

# Abnormal neural oscillations and synchrony in schizophrenia

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**Abstract** | Converging evidence from electrophysiological, physiological and anatomical studies suggests that abnormalities in the synchronized oscillatory activity of neurons may have a central role in the pathophysiology of schizophrenia. Neural oscillations are a fundamental mechanism for the establishment of precise temporal relationships between neuronal responses that are in turn relevant for memory, perception and consciousness. In patients with schizophrenia, the synchronization of beta- and gamma-band activity is abnormal, suggesting a crucial role for dysfunctional oscillations in the generation of the cognitive deficits and other symptoms of the disorder. Dysfunctional oscillations may arise owing to anomalies in the brain's rhythm-generating networks of GABA ( $\gamma$ -aminobutyric acid) interneurons and in cortico-cortical connections.

## Negative symptoms

An absence of behaviour, characterized by flat or blunted affect and emotion, poverty of speech (alogia), inability to experience pleasure (anhedonia) and lack of motivation (avolition).

Schizophrenia is characterized by prominent psychotic symptoms that include the false attribution of perceptual experience to an external source (hallucinations), grossly distorted thinking (delusions), reduction in affect and behaviour (negative symptoms) and disorganization of thought and language (thought disorder). In addition, patients with schizophrenia exhibit impairments in both basic sensory processing and higher cognitive functions, such as language, reasoning and planning.

Despite more than 100 years of research, the causes of schizophrenia are still unknown. Efforts to understand the pathophysiology of schizophrenia have concentrated on the identification of abnormalities in specific cortical regions that are related to the symptoms of the disorder. It is becoming increasingly clear, however, that the psychotic phenomena and cognitive dysfunctions that characterize this disorder are not due to a circumscribed deficit but rather represent a distributed impairment involving many cortical areas and their connectivity. Recent theories therefore highlight the possible role of a disconnection syndrome and/or disturbed dynamic coordination in the pathophysiology of schizophrenia<sup>1,2</sup>. Accordingly, mechanisms that mediate the generation of coherent and coordinated activity in cortical circuits are prime candidates for understanding the pathophysiology of schizophrenia.

Neural oscillations are a fundamental mechanism for enabling coordinated activity during normal brain functioning<sup>3–6</sup> and are therefore a crucial target for schizophrenia research. Neural oscillations in the low (theta and alpha) and high (beta and gamma) frequency ranges establish precise temporal correlations

between distributed neuronal responses. Oscillations in the beta and gamma range establish synchronization with great precision in local cortical networks<sup>7,8</sup> (FIG. 1), whereas lower frequencies preferentially establish synchronization over longer distances<sup>9</sup>.

These temporal correlations are functionally relevant as there is abundant evidence for a close relationship between the occurrence of oscillations and cognitive and behavioural responses, such as perceptual grouping, attention-dependent stimulus selection, working memory and consciousness (TABLE 1) (for a recent review see REF. 10). Schizophrenia is associated with disturbances in all these functions<sup>11–13</sup> and over the past decade it has been recognized that cognitive impairments, which remain largely stable throughout the course of the disorder, could provide a more direct target for efforts to identify basic pathophysiological mechanisms than psychotic symptoms. Importantly, cognitive deficits are not modified by current pharmacological treatments and underlie the poor functional outcome in most patients<sup>14</sup>.

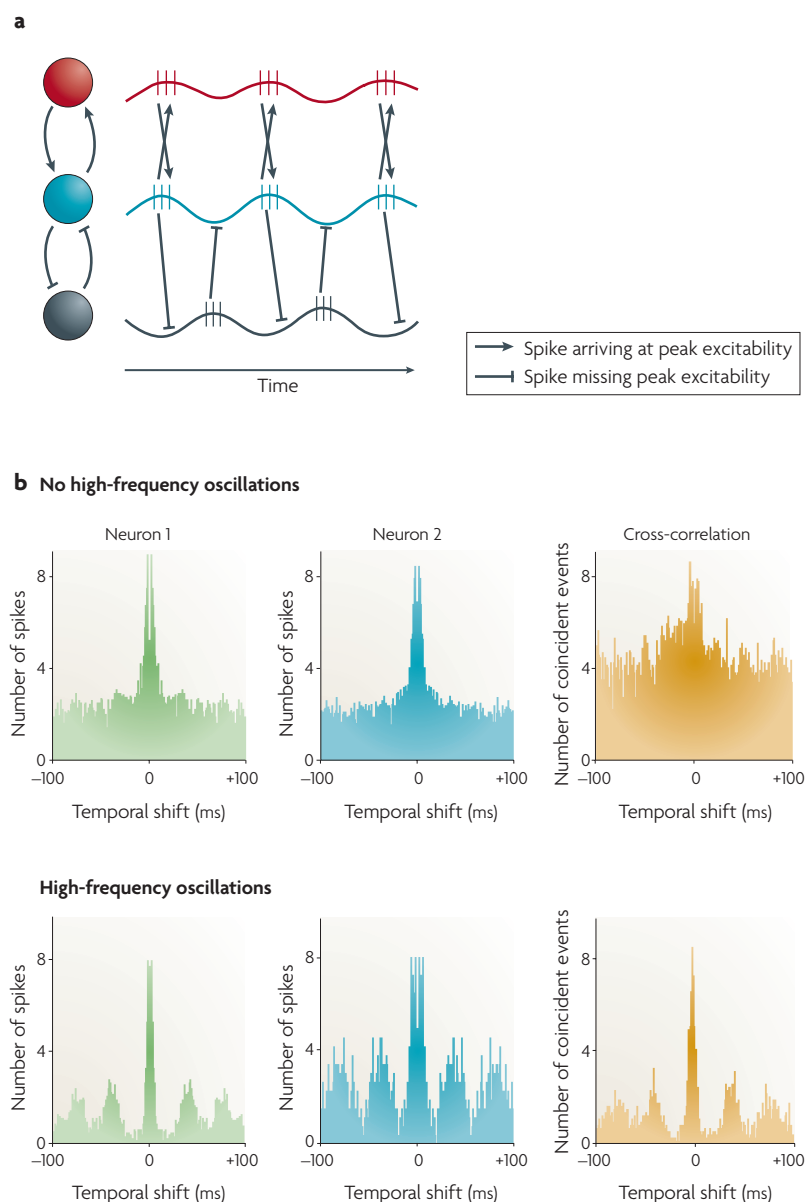
Furthermore, synchronized oscillations have been shown to establish the precision in spike timing that is crucial for use-dependent synaptic plasticity<sup>15–18</sup>. Although there is not yet direct evidence that synaptic plasticity is impaired in schizophrenia, indirect evidence for this hypothesis comes from studies that have demonstrated impairments in motor circuit reorganization after transcranial magnetic stimulation (TMS)-mediated disturbance of the motor cortex<sup>19</sup> and from impairments in the mismatch negativity event-related potential (ERP)<sup>20</sup>, a phenomenon thought to depend on synaptic plasticity<sup>21</sup>.

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**Figure 1 | Neural oscillations and synchrony in cortical networks. a** | The timing of rhythmic activity in cortical networks influences communication between neuronal populations. Three groups of interconnected neurons, each of which is rhythmically active, are shown on the left. On the right are local field potential oscillations and action potentials (spikes; indicated by vertical lines) in the three populations. Spikes either arrive at the postsynaptic neuron during a peak in its local field potential (arrows), corresponding to a peak in its excitability, or miss these peaks (blunt arrows). The timing of the activity of two groups of neurons is thus either aligned, enabling effective communication (red and blue group), or not aligned (blue and grey group), preventing communication. **b** | Synchronization between neurons in local cortical networks depends on the occurrence of gamma oscillations<sup>7</sup>. The panels show auto- (left-hand panels) and cross-correlograms (right-hand panels) of the responses of two neurons (green and blue) in cortical area 17 in anaesthetized cats to a drifting grating stimulus recorded at different times. Cross-correlograms are an index of the temporal correlation between neuronal responses, whereas auto-correlograms reflect the temporal structure of a single channel. Autocorrelograms in the upper and lower rows respectively indicate phases with weak and strong oscillatory modulation of responses. The cross-correlograms indicate synchronization only in the presence of oscillations of ~25 Hz (bottom row). Part **a** is modified, with permission, from REF. 137 © (2005) Elsevier. Data in part **b** are courtesy of D. Nikolić, Max-Planck Institute for Brain Research, Frankfurt am Main, Germany.

In this Review, we highlight the role of dysfunctional neural oscillations in schizophrenia by reviewing the evidence from studies that have examined oscillatory activity and its synchronization in patients with schizophrenia using electroencephalography (EEG) and magnetoencephalography (MEG) (BOX 1). Furthermore, we examine the possible neurobiological causes of impaired oscillations and the involvement of aberrant oscillatory activity in the neurodevelopment of schizophrenia.

### Neural oscillations in schizophrenia

As noted above, neural oscillations are thought to be a fundamental mechanism for the coordination of neuronal responses throughout the cortex, and impairments in these oscillations are a candidate mechanism for a pervasive network impairment in schizophrenia. This is supported by the results of EEG and MEG studies (FIG. 2; see [Supplementary information S1](#) (table)) that have examined neural oscillations at different temporal and spatial scales during cognitive tasks and at rest. Studies investigating task-related oscillations have measured both evoked oscillations, which reflect sensory-driven oscillatory activity and self-generated oscillations (induced oscillations) and their large-scale synchronization.

**Steady-state evoked potentials.** Steady-state evoked potentials (SSEPs) are a basic neural response to a temporally modulated stimulus to which SSEPs are synchronized in frequency and phase. Steady-state paradigms can probe the ability of neuronal networks to generate and maintain oscillatory activity in different frequency bands. Consistent evidence for a deficit in the SSEPs evoked by auditory stimuli in patients with schizophrenia has been obtained from eight studies<sup>22–29</sup>, although one study<sup>30</sup> demonstrated impaired auditory SSEPs in first-degree relatives of patients with chronic schizophrenia but not in the patients themselves. Dysfunctions in the auditory SSEP to trains of clicks presented at gamma frequency, in particular at 40 Hz, have been shown to be pronounced, but deficits in SSEPs in response to the presentation of stimuli at lower frequency bands have also been shown<sup>25,26</sup>. Deficits have also been reported for visual SSEPs, in particular to stimuli in the beta frequency range<sup>31</sup>.

Initially, it was unclear whether the auditory SSEP is an intrinsic oscillatory process or whether it reflects the temporal overlap of potentials elicited by single events<sup>32</sup>. However, recent evidence does not support the concept of superimposed evoked responses. For example, a perturbation in the auditory SSEP can be induced by omitting a click in a stimulus series, an observation that cannot be explained in terms of transient responses to individual clicks<sup>33</sup>. In addition, the temporal profile of the response to stimuli at 40 Hz, which begins 200 ms after stimulus onset and continues after stimulus offset<sup>34</sup>, and the frequency-specific modulation of the 40 Hz auditory SSEPs by attention<sup>35</sup> support the notion that the 40 Hz response is indeed reflecting an oscillatory process.

