correlation between the distance over which synchronisation is observed and the frequency of the synchronised oscillations. Short distance synchronisation tends to preferentially occur at higher frequencies (gamma band) than long-distance synchronisation, which often manifests itself in the beta- but also in the theta- (4–8 Hz) and alpha- (8–12 Hz) frequency range [64,65].

strengthening or weakening of synaptic contacts occurs. Accordingly, the extensive modifications of synaptic connections during the development of cortical networks are critically dependent upon precise timing of neural activity.

Synchronisation of oscillatory activity is furthermore an important index of the maturity and efficiency of cortical networks. Neural oscillations are an energy efficient mechanism for the coordination of distributed neural activity [1] that are functionally related to anatomical and physiological parameters that undergo significant changes during development. Thus, synchronisation of oscillatory activity in the beta- and gamma-frequency range is dependent upon cortico-cortical connections that reciprocally link cells situated in the same cortical area, across different areas or even across the two hemispheres [10,11]. Furthermore, GABAergic interneurons play a pivotal role in establishing neural synchrony in local circuits as indicated by research that shows that a single GABAergic neuron might be sufficient to synchronise the firing of a large population of pyramidal neurons [12] and the duration of the inhibitory postsynpatic potential (IPSP) can determine the dominant frequency of oscillations within a network [13]. In addition to chemical synaptic transmission, direct electrotonic coupling through gap-junctions between inhibitory neurons also contributes to the temporal patterning of population activity and, in particular, to the precise synchronisation of oscillatory activity [14,15].

Gap-junctions are functionally important during early brain development [16]. Postnatally, changes in both GABAergic neurotransmission [17,18] and the myelination of long axonal tracts [19,20] occur. Thus, changes can be expected in the frequency and 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 review, we will provide evidence for this hypothesis by summarising the literature on resting state activity as well as during cognitive tasks that indicate important changes in parameters of neural synchrony during childhood and adolescence. Although high-frequency activity emerges during early development, 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: development of frequency, amplitude and synchronisation

Changes in the frequency spectrum during development 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 21]. In adults, resting-state activity is characterised by prominent alpha-oscillations over occipital electrodes whereas 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 [22] (Figure 2a). These development changes occur more rapidly in posterior than in frontal regions [21] and follow a linear trajectory until age 30 [22]. When the relative magnitude is taken into account, oscillations in the alpha- and beta-range increase whereas activity in lower frequency decreases with age.

Changes in resting-state activity during adolescence can also be observed during sleep. Campbell and Feinberg [23] analysed delta and theta activity during non-rapid eye movement sleep (non-REM) in a sample of 9- and 12-year-old cohort 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 and 11 years but then showed a reduction by over 60 per cent until 16.5 years. Similar results were obtained for oscillations in the theta band. According to the authors, the decrease in the power of slow-frequency oscillations reflect synaptic pruning and are 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 [24]. Correlation between the amplitude over frontal electrodes and development of language and cognitive skills indicate a functional role of early gamma band activity in the maturation of cognitive functions [25].

Changes in the amplitude of oscillations are accompanied by developmental trends in the synchrony of oscillations. Thatcher *et al*. [26] tested the hypothesis that white matter maturation involves the differential development of short- and long-range fibre connections and is