Table 1 | **Neural oscillations in cortical networks**

Frequency band	Anatomy	Function
Theta (4–7 Hz)	Hippocampus <sup>134</sup> , sensory cortex <sup>140</sup> and prefrontal cortex <sup>141</sup>	Memory <sup>142,143</sup> , synaptic plasticity <sup>18</sup> , top-down control <sup>9</sup> and long-range synchronization <sup>9</sup>
Alpha (8–12 Hz)	Thalamus <sup>144</sup> , hippocampus <sup>145</sup> , reticular formation <sup>145</sup> , sensory cortex <sup>146</sup> and motor cortex <sup>147</sup>	Inhibition <sup>148</sup> , attention <sup>149</sup> , consciousness <sup>150</sup> , top-down control <sup>9</sup> and long-range synchronization <sup>151</sup>
Beta (13–30 Hz)	All cortical structures, subthalamic nucleus <sup>152</sup> , basal ganglia <sup>152</sup> and olfactory bulb <sup>153</sup>	Sensory gating <sup>154</sup> , attention <sup>155</sup> , motor control <sup>156</sup> and long-range synchronization <sup>157</sup>
Gamma (30–200 Hz)	All brain structures, retina <sup>158</sup> and olfactory bulb <sup>159</sup>	Perception <sup>7</sup> , attention <sup>160</sup> , memory <sup>161</sup> , consciousness <sup>162</sup> and synaptic plasticity <sup>16</sup>

**Evoked oscillations.** Consistent with the evidence that early sensory processes are impaired in schizophrenia<sup>13</sup>, several studies<sup>36–40</sup> have demonstrated abnormalities in the stimulus-locked activity that occurs within 50–150 ms after a stimulus is presented. For example, reductions in the amplitude and phase locking of evoked oscillations have been shown during the processing of visual information<sup>37,40</sup>, suggesting an impaired ability to precisely align oscillatory activity with incoming sensory information.

The evidence for deficits in evoked activity in the auditory domain is less consistent. Several studies have shown that patients with schizophrenia are characterized by reduced amplitude and phase locking of the early (50–150 ms) evoked beta- and gamma-band response<sup>36,38,39</sup>, but a recent study<sup>40</sup> did not confirm this finding. In addition, another study<sup>41</sup> observed reductions in evoked gamma oscillations only in a latency range of 220–350 ms over frontal electrodes.

Reductions in evoked gamma-band oscillations have also been demonstrated in frontal regions, an area that has been a traditional focus of schizophrenia research, through measurement of EEG responses following the application of TMS to the premotor cortex<sup>42</sup>. Relative to healthy controls, schizophrenia patients had a marked decrease in gamma oscillations within the first 100 ms after TMS, particularly in a cluster of electrodes located in a fronto-central region. Source analyses revealed that in schizophrenia patients the gamma-band oscillations triggered by TMS did not propagate beyond the area of stimulation, whereas in controls activity was found in several motor and sensorimotor areas.

**Induced oscillations.** Patients with schizophrenia also demonstrate reduced amplitude and synchronization of self-generated, rhythmic activity in several cortical regions. Preliminary evidence for a deficit in high-frequency (60–120 Hz) gamma-band activity comes from a recent study that tested gamma-band oscillations with MEG during a perceptual organization task<sup>43</sup>. Impaired performance in patients with schizophrenia was accompanied by a widespread reduction in the power of gamma-band oscillations in the right temporal lobe in a time window of 50–300 ms after stimulus onset.

The finding that there are intrinsic deficits in neural oscillations in frontal circuits in schizophrenia is compatible with EEG studies that have tested frontal gamma

and theta oscillations during executive and working memory tasks. Patients with schizophrenia were characterized by a reduced amplitude of gamma and theta oscillations in frontal regions<sup>44–46</sup> and an impaired stimulus-induced phase resetting of ongoing oscillations at low and high frequencies<sup>47</sup>.

Reductions in the amplitude of neural oscillations during cognitive tasks are accompanied by reduced phase synchronization of induced oscillatory activity. Phase synchronization has been proposed to provide an effective mechanism for the integration of neural responses in distributed local cortical networks<sup>48</sup> (see figure part a in [Supplementary information S2](#) (figure)). Several studies have shown that in patients with schizophrenia the phase synchronization of oscillations in the beta and gamma frequency bands during visuo-perceptual organization and auditory processing is reduced<sup>49–51</sup>. These findings suggest that impaired synchronization of beta- and gamma-band oscillations underlies the proposed functional disconnectivity of cortical networks in schizophrenia<sup>1,2</sup>. It is currently unclear, however, to what extent impairments in local circuits contribute to long-range synchronization impairments or whether these are two independent phenomena.

**Resting-state oscillations.** Changes in neural oscillations have also been demonstrated during rest in schizophrenia: studies have reported an increase in low-frequency<sup>52</sup> activity and a reduction in high-frequency activity<sup>53</sup>. In addition, a decrease in the amplitude of oscillations has been shown to be accompanied by reductions in the coherence of oscillations at theta frequency<sup>54</sup>.

**Are there medication effects?** An important question is to what extent the impaired neural oscillations seen in patients with schizophrenia might be related to the effects of medication. There is preliminary evidence that patients treated with atypical antipsychotic medication may have intact — that is, within the normal range — gamma-band oscillations in the auditory SSEP paradigm<sup>30</sup>. In addition, other studies have shown that deficits in neural oscillations are present regardless of medication status<sup>41,43</sup>. For example, preliminary evidence suggests that the reductions in gamma-band oscillations in MEG data during perceptual organization are also present in never-medicated, first-episode patients with schizophrenia, albeit to a lesser degree than in chronic, medicated patients<sup>45</sup>. Another

**Perceptual grouping**

The ability of perceptual systems to organize sensory information into coherent representations that can serve as the basis of our phenomenal experience of the world.

**Transcranial magnetic stimulation**

(TMS). A non-invasive method to excite neurons in the brain by inducing weak electric currents in the tissue using rapidly changing magnetic fields.

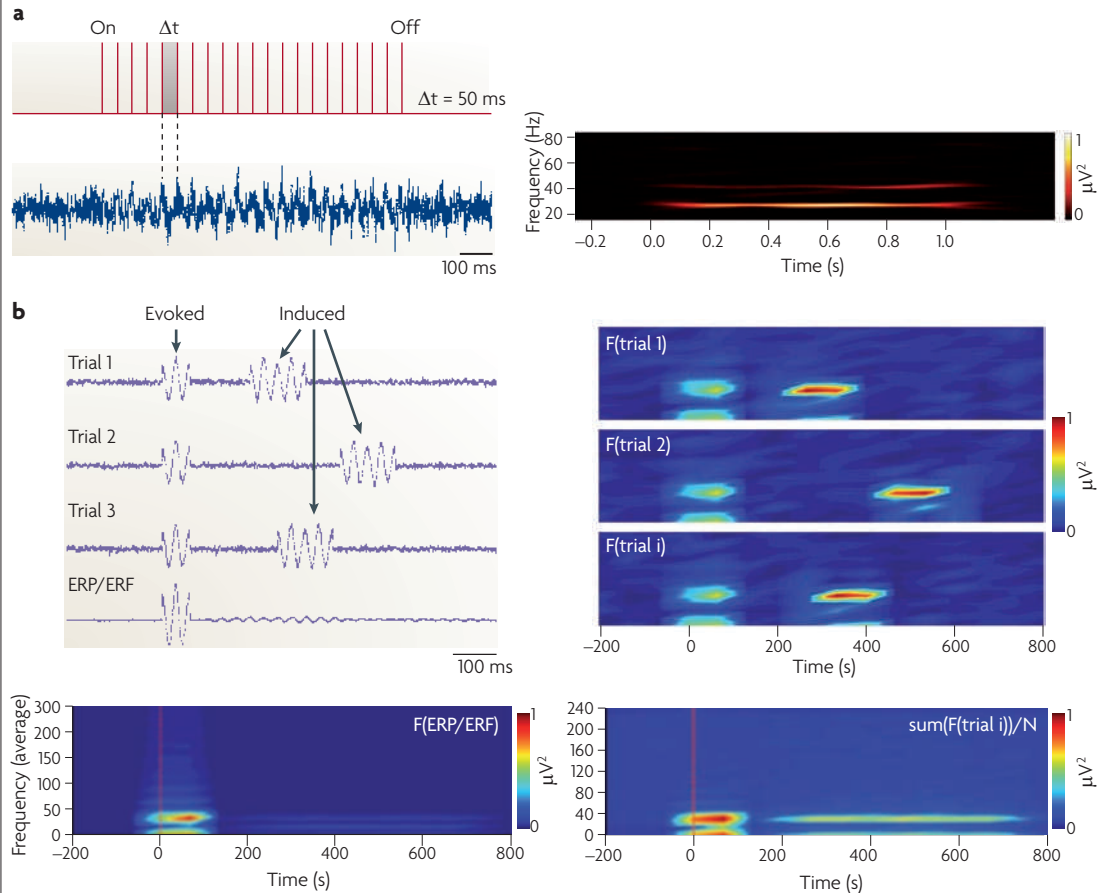
**Mismatch negativity**

An event-related potential that is elicited when a sequence of repeated stimuli (standards) is interrupted by stimuli that deviate in sensory characteristics such as intensity, frequency or duration (deviants).

study<sup>41</sup> showed a reduction in evoked gamma-band activity during an auditory oddball paradigm in medication-naïve first-episode patients with schizophrenia. In addition, several studies have reported abnormalities

in the amplitude and phase of gamma-band oscillations in patients who were treated only for a brief period with antipsychotic medication<sup>27,51</sup>. Thus these data suggest that dysfunctions in neural oscillations and synchronization are

Box 1 | Measuring neural oscillations in EEG and MEG signals



To measure the amplitude and synchrony of oscillations in electroencephalography (EEG) and magnetoencephalography (MEG) data the electrophysiological signal must be transformed into the frequency domain<sup>136</sup>. Measures of the amplitude of oscillations can be further differentiated into steady-state evoked potentials as well as evoked and induced components.

**Measurement of steady-state evoked potentials**

The left panel in part a of the figure illustrates a steady-state stimulation at a frequency of 20 Hz. Each vertical line corresponds to a stimulus. Below this is a voltage trace recorded from an EEG or MEG electrode. The amplitude of the signal is modulated by the stimulation frequency. The right-hand panel shows the spectral power of oscillations (indicated by the colour scale). A peak of spectral power that corresponds to the stimulation frequency (20 Hz) and a harmonic response at 40 Hz are shown. Steady-state evoked potentials can probe the ability of neuronal networks to generate and maintain oscillatory activity in different frequency bands.

**Measuring evoked and induced oscillatory activity**

Evoked oscillations occur at a consistent time lag after the onset of an external event and can be identified by averaging the responses of several trials. By contrast, induced oscillations are not locked to the onset of a stimulus. Analysis of induced oscillations must therefore be performed on a single-trial basis because averaging across trials would cancel out oscillations owing to random phase shifts. The top left panel of part b of the figure shows the EEG or MEG signal recorded across individual trials and the average of the signal across trials (the event-related potential (ERP) or event-related field (ERF)). The bottom left panel is a time–frequency map of the ERP/ERF, showing the spectral power (indicated by the colour scale). The peak of spectral power corresponds to the onset of the evoked oscillations. The top right panel shows three single-trial time–frequency maps. This reveals two peaks of spectral power, corresponding to the evoked and the induced oscillations. The bottom right panel shows an average of the single-trial time–frequency maps.

Evoked and induced oscillations thus reflect different aspects of information processing in cortical networks. Owing to its close temporal relationship with the incoming stimulus, evoked activity reflects bottom-up sensory transmission. Induced oscillations represent the internal dynamics of cortical networks and have been related to higher cognitive functions. Images courtesy of F. Roux, Max-Planck Institute for Brain Research, Frankfurt am Main, Germany.

**Endophenotype**

A neurophysiological, neuroanatomical, cognitive or neuropsychological marker that points to the genetic underpinnings of a clinical syndrome. An endophenotype must be heritable and state independent, and within families the endophenotype and illness must co-segregate.

**Positive symptoms**

A range of psychotic symptoms that most individuals do not normally experience. Typical symptoms are hallucinations in various modalities (auditory, visual and tactile) and delusions (paranoid delusions and delusions of reference).

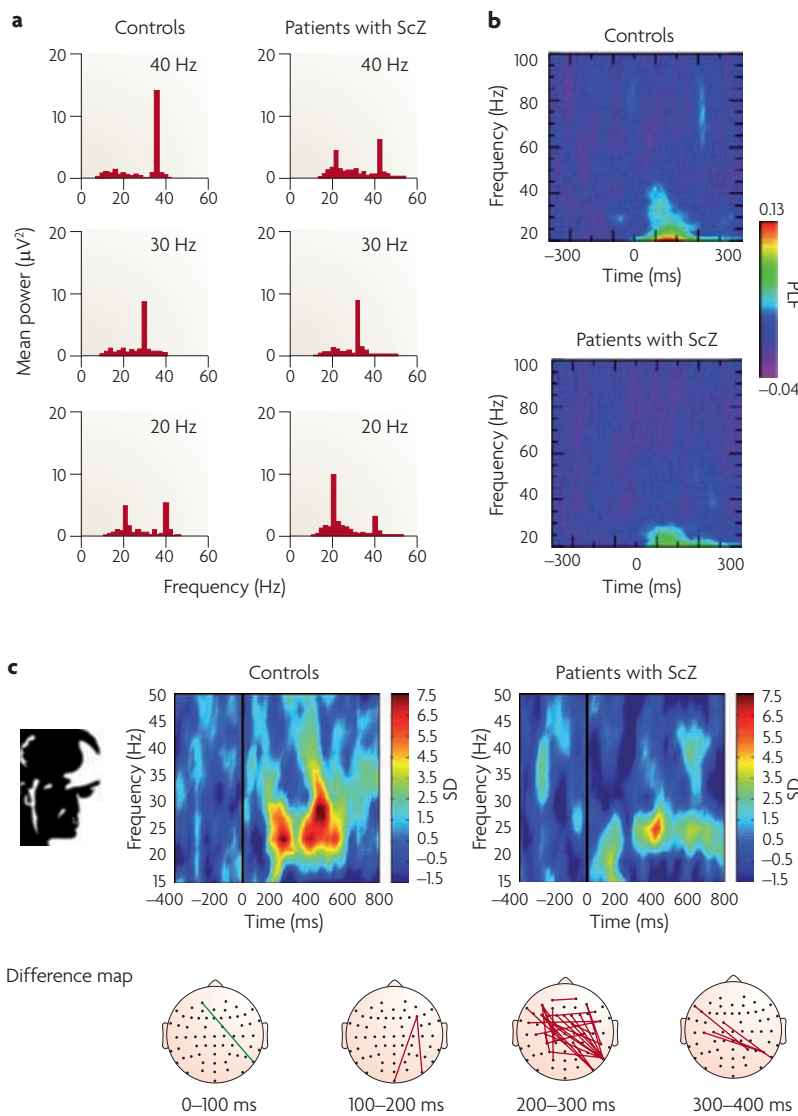
present at illness onset and are not due to the confounding influences of medication. Nevertheless, more research is necessary to address this important issue.

**Oscillations as an endophenotype.** Recent evidence indicates that dysfunctional neural oscillations represent an endophenotype of schizophrenia. Work in healthy twins has demonstrated that the power and temporal correlations of oscillations during the resting state are highly heritable<sup>55</sup>, indicating that neural oscillations can be exploited in the search for genetic contributions to schizophrenia. Indeed, a recent study<sup>56</sup> has provided important evidence for the relationship between impaired neural oscillations and genetic predisposition to schizophrenia. The authors examined the heritability of deficits in the time-frequency-transformed ERP during sensory gating in a large sample of patients with schizophrenia, their first-degree relatives and healthy control participants. Theta- and alpha-band oscillations were impaired in patients and first degree-relatives and this impairment was more heritable than the traditional P50 measure. The

same group also reported a deficit in the auditory SSEP in first-degree relatives of patients with schizophrenia<sup>30</sup>.

**Neural oscillations and the core symptoms of schizophrenia.**

There is also evidence that aberrant oscillatory activity could be related to the core symptoms of schizophrenia, such as hallucinations, thought disorder and negative symptoms. Several studies have found that positive symptoms of schizophrenia are correlated with enhanced amplitude and phase synchronization of evoked and induced beta- and gamma-band activity in circumscribed brain regions<sup>27,28,37,49,50,57,58</sup>, whereas disorganization and negative symptoms have been related to both enhanced<sup>37</sup> and reduced high-frequency oscillations<sup>43,57</sup>. This association is particularly robust for the presence of auditory and visual hallucinations. There is evidence of greater high-frequency activity during the resting state as well as during auditory and visual sensory processing in sensory areas in patients with hallucinations than in those without<sup>27,28,37,57,58</sup>. These findings suggest that the cortical areas involved in generating hallucinations might



**Figure 2 | Neural oscillations and synchrony in schizophrenia.** **a** | Auditory steady-state responses in patients with schizophrenia (ScZ). The left-hand panels show the spectral power over a midline frontal electrode site in controls ( $n = 15$ ) and patients with schizophrenia ( $n = 15$ ) during the presentation of click trains at 40 Hz, 30 Hz and 20 Hz. Patients with schizophrenia show lower power to stimulation at 40 Hz than control subjects, but no difference at lower frequencies of stimulation. **b** | Sensory evoked oscillations during a visual oddball task in patients with schizophrenia. The coloured scale indicates the phase locking factor (PLF; see figure part b Supplementary information S2 (figure)) — a measure of the degree of phase locking that can range from 0 (random distribution) to 1 (perfect phase locking) — of oscillations in the 20–100 Hz frequency range in the occipital cortex (electrode O1) for healthy controls and patients with schizophrenia. Control participants show an increase in phase locking for gamma oscillations ~ 100 ms after stimulus presentation. However, this is significantly smaller in patients with schizophrenia, indicating a dysfunction in early sensory processes. **c** | Dysfunctional phase synchrony during Gestalt perception in schizophrenia. Mooney faces were presented in an upright and inverted orientation and participants indicated whether a face was perceived. The top right panels show the average phase synchrony (indicated by the coloured scale) over time for all electrodes. In patients with schizophrenia, phase synchrony between 200–300 ms was significantly reduced relative to controls. In addition, patients with schizophrenia showed a desynchronization in the gamma band (30–55 Hz) in the 200–280 ms interval. The bottom panel shows differences in the topography of phase synchrony in the 20–30 Hz frequency range between groups. Red lines indicate less synchrony between two electrodes in patients with schizophrenia than in controls. Green lines indicate greater synchrony for patients with schizophrenia. SD, standard deviation. Part **a** is modified, with permission, from REF. 24 © (1999) American Medical Association. Part **b** is modified, with permission, from REF. 41 © (2004) Elsevier. Part **c** is modified, with permission, from REF. 49 © (2006) Society for Neuroscience.

be hyperexcitable, a hypothesis that is consistent with the increased haemodynamic responses that have been observed in the respective primary sensory areas<sup>59</sup>.

The local increase in neural oscillations seen in patients with positive symptoms is accompanied by a deficit in the precise synchronization of oscillations between cortical areas, which might lead to an impairment in corollary discharge. Several authors have argued that a failure of corollary discharge underlies the impaired ability of patients with schizophrenia to distinguish self-generated and externally generated percepts and actions<sup>12,60,61</sup>. One study<sup>62</sup> examined the coherence of theta oscillations between frontal and temporal lobes in patients with and without auditory hallucinations and in healthy controls as participants either listened to their own played back speech or were instructed to talk aloud. In the controls and patients with schizophrenia without hallucinations, talking was associated with an increase in theta coherence between left frontal and temporal electrodes relative to the listening condition. In patients with schizophrenia with hallucinations, this modulation was absent, suggesting a failure in the preparation of temporal areas for speech production that could lead to the misattribution of self-generated speech to an external source. The same group also reported reduced gamma-band oscillations before movement initiation in schizophrenia<sup>63</sup>, suggesting that reduced neural oscillations could also underlie dysfunctions in sensorimotor communication and associated impairments in the initiation of willed action<sup>12</sup>.

These data highlight the fact that, although the power and synchrony of neural oscillations are decreased in specific frequency bands in schizophrenia, positive symptoms may be associated with circumscribed increases in oscillatory activity that may reflect the read-out of stored experiences, consistent with the role of high-frequency activity in the generation of internal representations<sup>64</sup>. The increase in the power and synchrony of oscillations in local circuits may be accompanied by impaired corollary discharge mechanisms, as described above. However, more research is required to provide direct evidence for this hypothesis.

### Neurobiology of abnormal oscillations

The neuronal mechanisms responsible for generating oscillatory activity and its synchronization have been studied extensively both *in vivo* and *in vitro* (FIG. 3). This has enabled the identification of anatomical deficits and abnormalities in neurotransmitter systems in schizophrenia (FIG. 4) that may underlie the abnormalities seen in EEG and MEG studies (FIG. 2).

**Anatomical deficits.** Neural oscillations and their synchronization are dependent on the integrity of the synaptic contacts in local cortical circuits. Schizophrenia is associated with widespread reductions in the volume of grey matter<sup>65</sup> that are thought to reflect a reduction of synaptic connectivity, whereas the overall number of neurons is largely preserved<sup>66</sup>. This may explain the observed reductions in the power of neural oscillations, as previous studies have demonstrated relationships

between the degree of grey matter reduction and decreases in the amplitude of ERPs<sup>67–69</sup>.

Synchronization of oscillatory activity in the beta and gamma frequency range is dependent on cortico-cortical connections that reciprocally link cells situated in the same cortical area, in different areas or even in different hemispheres<sup>70,71</sup> (FIG. 3b). Accordingly, disruptions in the volume and organization of anatomical connectivity should impair long-range synchronization. Evidence from *in vivo* and post-mortem studies suggests that white matter volume and integrity are altered in patients with schizophrenia. These studies have found reduced volume of white matter in several brain regions as well as reduced organization of cortico-cortical connections as disclosed by diffusion tensor imaging (DTI)<sup>72–74</sup> (FIG. 4a).