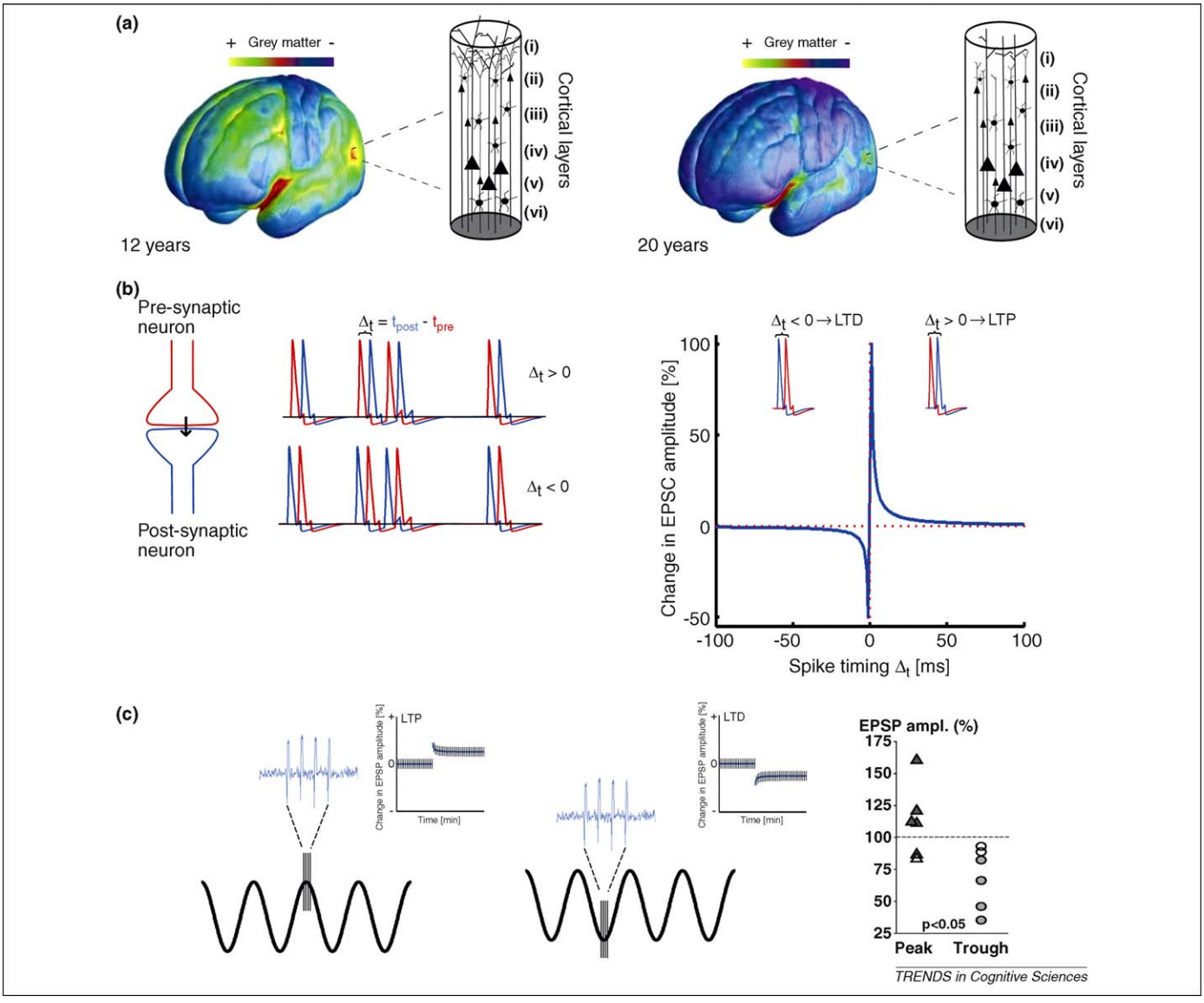

Figure 1. Synchrony, oscillations and network development. **(a)** Development of cortical networks. Left panel: Cortical surface representation of grey matter (left) at age 12 (n = 13) and at age 20 (n = 13) (right panel) (adapted from [66]). The colour scale indicates variations in cortical volume and highlight the reduction of grey matter during the adolescent period. A schematic display of a cortical column shows a relative abundance of dendritic arborizations from pyramidal cells in the adolescent brain (left) compared to the adult cortex (right). This pruning process could underlie the observed reductions of grey matter in MR-studies. **(b)** Spike timing dependent plasticity. Left panel: The difference (Δt) at which a pre- (red) and postsynaptic (blue) spike occur is a measure of the temporal order between these spikes. This difference is positive whenever a presynaptic spike precedes a postsynaptic spike. Right panel: Effects of spike timing on synaptic plasticity. If the presynaptic neuron fires prior to the postsynaptic neuron ($\Delta t > 0$), the EPSP of the postsynaptic cell is potentiated (long-term potentiation, LTP). However, if the postsynaptic cell fires first ($\Delta t < 0$), this effect is reversed and the EPSP of the postsynaptic cell undergoes depression (long-term depression, LTD) (modified and adapted from [67]). **(c)** Phase-sensitivity of synaptic modifications. Left panel: Simulated local field potential (LFP)-oscillations (black line) and a burst of high-frequency stimulation (blue line) occurring at the peak of oscillatory cycle. This results in a potentiation of the synaptic potential (LTP) as indicated by the increase in the membrane potential. Middle panel: Stimulation at the through of the oscillation cycle results in a depression of the synaptic membrane potential (LTD). Right panel: Experimental evidence for the phase-sensitivity of synaptic modifications during sustained high-frequency oscillations (40 Hz) in rats. EPSP amplitudes of pyramidal cells in visual cortex are shown during extracellular stimulation. A strong increase in the amplitude of the EPSP is observed when stimulation at the oscillation peak occurs, whereas stimulation at the though decreases the EPSP amplitude (adapted from [9]).