**Neurotransmitter systems.** Several neurotransmitter systems that are abnormal in schizophrenia are also crucially involved in the generation and synchronization of cortical beta and gamma oscillations. Of particular importance is the network of GABA ( $\gamma$ -aminobutyric acid)-ergic interneurons that acts as a pacemaker in the generation of high-frequency oscillations by producing rhythmic inhibitory postsynaptic potentials (IPSPs) in pyramidal neurons. IPSPs generated by a single GABAergic neuron may be sufficient to synchronize the firing of a large population of pyramidal neurons<sup>75</sup>, and the duration of the IPSP can determine the dominant frequency of oscillations in a network<sup>76</sup> (FIG. 3a). Interneurons that express the Ca<sup>2+</sup>-binding protein parvalbumin are of particular relevance as these are fast-spiking cells and their activity has been demonstrated to be causally related to the generation of gamma oscillations in mice *in vivo*<sup>77</sup>.

A large body of work suggests that schizophrenia involves alterations in GABAergic neurotransmission<sup>78</sup> (FIG. 4b). One widely replicated finding is a reduction in the mRNA of *GAD67* (also known as glutamate decarboxylase 1), an enzyme that synthesizes GABA, in several cortical areas in patients with schizophrenia<sup>79,80</sup>. The decrease is specific to layers 3–5 (REFS 79,80) and is accompanied by reduced expression of the GABA membrane transporter 1 (*GAT1*; also known as *SLC6A1*)<sup>81</sup>, indicating that there is impaired synthesis and reuptake of GABA in interneurons in schizophrenia. Further studies revealed that these deficits are particularly pronounced in parvalbumin-positive interneurons: *GAD67* mRNA was not detectable in 50% of these cells in patients with schizophrenia, whereas the overall number of cells was unchanged<sup>82</sup>.

Several studies have provided direct links between abnormal GABAergic neurotransmission and altered neural oscillations. A recent study<sup>23</sup> showed that in a network simulation of the auditory cortex an increase in the decay time of IPSPs produced a pronounced oscillatory response at 20 Hz stimulation, whereas neural oscillations were reduced at 40 Hz. MEG data from patients with chronic schizophrenia revealed a similar profile of abnormal neural oscillations. The authors suggested that the reduced availability of *GAT1* is a candidate mechanism of the extended IPSPs that in turn results in the auditory SSEP deficits in schizophrenia.

#### Phase synchrony

Phase synchrony and coherence are estimates of the synchrony of brain oscillations. Phase synchrony provides an estimate of synchrony independent of the amplitude of oscillations. This contrasts with measures of coherence, in which synchrony and amplitude are intertwined.

#### Corollary discharge

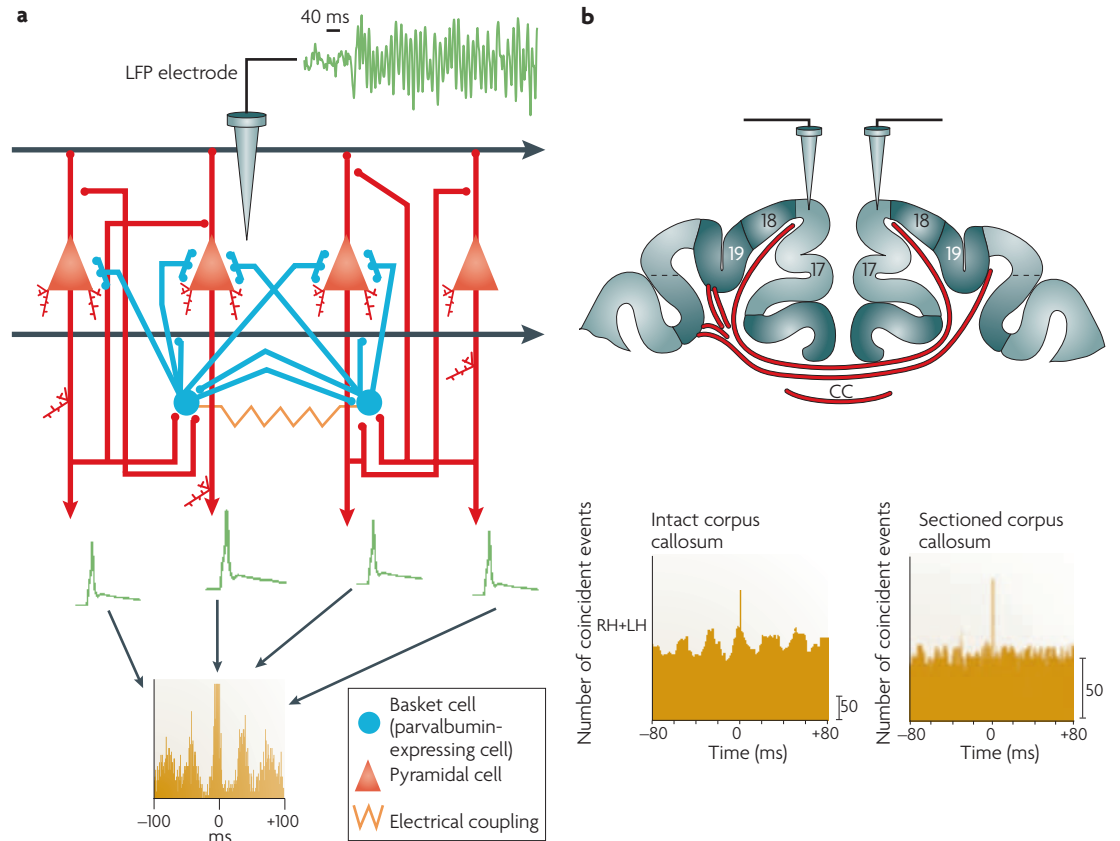
The estimate of sensory feedback that is derived from the internal copy of the motor signal (the efference copy).

#### Diffusion tensor imaging

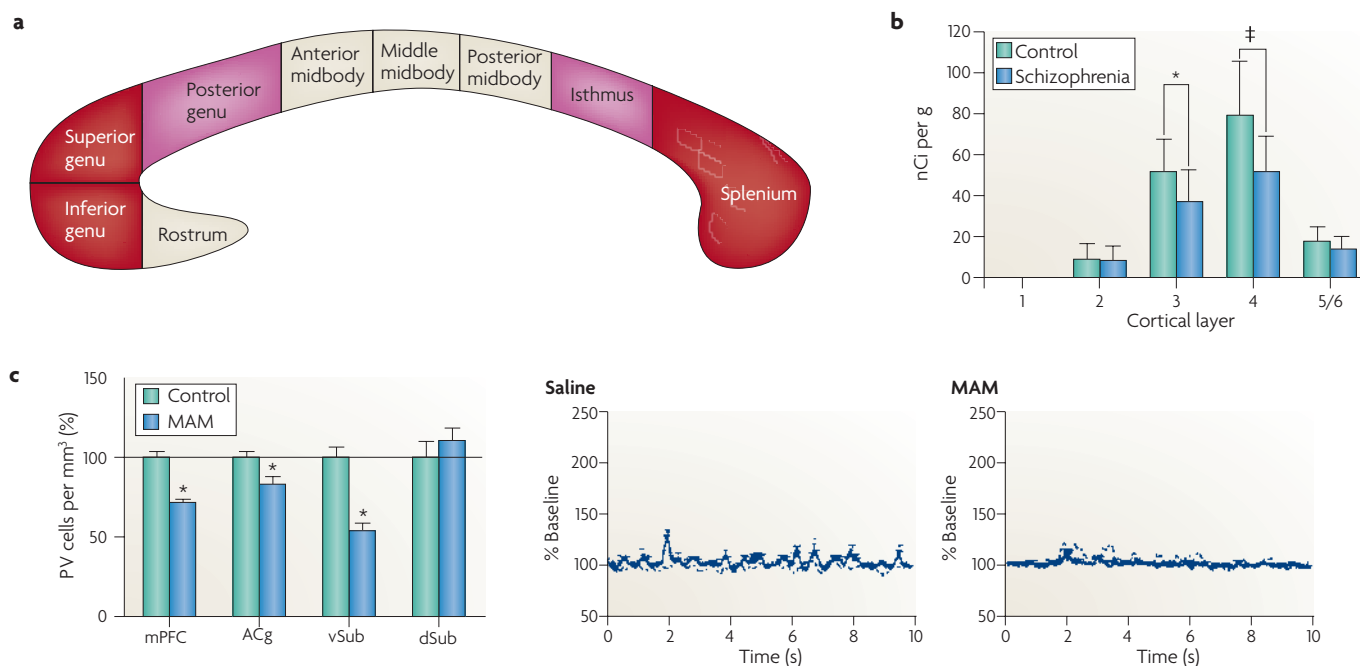
(DTI). An MRI technique used to map three-dimensional diffusion of water in brain tissue. It provides information about the microstructural integrity of the white matter, including axonal density and thickness, myelination and axonal fibre direction.

Data from two animal models of schizophrenia further support a link between abnormal parvalbumin expression and impairments in gamma-band oscillations. Treatment of rats with methylazoxymethanol acetate led to decreased expression of parvalbumin in interneurons in the medial prefrontal cortex and in the ventral subiculum of the hippocampus that was accompanied by a reduction in gamma-band

responses to a conditioned tone during a latent inhibition paradigm<sup>83</sup> (FIG. 4c). Similarly, lysophosphatidic acid receptor 1-deficient mice, which display a range of cognitive and neurochemical deficits similar to those seen in schizophrenia, are characterized by a reduction in gamma oscillations and in the numbers of parvalbumin-positive interneurons in the medial entorhinal cortex<sup>84</sup>.



**Figure 3 | Mechanisms underlying the generation of gamma oscillations and synchrony. a** | A neocortical circuit involved in the generation of gamma-band oscillations. Generation of synchronized neural activity in neocortical circuits is dependent on negative feedback inhibition of pyramidal cells by GABA (γ-aminobutyric acid)-ergic interneurons that express the Ca<sup>2+</sup>-binding protein parvalbumin. These receive glutamate receptor-mediated feedforward excitatory inputs, which makes them susceptible to changes in glutamatergic drive. Transient excitation of parvalbumin-expressing interneurons leads to a depolarization of many interneurons, which are themselves reciprocally interconnected through gap junctions and chemical GABAergic synapses. Electrical synapses are important for the synchronization of network activity because they rapidly propagate activity. Conversely, mutual inhibition through chemical synapses is a crucial determinant of the network frequency, as the duration of inhibitory postsynaptic potentials determines the dominant oscillation frequency. The resulting rhythmic inhibitory postsynaptic potentials can synchronize the firing of a large population of pyramidal neurons as the axon of an individual GABAergic neuron makes multiple postsynaptic contacts onto several pyramidal cells. This phasic inhibition leads to the synchronization of spiking activity that can be recovered with a cross-correlogram. A local field potential (LFP) recorded with an extracellular electrode reflects the average of the transmembrane currents that fluctuate at gamma-band frequency. Its extracranial counterpart can be reflected in electroencephalography (EEG) or magnetoencephalography (MEG) signals. **b** | Cortico-cortical connections mediate long-distance synchronization. The relationship between the integrity of the corpus callosum and interhemispheric synchronization of gamma-band oscillations in the cat visual cortex is illustrated. Recording electrodes were placed in the vicinity of the border of areas 17 and 18 of the right (RH) and left (LH) cortical hemispheres during stimulation with a light bar. In the bottom panels are cross-correlograms between responses from different recording sites in the LH and RH that indicate the degree of interhemispheric synchronization. When the corpus callosum was intact (left-hand panel), strong interhemispheric synchronization occurred with no phase lag between the LH and RH recording sites. Sectioning of the corpus callosum (right-hand panel) abolished interhemispheric synchronization while leaving synchronization within hemispheres intact. These data show that synchronization can occur over long distances with high precision and is crucially dependent on the integrity of cortico-cortical connections. The upper panel of part b is modified with permission, from REF. 163 © (1972) Elsevier. The lower panel of part b is modified, with permission, from REF. 70 © (1991) American Association for the Advancement of Science.



**Figure 4 | Neurobiological correlates of deficits in neural oscillations and synchrony in schizophrenia.**  
**a** | Connectivity of the corpus callosum and its abnormalities in schizophrenia as reflected in diffusion tensor imaging data. Changes in connectivity were measured by fractional anisotropy in the corpus callosum of 24 patients with schizophrenia and 24 healthy controls. Fractional anisotropy values estimate the presence and coherence of oriented structures, such as myelinated axons. Regions marked in dark red were significantly different between patients and controls at Bonferroni corrected  $p < 0.0055$ . Regions marked with light red were significantly different only at the uncorrected level of  $p < 0.05$ . Patients with schizophrenia show significantly less organization in subdivisions of the corpus callosum than controls. **b** | Expression of parvalbumin (PV) mRNA in layers 3–4 of the dorsolateral prefrontal cortex is reduced in patients with schizophrenia. Together with other data showing that the number of parvalbumin-positive interneurons is unchanged in schizophrenia<sup>138</sup>, these findings suggest that the ability of parvalbumin-positive interneurons to express important genes is impaired in schizophrenia. **c** | Reduction in gamma oscillations and parvalbumin-positive neurons in the medial prefrontal cortex (mPFC) in an animal model of schizophrenia. Rats are treated with methylazoxymethanol acetate (MAM) *in utero* at gestational day 17. This model reproduces the anatomical changes, behavioural deficits and altered neuronal information processing observed in patients<sup>139</sup>. Treated rats display a regionally specific reduction in the density of parvalbumin-positive neurons throughout the mPFC and ventral subiculum (vSUB). As shown in the middle and right-hand panels, the presentation of a tone induces a mild increase in prefrontal gamma (30–55 Hz) oscillations in saline- but not MAM-treated rats. \* indicates statistically significant difference from control ( $p=0.05$ ). † indicates significance level  $p=0.005$ . ACg, anterior cingulate cortex. dSub, dorsal subiculum. Part **a** is modified, with permission, from REF. 73 © (2008) Academic Press. Part **b** is modified, with permission, from REF. 82 © (2003) Society for Neuroscience. Part **c** is modified, with permission, from REF. 83 © (2009) Society for Neuroscience.

A crucial issue is whether the observed impairments in GABAergic interneurons are primary or secondary to alterations in other neurotransmitter systems. Parvalbumin-expressing interneurons receive excitatory inputs through NMDA (*N*-methyl-*D*-aspartate) receptors<sup>85</sup>, particularly the NR2A/NR2B subtype, which makes them susceptible to changes in glutamatergic drive. Several lines of evidence support the notion that NMDA receptor dysfunction may be related to altered GABA neurotransmission. Application of NMDA antagonists that produce psychosis in healthy participants<sup>86</sup> also causes changes in inhibitory synaptic transmission. Similarly, acute administration of ketamine to mice reduces the amplitude and frequency of IPSPs<sup>87</sup> and decreases the power of gamma-band oscillations in superficial layers of the medial entorhinal cortex<sup>84</sup>. Furthermore it seems that the acute effects of NMDA antagonists on parvalbumin-positive interneurons are mediated by oxidative stress<sup>88,89</sup>.

Recent evidence from animal models suggests that the effects of NMDA receptor blockade on neural oscillations may be region specific and in some instances can also lead to an increase in high-frequency oscillations<sup>90</sup>. For example, application of NMDA antagonists produced an increase in gamma-band oscillations in local circuits in the auditory cortex in humans<sup>91</sup> and in the neocortex of rats<sup>92</sup>. This paradoxical result could be due to the disinhibition of principal cells as a result of reduced interneuron excitation<sup>93</sup>, which would facilitate the transient and uncoordinated generation of gamma oscillations. NMDA receptors are candidates for the long-range synchronization of local circuits as they are prominent in the superficial cortical layers that are the main recipients of long cortico-cortical connections. Thus, disruption of NMDA receptors may lead to a decoupling of local gamma oscillators from the controlling influence of extended networks, resulting in a pathological

and short-term increase of gamma-band power. This scenario resembles the changes observed during the production of hallucinations in schizophrenia<sup>58,62</sup>.

In addition to the involvement of GABA- and NMDA-receptor mediated neurotransmission, data from animal models have suggested that alterations in the dopaminergic and cholinergic systems may contribute to abnormal oscillations<sup>94</sup>. However, this hypothesis has not been thoroughly explored. Recent evidence indicates that cholinergic modulation has a crucial role in the fast, state-dependent facilitation of high-frequency oscillations and the associated response synchronization in animal models<sup>95,96</sup>. Accordingly, alterations in cholinergic neurotransmission may be relevant for dysfunctions in neural oscillations in schizophrenia<sup>97</sup>. In particular, there is evidence that the  $\alpha 7$  nicotinic receptor that is expressed by GABAergic interneurons<sup>98</sup> is abnormal in patients with schizophrenia<sup>99,100</sup>.

Dopamine is a neuromodulator that has traditionally been implicated in the pathophysiology of schizophrenia. However, evidence for a direct impact of dopaminergic transmission on neural oscillations in schizophrenia is lacking. Interestingly, there is evidence suggesting that dopamine agonists decrease pathological beta-band oscillations and increase gamma-band oscillations in cortical and subcortical networks<sup>101</sup> in patients with Parkinson's disease, highlighting the impact of dopaminergic signalling on neural oscillations. Dopamine could affect neural oscillations in cortical networks by modulating frequency-dependent signal transmission, as has been recently demonstrated in the hippocampus<sup>102</sup>.

### Neurodevelopmental hypothesis and oscillations

**Neurodevelopment and schizophrenia.** Schizophrenia is characterized by abnormal brain maturation at several stages of development<sup>103</sup>. Children who are later diagnosed with schizophrenia have cognitive and behavioural impairments<sup>104</sup>, suggesting that an early pre- or perinatal event may contribute to the pathogenesis of the disorder. Several environmental risk factors, such as obstetric complication and viral infections, in addition to the genetic contribution may lead to altered development of neural circuits<sup>103</sup>. Schizophrenia, however, typically manifests during late adolescence and early adulthood, raising the question of the contribution of later developmental processes. For example, it has been proposed that the appearance of psychosis is related to overpruning of synaptic contacts during adolescence<sup>105</sup>.

**Oscillations and synchrony in the development of cortical networks.** Neural oscillations are involved in the maturation and plasticity of cortical networks at several developmental stages. During early pre- and perinatal periods, spontaneous correlated neural activity is a hallmark of the developing nervous system<sup>106-109</sup>. For example, patterned retinal activity synchronizes the activity of neurons in the neonatal visual cortex<sup>110-111</sup> and is essential for organizing connections in the visual circuitry<sup>112,113</sup>. Similarly, whisker-triggered oscillations act as a topographic template by synchronizing the activity

of neurons in columns in the neonatal barrel field of the cortex before the emergence of cortical barrels<sup>114</sup>.

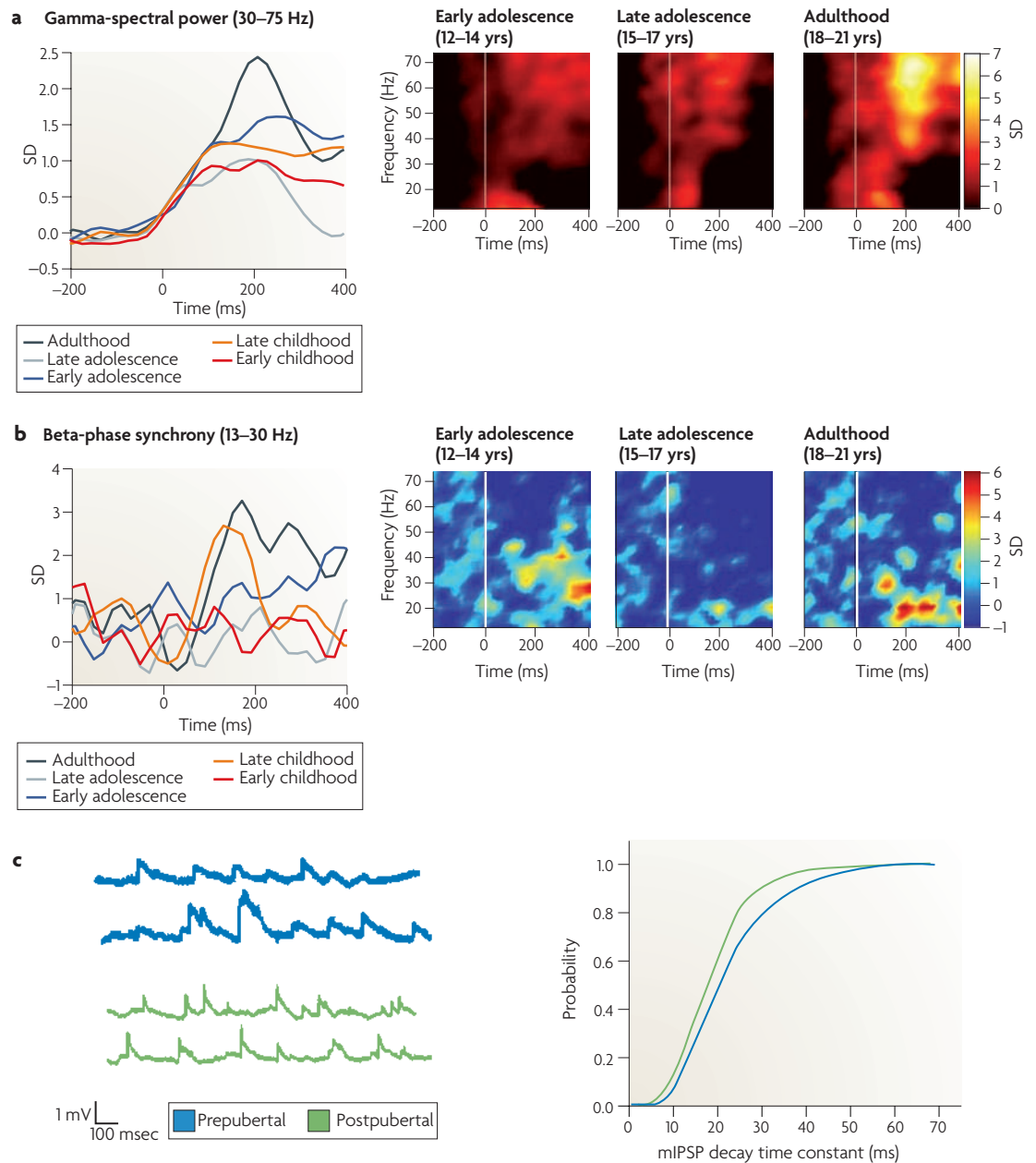
At later stages, experience-dependent modification of cortical circuits contributes to the shaping and development of cortical networks. Modification of synaptic contacts is dependent on the precise temporal coordination of neural activity<sup>115</sup>. For spike timing-dependent plasticity to occur, pre- and postsynaptic spiking is required within a critical window of tens of milliseconds<sup>116</sup>. Stimulation of neurons during the depolarizing peak of the theta cycle in the hippocampus favours long-term potentiation, whereas stimulation in the trough causes depression<sup>18</sup>. The same relationship holds for oscillations in the beta and gamma frequency range<sup>16</sup>, indicating that oscillations allow the precise alignment of the amplitude and temporal relations of presynaptic and postsynaptic activity that determine whether a synaptic contact is strengthened or weakened<sup>16</sup>. Accordingly, aberrant neural oscillations during early critical periods may lead to imprecise temporal coordination of neural activity and result in the pathological modification of cortical circuits.