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) whereas 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*. [27]. 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 indicate 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 indicating 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 synchronised in frequency and phase. Thus, steady-state paradigms are ideally suited to probe the ability of

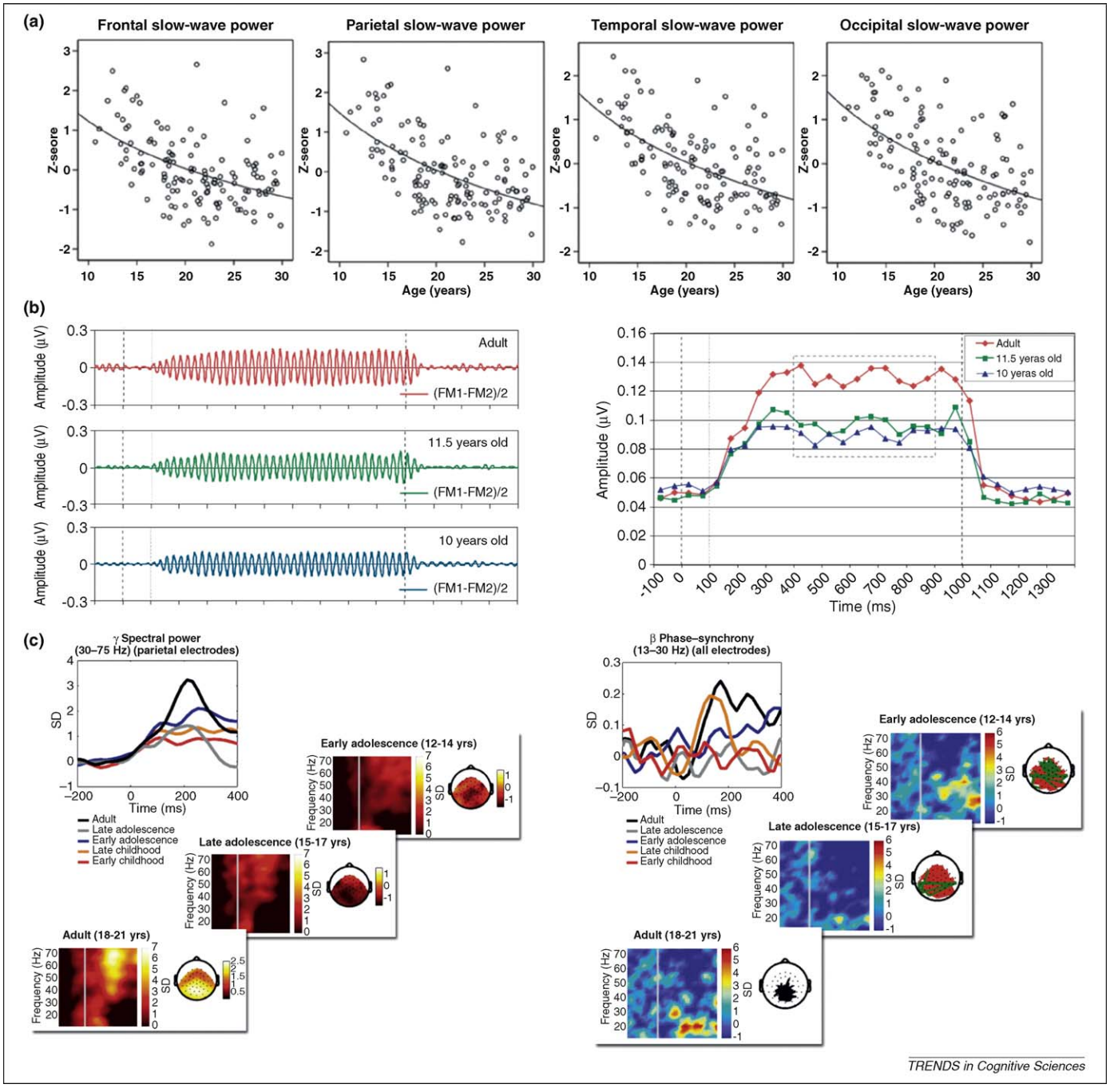

Figure 2. Maturation of neural synchrony during the development of cortical networks. **(a)** Development of resting state activity in the 0.5–7.5 Hz frequency range in a sample of children, adolescent and adult participants (n = 130) (10–30 years) over temporal and occipital electrodes. The amplitude of delta and theta oscillations decreases over the course of adolescence and early adulthood and is accompanied by reductions in grey matter volume. **(b)** Late maturation of auditory steady state responses. Left panel: Average-referenced, grand-average 40-Hz auditory steady state response (ASSR) at electrode Cz, 30–50-Hz band-pass filtered, for adults (red), children at 10 years of age (blue) and 11.5 years of age (green). Dashed lines indicate time of stimulus onset and offset; dotted lines indicate onset of frequency modulation. Right panel: Root mean square amplitude of ASSRs in 50-ms bins. Data from individual subjects within the time window indicated by the boxed area were subjected to subsequent statistical analyses. Independent-sample *t*-tests revealed that the amplitude of the 40-Hz ASSR was significantly larger in adults than the children at both 10 and 11.5 years of age (adapted from [30]). **(c)** 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 and 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 (adapted from [33]).

neuronal networks to generate and maintain oscillatory activity in different frequency bands. Previous research had shown that the power of the auditory SSR (ASSR) is largest in the 40 Hz range [28], indicating a natural resonance frequency of cortical networks.

Developmental studies have so far focused on the ASSR. Rojas *et al*. [29] examined the 40 Hz ASSR in MEG data in 69 participants in the age range from 5 to 52 years. Regression analyses showed a significant effect for age indicating that the amplitude of the 40 Hz ASSR between

200 and 500 ms increased significantly during development. Specifically, a marked increase in 40 Hz power was observed during childhood and adolescence and seemed to reach a plateau during early adulthood.

The protracted maturation of the ASSR was confirmed in a recent study by Poulsen *et al*. [30] (Figure 2b). 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 during motor, cognitive and perceptual processes

Csibra *et al*. [31] measured gamma band responses in EEG data in 6- and 8-months-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 hypothesised 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 and 320 ms over frontal electrodes that was not present in the younger group, indicating 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*. [32] tested the amplitude and phase-stability of evoked gamma band oscillations 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 and 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, although 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 by Uhlhaas *et al*. [33] in a study that investigated children's, adolescent participants' and young adults' perception of Mooney faces (Figure 2c). 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-synchronisation 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*. [34] assessed differences in oscillatory activity between 0 and 12 Hz in young children (9–11 years), older children (11–13 years), young adults (18–25 years) and older adults (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, indicating 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 [35].

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 [36]. 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*. [37] analysed the coherence of EMG-signals in the 1 to 45 Hz frequency range during development in a sample of 50 participants (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.

In addition to the increase in the synchrony of EMG signals, there is evidence that long-range synchronisation of oscillations between the primary motor cortex and muscles undergoes significant changes during development. James *et al*. [38] examined EEG recordings over primary motor cortex and EMG data from the contralateral wrist extensor muscle in a sample of 48 participants (0–58 years). In the youngest age groups (0–3 and 4–10 years) coherence values between EEG and EMG signals were randomly distributed across different frequencies indicating that the drive from corticospinal pathways to motorneurons is not oscillatory. By contrast, significant coherence values were found in adolescent participants

between 12 and 17 years that showed, however, a less pronounced clustering in the beta band than in adult participants. Accordingly, these findings indicate that coherence between motor cortex and muscles increases during adolescence and is accompanied by a reduction in variance of frequencies at which such interactions occur.

Neural synchrony during development: relationship to anatomy and physiology

Our review highlights ongoing modifications of cortical circuits during childhood and adolescence that are reflected in the frequency and synchronisation of oscillatory activity. Following the emergence of gamma band oscillations during infancy [24,25], continued development of neural synchrony is observed whereby oscillations shift to higher frequencies and synchronisation becomes more precise [29,30,33,34,38]. One fact highlighted in the current review is that this development is not complete until early adulthood and that neural synchrony continues to mature throughout the adolescent period that represents a critical phase of brain maturation. However, several issues remain to be addressed for future research (Box 2).

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 [39] as well as with concurrent changes in anatomy and physiology [40] (Figure 3). Specifically, late development of gamma band oscillations is compatible with recent data indicating important changes in the GABAergic neurotransmission during adolescence. Hashimoto *et al*. [17] (Figure 3c) 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 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 because α_1 subunits predominate at synapses of parvalbumin (PV) -positive basket cells (BCs) [41] that are crucially involved in the generation of gamma band oscillations [42].

Box 2. Questions for future research

- How is the development of different frequency bands related to the maturation of different cognitive functions?
- What are the precise underlying physiological and anatomical parameters underlying the differential expression of oscillations during development?
- Is there a relationship between changes in hormone levels and the maturation of neural synchrony in cortical networks during adolescence?
- Changes in both task- and resting-state conditions have been found during development. Do the changes reflect the same maturational mechanisms?
- The strength of oscillations and precision of synchrony increases until adulthood. Are there changes in neural synchrony during old age? If so, are they related to the emergence of cognitive deficits?
- Is there a relationship between the development of neural synchrony and changes in event-related potentials?

The decrease in the slow-wave oscillations (delta, theta) has been related to synapting pruning [43]. According to this view, the higher number of synapses during childhood could explain the excess of delta and theta oscillations as well as the increase in metabolic rate that then become reduced during adolescence leading to reduced slow-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 continued anatomical changes. The development of white matter that continues until early adulthood [19,44] (Figure 3a) 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 (Figure 3b). 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 [45] and during the resting-state [46]. These studies revealed a developmental pattern whereby brain areas crucial for task performance become increasingly activated [47]. 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 [48–50]. As the amplitude of the BOLD-signal is closely and positively correlated with the entrainment of neurons into synchronised gamma band oscillations [51], the fMRI data are fully compatible with the conclusions drawn from the present review that the ability of cortical networks to engage in precisely synchronised high-frequency oscillations increases during development and is a hallmark of maturity.