### Neural oscillations and adolescent brain development.

Recent evidence<sup>117</sup> (FIG. 5a,b) points to profound changes in neural oscillations during late adolescence and early adulthood that could provide important clues to the emergence of psychosis. During early adulthood theta-, beta- and gamma-band oscillations and their long-range synchronization increase dramatically. Interestingly, this increase is preceded by a significant reduction of beta and gamma oscillations during late adolescence, suggesting that a transient destabilization occurs before the emergence of mature cortical networks. This highlights late adolescence as a critical developmental period that is associated with a rearrangement of functional networks and with an increase in the temporal precision and spatial focusing of neuronal interactions. We therefore suggest that in schizophrenia cortical circuits that are characterized by imprecise temporal dynamics are unable to support the neural coding regime that emerges during the late adolescent period, leading to a breakdown of coordinated neural activity and the emergence of psychosis and cognitive dysfunctions.

Several facts support the proposed expression of high-frequency oscillations during late adolescence. One is the continued maturation of cortico-cortical connections, involving increased myelination of long axonal tracts<sup>118,119</sup>. As a result, transmission delays between brain regions are reduced during adolescence<sup>120</sup>, supporting precise temporal coordination of distributed neural activity. Development of cortico-cortical connections<sup>73</sup> and maturation of grey matter have been found to be abnormal in patients with schizophrenia<sup>121,122</sup> and may lead to abnormalities in the occurrence of neural oscillations and synchrony at different spatial scales.

Recent evidence points to important changes in GABAergic neurotransmission during the adolescent period that could affect the development and synchronization of gamma-band oscillations (FIG. 5c). A predominance of GABA  $\alpha_2$  subunits was observed in the monkey dorsolateral prefrontal cortex during early



**Figure 5 | Emergence of high-frequency oscillations and synchrony during the transition from adolescence to adulthood.** **a** | The graph shows the spectral power of oscillations in the 30–75 Hz range 100–300 ms after the presentation of Mooney faces at different ages. The right-hand panels show time–frequency maps for early adolescent, late adolescent and adult participants. Gamma oscillations increase significantly during the transition from adolescence to adulthood. **b** | The graph shows phase synchrony in the 13–30 Hz frequency range for all electrode pairs 100–300 ms after stimulus presentation at different ages. The right-hand panels show phase synchrony (indicated by the coloured scale) of oscillations in the beta and gamma bands averaged across all electrodes for early adolescent, late adolescent and adult participants. The phase synchrony of beta-band oscillations increased until early adolescence and was then substantially reduced during late adolescence, suggesting that cortical networks reorganize during the transition from adolescence to adulthood. **c** | Changes in GABA<sub>A</sub> (γ-aminobutyric acid type A) receptor-mediated neurotransmission in the monkey dorsolateral prefrontal cortex during adolescence. The left-hand panel shows postnatal development of miniature inhibitory postsynaptic potentials (mIPSPs) recorded from pyramidal neurons of prepubertal and postpubertal monkeys in the dorsolateral prefrontal cortex. The right-hand panel shows cumulative probability distribution curves of the mIPSP decay time constant in prepubertal (blue) and postpubertal (green) animals. The left shift of the curve from prepubertal to postpubertal animals indicates a higher fraction of shorter mIPSPs in postpubertal animals than in prepubertal animals. As the decay time of IPSPs is a critical factor for the dominant frequency of oscillations in a network<sup>68</sup>, these data provide one mechanism for the late maturation of high-frequency oscillations in electroencephalography data<sup>117</sup>. SD, standard deviation. Parts **a** and **b** are modified, with permission, from REF. 117 © (2009) National Academy of Sciences. Part **c** is modified, with permission, from REF. 123 © (2009) Elsevier.

development, whereas in adult animals  $\alpha_1$  subunits are expressed<sup>123</sup>. 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  $\alpha$ -subunit expression could provide a direct correlate of the observed increase in gamma-band oscillations, as  $\alpha_1$  subunits predominate at synapses of parvalbumin-positive basket cells<sup>124</sup>, which are crucially involved in the generation of gamma-band oscillations<sup>77</sup>. Recent data<sup>125</sup> also suggest that there are significant changes in the signalling properties of basket cells during later developmental periods, as indicated by a decrease in action potential duration, propagation time, duration of the release period and the decay time constant of inhibitory postsynaptic currents.

### Conclusions

Current evidence points to a crucial role for altered neural oscillations and synchrony in the pathophysiology of schizophrenia. Reductions of beta and gamma oscillations and their synchronization have been demonstrated during cognitive tasks and at rest, suggesting that there is an intrinsic deficit in the temporal coordination of distributed neural activity. Correlations with the core symptoms of schizophrenia furthermore highlight the potential role of neural oscillations in the production of psychotic symptoms. Finally, these impairments are present at illness onset, are likely to be independent of medication status and are highly genetically heritable, raising the possibility that abnormal oscillations and synchrony in schizophrenia directly reflect the biological processes that underlie the syndrome.

We posit that the genetic vulnerability for schizophrenia is translated into imprecise temporal coordination of neural activity. Several risk genes for schizophrenia, including the neuregulin genes, *CHRNA7*, *dysbindin* (also known as *DTNBP1*) and *GAD1*, modulate GABAergic, cholinergic and NMDA receptor-mediated neural transmission<sup>94</sup>, and these transmitter systems are in turn crucially involved in the generation of neural oscillations. Recent evidence has furthermore provided direct links between polymorphisms of risk genes and changes in neural oscillations. Polymorphisms in *neuregulin 1* strongly modulate the amplitude of gamma oscillations in rat hippocampal slices<sup>126</sup>. Similarly, polymorphisms in the genes that encode dopamine receptor D4 (*DRD4*) and dopamine transporter (*SLC6A3*) modulate the pattern of evoked gamma responses in humans<sup>127</sup>.

Abnormal temporal dynamics of cortical circuits may result in impairments in synaptic plasticity (see REF. 21 for a similar perspective). Impaired plasticity is a candidate mechanism for the enduring cognitive deficits and aberrant neurodevelopment observed in schizophrenia, and there is evidence that neural oscillations and synchrony may have a crucial role in synaptic modifications. As behavioural impairments are already detectable in children who later develop the disorder, dysfunctional neural oscillations and plasticity are likely to cause aberrant early pre- and perinatal development, leading to maladaptive formation of cortical networks and faulty programming of synaptic connections. Accordingly,

we propose that this fundamental impairment remains silent until the late adolescent period when cortical networks fully exploit neural oscillations, in particular in the beta and gamma range, for the coordination of distributed brain processes.

Impaired neural oscillations in schizophrenia may lead to functional disconnections between and within cortical regions, as previously proposed by several theories<sup>1,2</sup>. Here, we note that most studies in schizophrenia have used functional MRI (fMRI) to study functional connectivity. fMRI, however, lacks the required temporal resolution, as dynamic neural interactions occur in the time range of milliseconds. EEG and MEG are appropriate tools with which to test functional connectivity anomalies, and several groups have demonstrated the feasibility of this approach. Recent advances in source localization<sup>128</sup> have also improved the spatial resolution of EEG and MEG measurements.

Research into neural oscillations is likely to contribute to the further delineation of the biological causes and mechanisms of schizophrenia and to the eventual development of pathophysiologically based treatment interventions. Neural oscillations and the molecular mechanisms and circuits that underlie them are highly conserved in insects, birds and mammals. This allows hypotheses regarding the biological mechanisms that underlie impaired neural oscillations to be directly tested in animal models and in *in vitro* preparations. Indeed, such work is already under way<sup>84</sup> and may help to link data from EEG and MEG experiments with patient populations to alterations in neurotransmitter systems. This possibility may not be offered by other imaging techniques, such as fMRI, for which the biological mechanisms of signal generation are less clear and the direct translation of findings from data obtained with human experiments to animal models is more difficult to accomplish. Neural oscillations could therefore be considered an ideal intermediate phenotype that potentially allows the direct mapping of genetic mechanisms of schizophrenia onto the neurobiology<sup>129</sup>.

Despite this enthusiasm, numerous unresolved issues need to be addressed. One is the diagnostic specificity of deficits in neural oscillations. A generalized impairment of neural oscillations across diverse brain disorders will strongly reduce their utility as a biomarker and intermediate phenotype. Thus, at present we cannot discard the possibility that altered neural oscillations and synchrony are nonspecific features of several brain disorders reflecting diverse pathophysiological processes. There is already evidence that several disorders are associated with abnormal neural oscillations<sup>130</sup>, the genetic and behavioural phenotypes of some of which overlap with those of schizophrenia. For example, patients with bipolar disorder display impairments in auditory SSEPs similar to those of patients with schizophrenia<sup>131</sup>. Furthermore, adults with autism spectrum disorders are also characterized by an impairment in gamma oscillations during perceptual organization<sup>132</sup>. However, comparison with first-episode schizophrenia patients revealed differences between the two disorders: gamma-band dysfunctions

in participants with autism spectrum disorders extended to low gamma-band oscillations (30–60 Hz), which were intact in patients with schizophrenia.