Neural synchrony during development: implications for psychopathology

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 [52,53]. Considering the important role of neural synchrony in the shaping of cortical circuits at different developmental periods, we hypothesise that in ASDs abnormal brain maturation during early prenatal and postnatal periods results in cortical circuits that are unable to support the expression of high-frequency oscillations during infancy. These impaired oscillations might in turn reduce the temporal precision of coordinated firing patterns and thereby disturb activity-dependent circuit selection during further development. In schizophrenia, by contrast, clinical symptoms manifest typically 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

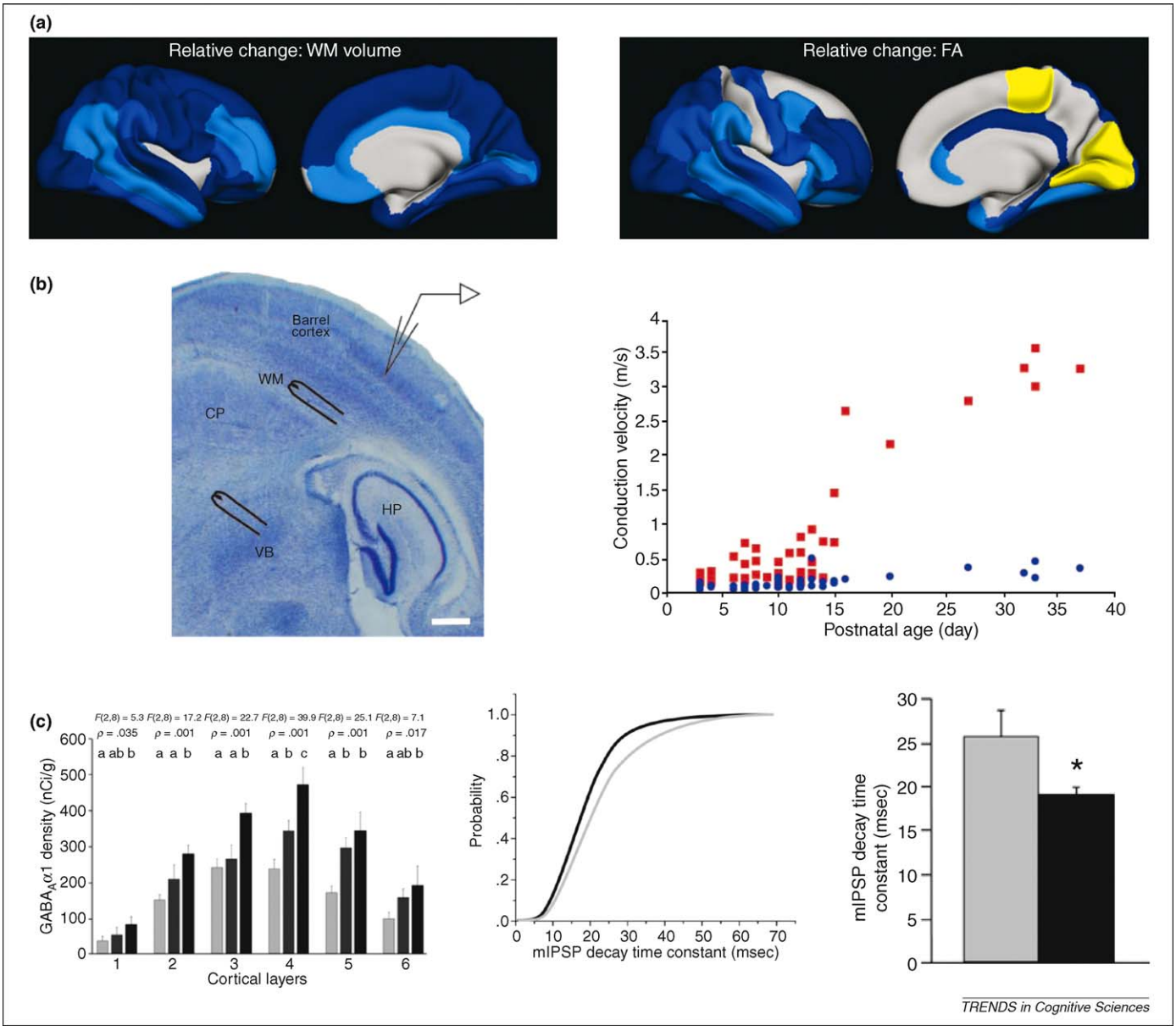

Figure 3. Changes in physiology and anatomy during adolescence. **(a)** Relative magnitude of developmental changes over the age span from 8 to 30 years in white matter. WM volume (left panel) and Fractional Anistropy (FA) (right panel) are colour coded and projected onto the surface of a semi-inflated average template brain. Diffusion measures are derived from voxels in underlying WM regions that overlapped with major tracts. Increases in volume of 15% or more were observed in most regions over the age span studied. The largest relative increase was observed for deep WM, which increased by 58% from 8 to 30 years. For FA, there were increases of 20% or more in regions on the lateral side of the occipital, parietal and frontal lobes, as well as in the cingulum, the parahippocampus, and the inferior temporal lobe. There were also moderate increases medially in the parietal and occipital lobes (adapted from [68]). **(b)** The relationship between myelination and conduction velocity (CV). Left panel: A photomicrograph of a thalamocortical slice, Nissl stained, representing the experimental procedure. Stimulation and recording sites are schematically illustrated. HP, hippocampus; CP, caudate putamen (Bar, 500 μm). Right panel: The CV of two portions of thalamocortical axons, calculated by the latencies and distances between the stimulated ventrobasal nucleus of the thalamus and white matter (CV $_{VB\text{-}WM}$). CV $_{VB\text{-}WM}$ (red squares) was calculated from the distance between VB and WM divided by the latency difference between VB and WM stimulation. CV $_{WM}$ (blue circles) was obtained by the simple calculation using distance between stimulated (WM) and recorded sites, divided by the latency evoked by WM stimulation. As can be seen, both CV_{WM} and $CV_{VB\text{-}WM}$ increase strongly with age extending into postnatal week 5 (adapted from [44]). **(c)** Cortical layer comparisons of gamma-aminobutyric acid (GABA) A receptor-subunit α1 and in 1-week old, prepuberty, and adult groups of monkeys. Left panel: The means (SD) of GABA A receptor α 1 subunit expression levels in each age group were plotted across cortical layers. Layers 2–3 showed a prominent increase during adolescence, whereas layer 5 showed a significant increase in the preadolescent period. Right panel: Cumulative probability distribution curves of the mIPSP decay time constant in prepubertal (grey) and postpubertal (black) animals. The left shift of the curve from prepubertal to postpubertal animals indicates a higher fraction of shorter mIPSPs in postpubertal animals compared with prepubertal animals. Bar graph summarising the differences between age groups (Student's *t* test, $*p = 0.05$, $n = 11$ cells for each group). Because the decay time of IPSPs is a critical factor for the dominant frequency of oscillations within a network [13], these data together with the changes in α1 subunit expression provide one mechanism for the late maturation of high-frequency oscillations in EEG-data [as reported in 33] (adapted from [17]).

circuits are unable to support the neural coding regime that emerges during late adolescence that relies on temporally more precise and spatially more focused synchronisation patterns. This then leads to a breakdown of coordinated neural activity and the emergence of psychosis and cognitive dysfunctions.

Concluding remarks

We have reviewed evidence on developmental changes in neural synchrony during childhood and adolescence that highlights the relationship between brain maturation and changes in the frequency, amplitude and synchronisation of neural oscillations. These data indicate that, in addition

to providing a mechanism for the coordination of distributed neural responses that underlies cognitive and perceptual functions, neural synchrony is closely related to the development of cortical circuits. This is indicated by the relationship between the emergence of specific patterns of oscillatory activity and certain cognitive functions and by the correlation between the appearance of certain brain disorders at different developmental periods and electrographic signs of abnormal temporal coordination. Accordingly, such data support the view that neural synchrony is not epiphenomenal but plays a role in the functions of cortical networks. Future research should further address the role of neural synchrony during brain development by directly investigating relationships with the underlying anatomical and physiological changes as well as by using novel techniques that allow a more precise characterisation of development changes in neural synchrony.