These data highlight the need to carefully characterize neural oscillations in specific disorders across different spatial and temporal scales. Further research into neural oscillations should also take into account the possibility that the impairments in high-frequency oscillations are related to alterations in low-frequency activity, in particular in the theta-frequency range, which have been less explored so far. Neural oscillations across different frequencies form a hierarchical system in which different frequencies interact by coupling the amplitude and phase of ongoing oscillations<sup>133</sup>. For example, the amplitude of gamma-band oscillations is tightly linked to the phase of theta oscillations<sup>134</sup>, and this has been proposed to provide a general coding scheme in cortical networks.

Although greater understanding of these aspects of neural oscillations is needed to establish a complete

picture of the nature of brain functions and their impairment in schizophrenia, we firmly believe that neural oscillations are a crucial factor in the pathophysiology of schizophrenia and that further investigation will eventually lead to an understanding of the syndrome as a disorder of temporal coordination and to evidenced-based pharmacological interventions that correct these alterations. This reconceptualization of schizophrenia is part of a wider paradigm shift in the neurosciences in which the brain is increasingly viewed as a self-organizing system with complex and nonlinear dynamics in which cognitive processes arise out of the dynamic interaction between multiple brain regions<sup>135</sup>. Thus, understanding the mechanisms that give rise to this enigmatic disorder and that have now been elusive for over a century may also provide important insights into the biological mechanisms that underlie the mental processes that are fundamentally altered in schizophrenia.

- Phillips, W. A. & Silverstein, S. M. Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behav. Brain Sci.* **26**, 65–82 (2003).
- Friston, K. J. Schizophrenia and the disconnection hypothesis. *Acta Psychiatr. Scand. Suppl.* **395**, 68–79 (1999).
- Buzsáki, G. & Draguhn, A. Neuronal oscillations in cortical networks. *Science* **304**, 1926–1929 (2004).
- Fries, P. Neuronal gamma-band synchronization as a fundamental process in cortical computation. *Annu. Rev. Neurosci.* **32**, 209–224 (2009).
- Buzsáki, G. *Rhythms of the Brain* (Oxford Univ. Press, New York, 2006).
- A brilliant and comprehensive overview of the role of neural oscillations in cortical processing.**
- Singer, W. Neuronal synchrony: a versatile code for the definition of relations? *Neuron* **24**, 49–65, 111–125 (1999).
- Gray, C. M., König, P., Engel, A. K. & Singer, W. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature* **338**, 334–337 (1989).
- The first study to show a close correspondence between synchronized gamma-band oscillations and Gestalt properties of visual stimuli in the primary visual cortex of anaesthetized cats.**
- Womelsdorf, T. *et al.* Modulation of neuronal interactions through neuronal synchronization. *Science* **316**, 1609–1612 (2007).
- von Stein, A., Chiang, C. & König, P. Top-down processing mediated by interareal synchronization. *Proc. Natl Acad. Sci. USA* **97**, 14748–14753 (2000).
- Uhlhaas, P. J. *et al.* Neural synchrony in cortical networks: history, concept and current status. *Front. Integr. Neurosci.* **3**, 17 (2009).
- Park, S. & Holzman, P. S. Schizophrenics show spatial working memory deficits. *Arch. Gen. Psychiatry* **49**, 975–982 (1992).
- Frith, C. D. *Neuropsychology of Schizophrenia* (Taylor and Francis, Hove, 1992).
- Uhlhaas, P. J. & Silverstein, S. M. Perceptual organization in schizophrenia spectrum disorders: empirical research and theoretical implications. *Psychol. Bull.* **131**, 618–632 (2005).
- Green, M. F. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am. J. Psychiatry* **153**, 321–330 (1996).
- Singer, W. & Gray, C. M. Visual feature integration and the temporal correlation hypothesis. *Annu. Rev. Neurosci.* **18**, 555–586 (1995).
- Wespatat, V., Tennigkeit, F. & Singer, W. Phase sensitivity of synaptic modifications in oscillating cells of rat visual cortex. *J. Neurosci.* **24**, 9067–9075 (2004).
- Pavlidis, C., Greenstein, Y. J., Grudman, M. & Winson, J. Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm. *Brain Res.* **439**, 383–387 (1988).
- Huerta, P. T. & Lisman, J. E. Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. *Nature* **364**, 723–725 (1993).
- Daskalakis, Z. J., Christensen, B. K., Fitzgerald, P. B. & Chen, R. Dysfunctional neural plasticity in patients with schizophrenia. *Arch. Gen. Psychiatry* **65**, 378–385 (2008).
- Shelley, A. M. *et al.* Mismatch negativity: an index of preattentive processing deficit in schizophrenia. *Biol. Psychiatry* **30**, 1059–1062 (1991).
- Stephan, K. E., Friston, K. J. & Frith, C. D. Dysfunction in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. *Schizophr. Bull.* **35**, 509–527 (2009).
- Light, G. A. *et al.* Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. *Biol. Psychiatry* **60**, 1231–1240 (2006).
- Vierling-Claassen, D., Siekmeier, P., Stufflebeam, S. & Kopell, N. Modeling GABA alterations in schizophrenia: a link between impaired inhibition and altered gamma and beta range auditory entrainment. *J. Neurophysiol.* **99**, 2656–2671 (2008).
- Kwon, J. S. *et al.* Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. *Arch. Gen. Psychiatry* **56**, 1001–1005 (1999).
- The first demonstration of a deficit in the entrainment of gamma-band oscillations to click trains presented at 40 Hz in the auditory cortex in patients with schizophrenia.**
- Krishnan, G. P. *et al.* Steady state and induced auditory gamma deficits in schizophrenia. *Neuroimage* **47**, 1711–1719 (2009).
- Brenner, C. A., Sporns, O., Lysaker, P. H. & O'Donnell, B. F. EEG synchronization to modulated auditory tones in schizophrenia, schizoaffective disorder, and schizotypal personality disorder. *Am. J. Psychiatry* **160**, 2238–2240 (2003).
- Spencer, K. M., Salisbury, D. F., Shenton, M. E. & McCarley, R. W. Gamma-band auditory steady-state responses are impaired in first episode psychosis. *Biol. Psychiatry* **64**, 369–375 (2008).
- Spencer, K. M., Niznikiewicz, M. A., Nestor, P. G., Shenton, M. E. & McCarley, R. W. Left auditory cortex gamma synchronization and auditory hallucination symptoms in schizophrenia. *BMC Neurosci.* **10**, 85 (2009).
- Wilson, T. W. *et al.* Cortical gamma generators suggest abnormal auditory circuitry in early-onset psychosis. *Cereb. Cortex* **18**, 371–378 (2008).
- Hong, L. E. *et al.* Evoked gamma band synchronization and the liability for schizophrenia. *Schizophr. Res.* **70**, 293–302 (2004).
- Krishnan, G. P. *et al.* Steady state visual evoked potential abnormalities in schizophrenia. *Clin. Neurophysiol.* **116**, 614–624 (2005).
- Galambos, R., Makeig, S. & Talmachoff, P. J. A 40-Hz auditory potential recorded from the human scalp. *Proc. Natl Acad. Sci. USA* **78**, 2643–2647 (1981).
- Ross, B., Herdman, A. T. & Pantev, C. Stimulus induced desynchronization of human auditory 40-Hz steady-state responses. *J. Neurophysiol.* **94**, 4082–4093 (2005).
- Ross, B., Picton, T. W. & Pantev, C. Temporal integration in the human auditory cortex as represented by the development of the steady-state magnetic field. *Hear. Res.* **165**, 68–84 (2002).
- Skosnik, P. D., Krishnan, G. P. & O'Donnell, B. F. The effect of selective attention on the gamma-band auditory steady-state response. *Neurosci. Lett.* **420**, 223–228 (2007).
- Johannesen, J. K., Bodkins, M., O'Donnell, B. F., Shekhar, A. & Hetrick, W. P. Perceptual anomalies in schizophrenia co-occur with selective impairments in the gamma frequency component of midlatency auditory ERPs. *J. Abnorm. Psychol.* **117**, 106–118 (2008).
- Spencer, K. M. *et al.* Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc. Natl Acad. Sci. USA* **101**, 17288–17293 (2004).
- Hirano, S. *et al.* Abnormal neural oscillatory activity to speech sounds in schizophrenia: a magnetoencephalography study. *J. Neurosci.* **28**, 4897–4903 (2008).
- Roach, B. J. & Mathalon, D. H. Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. *Schizophr. Bull.* **34**, 907–926 (2008).
- Spencer, K. M., Niznikiewicz, M. A., Shenton, M. E. & McCarley, R. W. Sensory-evoked gamma oscillations in chronic schizophrenia. *Biol. Psychiatry* **63**, 744–747 (2008).
- Gallinat, J., Winterer, G., Herrmann, C. S. & Senkowski, D. Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. *Clin. Neurophysiol.* **115**, 1863–1874 (2004).
- Ferrarelli, F. *et al.* Reduced evoked gamma oscillations in the frontal cortex in schizophrenia patients: a TMS/EEG study. *Am. J. Psychiatry* **165**, 996–1005 (2008).
- Tillmann, C. *et al.* Source localization of high-frequency oscillations reveals widespread reductions in gamma-band activity during perceptual organisation in chronic and first-episode schizophrenia. *Soc. Neurosci. Abstr.* **54.2** (2008).
- Haenschel, C. *et al.* Cortical oscillatory activity is critical for working memory as revealed by deficits in early onset schizophrenia. *J. Neurosci.* **29**, 9481–9489 (2009).
- Schmiedt, C., Brand, A., Hildebrandt, H. & Basar-Eroglu, C. Event-related theta oscillations during working memory tasks in patients with schizophrenia and healthy controls. *Brain Res. Cogn. Brain Res.* **25**, 936–947 (2005).