Acknowledgements

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References

1 Buzsaki, G. and Draguhn, A. (2004) Neuronal oscillations in cortical networks. *Science* 304, 1926–1929
2 Fries, P. (2009) Neuronal gamma-band synchronization as a fundamental process in cortical computation. *Annu. Rev. Neurosci.* 32, 209–224
3 Singer, W. (1995) Development and plasticity of cortical processing architectures. *Science* 270, 758–764
4 Hebb, D.O. (1949) *The organization of behavior: A neuropsychological theory*, Wiley
5 Ben-Ari, Y. (2001) Developing networks play a similar melody. *Trends Neurosci.* 24, 353–360
6 Khazipov, R. and Luhmann, H.J. (2006) Early patterns of electrical activity in the developing cerebral cortex of humans and rodents. *Trends Neurosci.* 29, 414–418
7 Markram, H. *et al.* (1997) Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 275, 213–215
8 Huerta, P.T. and Lisman, J.E. (1993) Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. *Nature* 364, 723–725
9 Wespatat, V. *et al.* (2004) Phase sensitivity of synaptic modifications in oscillating cells of rat visual cortex. *J. Neurosci.* 24, 9067–9075
10 Engel, A.K. *et al.* (1991) Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science* 252, 1177–1179
11 Löwel, S. and Singer, W. (1992) Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. *Science* 255, 209–212
12 Cobb, S.R. *et al.* (1995) Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature* 378, 75–78
13 Wang, X.J. and Buzsaki, G. (1996) Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J. Neurosci.* 16, 6402–6413
14 Draguhn, A. *et al.* (1998) Electrical coupling underlies high-frequency oscillations in the hippocampus in vitro. *Nature* 394, 189–192
15 Hestrin, S. and Galarreta, M. (2005) Electrical synapses define networks of neocortical GABAergic neurons. *Trends Neurosci.* 28, 304–309
16 Montoro, R.J. and Yuste, R. (2004) Gap junctions in developing neocortex: a review. *Brain Res. Brain Res. Rev.* 47, 216–226
17 Hashimoto, T. *et al.* (2009) Protracted developmental trajectories of GABA(A) receptor alpha1 and alpha2 Subunit expression in primate prefrontal cortex. *Biol. Psychiatry* 65, 1015–1023
18 Doischer, D. *et al.* (2008) Postnatal differentiation of basket cells from slow to fast signaling devices. *J. Neurosci.* 28, 12956–12968
19 Ashtari, M. *et al.* (2007) White matter development during late adolescence in healthy males: A cross-sectional diffusion tensor imaging study. *Neuroimage* 35, 501–510
20 Perrin, J.S. *et al.* (2009) Sex differences in the growth of white matter during adolescence. *Neuroimage* 45, 1055–1066
21 Niedermeyer, E. and Da Silva, F.L., (2005) Maturation of the EEG: Development of Waking and Sleep Patterns. In: *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*, Lippincott Williams & Wilkins
22 Whitford, T.J. *et al.* (2007) Brain maturation in adolescence: concurrent changes in neuroanatomy and neurophysiology. *Hum. Brain Mapp.* 28, 228–237
23 Campbell, I.G. and Feinberg, I. (2009) Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation. *Proc. Natl. Acad. Sci. U S A* 106, 5177–5180
24 Takano, T. and Ogawa, T. (1998) Characterization of developmental changes in EEG-gamma band activity during childhood using the autoregressive model. *Acta Paediatr. Jpn* 40, 446–452
25 Benasich, A.A. *et al.* (2008) Early cognitive and language skills are linked to resting frontal gamma power across the first 3 years. *Behav. Brain Res.* 195, 215–222
26 Thatcher, R.W. *et al.* (2008) Development of cortical connections as measured by EEG coherence and phase delays. *Hum. Brain Mapp.* 12, 1400–1415
27 Srinivasan, R. (1999) Spatial structure of the human alpha rhythm: global correlation in adults and local correlation in children. *Clin. Neurophysiol.* 110, 1351–1362
28 Galambos, R. *et al.* (1981) A 40-Hz auditory potential recorded from the human scalp. *Proc. Natl. Acad. Sci. U S A* 78, 2643–2647
29 Rojas, D.C. *et al.* (2006) Development of the 40 Hz steady state auditory evoked magnetic field from ages 5 to 52. *Clin. Neurophysiol.* 117, 110–117
30 Poulsen, C. *et al.* (2009) Age-related changes in transient and oscillatory brain responses to auditory stimulation during early adolescence. *Dev. Sci.* 12, 220–235
31 Csibra, G. *et al.* (2000) Gamma oscillations and object processing in the infant brain. *Science* 290, 1582–1585
32 Werkle-Bergner, M. *et al.* (2009) EEG gamma-band synchronization in visual coding from childhood to old age: Evidence from evoked power and inter-trial phase locking. *Clin. Neurophysiology* 120, 1291–1302
33 Uhlhaas, P.J. *et al.* (2009) The development of neural synchrony reflects late maturation and restructuring functional networks in humans. *Proc. Natl. Acad. Sci. U. S. A.* 106, 9866–9871
34 Müller, V. *et al.* (2009) Lifespan differences in cortical dynamics of auditory perception. *Dev. Sci.* 12, 839–853
35 Yordanova, J.Y. *et al.* (1996) Developmental changes in the alpha response system. *Electroencephalogr. Clin. Neurophysiol.* 99, 527–538
36 Kilner, J.M. *et al.* (2000) Human cortical muscle coherence is directly related to specific motor parameters. *J. Neurosci.* 20, 8838–8845
37 Farmer, S.F. *et al.* (2007) Changes in EMG coherence between long and short thumb abductor muscles during human development. *J. Physiol.* 579, 389–402
38 James, L.M. *et al.* (2008) On the development of human corticospinal oscillations: age-related changes in EEG–EMG coherence and cumulant. *Eur. J. Neurosci.* 27, 3369–3379
39 Luna, B. *et al.* (2004) Maturation of cognitive processes from late childhood to adulthood. *Child Dev.* 75, 1357–1372
40 Toga, A.W. *et al.* (2006) Mapping brain maturation. *Trends Neurosci.* 29, 148–159
41 Klausberger, T. *et al.* (2002) Cell type- and input-specific differences in the number and subtypes of synaptic GABA(A) receptors in the hippocampus. *J. Neurosci.* 22, 2513–2521
42 Sohal, V.S. *et al.* (2009) Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature* 459, 698–702
43 Feinberg, I. and Campbell, I.G. (2010) Sleep EEG changes during adolescence: An index of a fundamental brain reorganization. *Brain Cogn.* 72, 56–65
44 Salami, M. *et al.* (2003) Change of conduction velocity by regional myelination yields constant latency irrespective of distance between thalamus and cortex. *Proc. Natl. Acad. Sci. U. S. A.* 100, 6174–6179

45 Casey, B.J. *et al.* (2008) The adolescent brain. *Ann. N. Y. Acad. Sci.* 1124, 111–126
46 Supekar, K. *et al.* (2009) Development of large-scale functional brain networks in children. *PLoS Biol.* 7, e1000157
47 Durston, S. *et al.* (2006) A shift from diffuse to focal cortical activity with development. *Dev. Sci.* 9, 1–8
48 Crone, E.A. *et al.* (2006) Neurocognitive development of the ability to manipulate information in working memory. *Proc. Natl. Acad. Sci. U. S. A.* 103, 9315–9320
49 Rubia, K. *et al.* (2007) Linear age-correlated functional development of right inferior fronto-striato-cerebellar networks during response inhibition and anterior cingulate during error-related processes. *Hum. Brain Mapp.* 28, 1163–1177
50 Golarai, G. *et al.* (2007) Differential development of high-level visual cortex correlates with category-specific recognition memory. *Nat. Neurosci.* 10, 512–522
51 Niessing, J. *et al.* (2005) Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science* 309, 948–951
52 Uhlhaas, P.J. and Singer. W. (2010) Abnormal oscillations and synchrony in schizophrenia. *Nat. Rev. Neurosci.*
53 Uhlhaas, P.J. and Singer, W. (2007) What do disturbances in neural synchrony tell us about autism. *Biol. Psychiatry* 62, 190–191
54 Gray, C.M. *et al.* (1989) Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature* 338, 334–337
55 Womelsdorf, T. *et al.* (2007) Modulation of neuronal interactions through neuronal synchronization. *Science* 316, 1609–1612
56 Herculano-Houzel, S. *et al.* (1999) Precisely synchronized oscillatory firing patterns require electroencephalographic activation. *J. Neurosci.* 19, 3992–4010
57 Gray, C.M. and Singer, W. (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proc. Natl. Acad. Sci. U. S. A.* 86, 1698–1702
58 Fries, P. *et al.* (2001) Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 291, 1560–1563
59 Uhlhaas, P.J. *et al.* (2009) Neural synchrony in cortical networks: history, concept and current status. *Front. Integr. Neurosci.* 3, 17
60 Kreiter, A.K. and Singer, W. (1996) Stimulus-dependent synchronization of neuronal responses in the visual cortex of the awake macaque monkey. *J. Neurosci.* 16, 2381–2396
61 Klimesch, W. *et al.* (2007) EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res. Rev.* 53, 63–88
62 Palva, S. and Palva, J.M. (2007) New vistas for alpha-frequency band oscillations. *Trends Neurosci.* 30, 150–158
63 Buzsaki, G. (2005) Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus* 15, 827–840
64 von Stein, A. *et al.* (2000) Top-down processing mediated by interareal synchronization. *Proc. Natl. Acad. Sci. U. S. A.* 97, 14748–14753
65 Kopell, N. *et al.* (2000) Gamma rhythms and beta rhythms have different synchronization properties. *Proc. Natl. Acad. Sci. U. S. A.* 97, 1867–1872
66 Gogtay, N. *et al.* (2004) Dynamic mapping of human cortical development during childhood through early adulthood. *Proc. Natl. Acad. Sci. U. S. A.* 101, 8174–8179
67 Mu, Y. and Poo, M.M. (2006) Spike timing-dependent LTP/LTD mediates visual experience-dependent plasticity in a developing retinotectal system. *Neuron* 50, 115–125
68 Tamnes, C.K. *et al.* (2010) Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. *Cereb. Cortex* doi:10.1093/cercor/bhp118
69 van Vugt, M.K. *et al.* (2007) Comparison of spectral analysis methods for characterizing brain oscillations. *J. Neurosci. Methods* 162, 49–63
70 Lachaux, J.P. *et al.* (1999) Measuring phase synchrony in brain signals. *Hum. Brain Mapp.* 8, 194–208