46. Cho, R. Y., Konecky, R. O. & Carter, C. S. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. *Proc. Natl Acad. Sci. USA* **103**, 19878–19885 (2006).
47. Winterer, G. *et al.* Schizophrenia: reduced signal-to-noise ratio and impaired phase-locking during information processing. *Clin. Neurophysiol.* **111**, 837–849 (2000).
48. Varela, F., Lachaux, J. P., Rodriguez, E. & Martinerie, J. The brainweb: phase synchronization and large-scale integration. *Nature Rev. Neurosci.* **2**, 229–239 (2001).
49. Uhlhaas, P. J. *et al.* Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J. Neurosci.* **26**, 8168–8175 (2006).
50. Spencer, K. M. *et al.* Abnormal neural synchrony in schizophrenia. *J. Neurosci.* **23**, 7407–7411 (2003).
51. Symond, M. P., Harris, A. W., Gordon, E. & Williams, L. M. "Gamma synchrony" in first-episode schizophrenia: a disorder of temporal connectivity? *Am. J. Psychiatry* **162**, 459–465 (2005).
52. Boutros, N. N. *et al.* The status of spectral EEG abnormality as a diagnostic test for schizophrenia. *Schizophr. Res.* **99**, 225–237 (2008).
53. Rutter, L. *et al.* Magnetoencephalographic gamma power reduction in patients with schizophrenia during resting condition. *Hum. Brain Mapp.* **30**, 3254–3264 (2009).
54. Koenig, T. *et al.* Decreased functional connectivity of EEG theta-frequency activity in first-episode, neuroleptic-naïve patients with schizophrenia: preliminary results. *Schizophr. Res.* **50**, 55–60 (2001).
55. Linkenkaer-Hansen, K. *et al.* Genetic contributions to long-range temporal correlations in ongoing oscillations. *J. Neurosci.* **27**, 13882–13889 (2007).
56. Hong, L. E. *et al.* Sensory gating endophenotype based on its neural oscillatory pattern and heritability estimate. *Arch. Gen. Psychiatry* **65**, 1008–1016 (2008).
- An important study that examined auditory sensory gating in patients with schizophrenia and their first-degree relatives, highlighting the utility of neural oscillations as an endophenotype in schizophrenia research.**
57. Lee, K. H., Williams, L. M., Haig, A. & Gordon, E. "Gamma (40 Hz) phase synchronicity" and symptom dimensions in schizophrenia. *Cogn. Neuropsychiatry* **8**, 57–71 (2003).
58. Lee, S. H. *et al.* Quantitative EEG and low resolution electromagnetic tomography (LORETA) imaging of patients with persistent auditory hallucinations. *Schizophr. Res.* **83**, 111–119 (2006).
59. Dierks, T. *et al.* Activation of Heschl's gyrus during auditory hallucinations. *Neuron* **22**, 615–621 (1999).
60. Ford, J. M. & Mathalon, D. H. Corollary discharge dysfunction in schizophrenia: can it explain auditory hallucinations? *Int. J. Psychophysiol.* **58**, 179–189 (2005).
61. Feinberg, I. Efference copy and corollary discharge: implications for thinking and its disorders. *Schizophr. Bull.* **4**, 636–640 (1978).
62. Ford, J. M., Mathalon, D. H., Whitfield, S., Faustman, W. O. & Roth, W. T. Reduced communication between frontal and temporal lobes during talking in schizophrenia. *Biol. Psychiatry* **51**, 485–492 (2002).
63. Ford, J. M., Roach, B. J., Faustman, W. O. & Mathalon, D. H. Out-of-synch and out-of-sorts: dysfunction of motor-sensory communication in schizophrenia. *Biol. Psychiatry* **63**, 736–743 (2007).
64. Gross, J., Schnitzler, A., Timmermann, L. & Ploner, M. Gamma oscillations in human primary somatosensory cortex reflect pain perception. *PLoS Biol.* **5**, e133 (2007).
65. Shenton, M. E., Dickey, C. C., Frumin, M. & McCarley, R. W. A review of MRI findings in schizophrenia. *Schizophr. Res.* **49**, 1–52 (2001).
66. Selemon, L. D. & Goldman-Rakic, P. S. The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol. Psychiatry* **45**, 17–25 (1999).
67. Onitsuka, T. *et al.* Functional and structural deficits in brain regions subserving face perception in schizophrenia. *Am. J. Psychiatry* **163**, 455–462 (2006).
68. McCarley, R. W. *et al.* Association between smaller left posterior superior temporal gyrus volume on magnetic resonance imaging and smaller left temporal P300 amplitude in first-episode schizophrenia. *Arch. Gen. Psychiatry* **59**, 321–331 (2002).
69. Salsbury, D. F., Kuroki, N., Kasai, K., Shenton, M. E. & McCarley, R. W. Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Arch. Gen. Psychiatry* **64**, 521–529 (2007).
70. Engel, A. K., König, P., Kreiter, A. K. & Singer, W. Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science* **252**, 1177–1179 (1991).
71. Löwel, S. & Singer, W. Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. *Science* **255**, 209–212 (1992).
72. Kubicki, M. *et al.* A review of diffusion tensor imaging studies in schizophrenia. *J. Psychiatr. Res.* **41**, 15–30 (2007).
73. Rotarska-Jagiela, A. *et al.* The corpus callosum in schizophrenia-volume and connectivity changes affect specific regions. *Neuroimage* **39**, 1522–1532 (2008).
74. Lim, K. O. *et al.* Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Arch. Gen. Psychiatry* **56**, 367–374 (1999).
75. Cobb, S. R., Buhl, E. H., Halasy, K., Paulsen, O. & Somogyi, P. Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature* **378**, 75–78 (1995).
76. Wang, X. J. & Buzsáki, G. Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J. Neurosci.* **16**, 6402–6413 (1996).
77. Sohal, V. S., Zhang, F., Yizhar, O. & Deisseroth, K. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature* **459**, 698–702 (2009).
- An elegant demonstration of the functional significance of parvalbumin-containing interneurons in the generation of gamma-band oscillations that used a novel combination of optogenetic technologies in mice to selectively modulate multiple distinct circuit elements in the neocortex.**
78. Lewis, D. A., Hashimoto, T. & Volk, D. W. Cortical inhibitory neurons and schizophrenia. *Nature Rev. Neurosci.* **6**, 312–324 (2005).
- An excellent review that highlights the role of inhibitory neurons in the pathophysiology of schizophrenia.**
79. Akbarian, S. *et al.* Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. *Arch. Gen. Psychiatry* **52**, 258–266 (1995).
80. Volk, D. W., Austin, M. C., Pierri, J. N., Sampson, A. R. & Lewis, D. A. Decreased glutamic acid decarboxylase67 messenger RNA expression in a subset of prefrontal cortical gamma-aminobutyric acid neurons in subjects with schizophrenia. *Arch. Gen. Psychiatry* **57**, 237–245 (2000).
81. Volk, D. W., Austin, M. C., Pierri, J. N., Sampson, A. R. & Lewis, D. A. GABA transporter-1 mRNA in the prefrontal cortex in schizophrenia: decreased expression in a subset of neurons. *Am. J. Psychiatry* **158**, 256–265 (2001).
82. Hashimoto, T. *et al.* Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. *J. Neurosci.* **23**, 6315–6326 (2003).
83. Lodge, D. J., Behrens, M. M. & Grace, A. A. Loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. *J. Neurosci.* **29**, 2344–2354 (2009).
84. Cunningham, M. O. *et al.* Region-specific reduction in entorhinal gamma oscillations and parvalbumin-immunoreactive neurons in animal models of psychiatric illness. *J. Neurosci.* **26**, 2767–2776 (2006).
85. Kinney, J. W. *et al.* A specific role for NR2A-containing NMDA receptors in the maintenance of parvalbumin and GAD67 immunoreactivity in cultured interneurons. *J. Neurosci.* **26**, 1604–1615 (2006).
86. Krystal, J. H. *et al.* Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch. Gen. Psychiatry* **51**, 199–214 (1994).
87. Zhang, Y., Behrens, M. M. & Lisman, J. E. Prolonged exposure to NMDAR antagonist suppresses inhibitory synaptic transmission in prefrontal cortex. *J. Neurophysiol.* **2**, 959–965 (2008).
88. Behrens, M. M. *et al.* Ketamine-induced loss of phenotype of fast-spiking interneurons is mediated by NADPH-oxidase. *Science* **318**, 1645–1647 (2007).
89. Do, K. Q., Cabungcal, J. H., Frank, A., Steullet, P. & Cuenod, M. Redox dysregulation, neurodevelopment, and schizophrenia. *Curr. Opin. Neurobiol.* **19**, 220–230 (2009).
90. Roopun, A. K. *et al.* Region-specific changes in gamma and beta2 rhythms in NMDA receptor dysfunction models of schizophrenia. *Schizophr. Bull.* **34**, 962–973 (2008).
91. Plourde, G., Baribeau, J. & Bonhomme, V. Ketamine increases the amplitude of the 40-Hz auditory steady-state response in humans. *Br. J. Anaesth.* **78**, 524–529 (1997).
92. Pinault, D. N-methyl D-aspartate receptor antagonists ketamine and MK-801 induce wake-related aberrant gamma oscillations in the rat neocortex. *Biol. Psychiatry* **63**, 730–735 (2008).
93. Homayoun, H. & Moghaddam, B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J. Neurosci.* **27**, 11496–11500 (2007).
94. Lisman, J. E. *et al.* Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci.* **31**, 234–242 (2008).
95. Rodriguez, R., Kallenbach, U., Singer, W. & Munk, M. H. Short- and long-term effects of cholinergic modulation on gamma oscillations and response synchronization in the visual cortex. *J. Neurosci.* **24**, 10369–10378 (2004).
96. Steriade, M., Dossi, R. C., Pare, D. & Oakson, G. Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proc. Natl Acad. Sci. USA* **88**, 4396–4400 (1991).
97. Sarter, M., Nelson, C. L. & Bruno, J. P. Cortical cholinergic transmission and cortical information processing in schizophrenia. *Schizophr. Bull.* **31**, 117–138 (2005).
98. Krenz, I. *et al.* Parvalbumin-containing interneurons of the human cerebral cortex express nicotinic acetylcholine receptor proteins. *J. Chem. Neuroanat.* **21**, 239–246 (2001).
99. Martin, L. F. & Freedman, R. Schizophrenia and the  $\alpha 7$  nicotinic acetylcholine receptor. *Int. Rev. Neurobiol.* **78**, 225–246 (2007).
100. Guan, Z. Z., Zhang, X., Blennow, K. & Nordberg, A. Decreased protein level of nicotinic receptor  $\alpha 7$  subunit in the frontal cortex from schizophrenic brain. *Neuroreport* **10**, 1779–1782 (1999).
101. Brown, P. *et al.* Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J. Neurosci.* **21**, 1035–1038 (2001).
102. Ito, H. T. & Schuman, E. M. Frequency-dependent gating of synaptic transmission and plasticity by dopamine. *Front. Neural Circuits* **1**, 1 (2007).
103. Lewis, D. A. & Levitt, P. Schizophrenia as a disorder of neurodevelopment. *Annu. Rev. Neurosci.* **25**, 409–432 (2002).
104. Walker, E. F., Savoie, T. & Davis, D. Neuromotor precursors of schizophrenia. *Schizophr. Bull.* **20**, 441–451 (1994).
105. Feinberg, I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J. Psychiatr. Res.* **17**, 319–334 (1982).
106. Khazipov, R. & Luhmann, H. J. Early patterns of electrical activity in the developing cerebral cortex of humans and rodents. *Trends Neurosci.* **29**, 414–418 (2006).
107. Ben-Ari, Y. Developing networks play a similar melody. *Trends Neurosci.* **24**, 353–360 (2001).
108. Katz, L. C. & Shatz, C. J. Synaptic activity and the construction of cortical circuits. *Science* **274**, 1133–1138 (1996).
109. Khazipov, R. *et al.* Early motor activity drives spindle bursts in the developing somatosensory cortex. *Nature* **432**, 758–761 (2004).
110. Hanganu, I. L., Ben-Ari, Y. & Khazipov, R. Retinal waves trigger spindle bursts in the neonatal rat visual cortex. *J. Neurosci.* **26**, 6728–6736 (2006).
111. Chiu, C. & Weliky, M. Spontaneous activity in developing ferret visual cortex *in vivo*. *J. Neurosci.* **21**, 8906–8914 (2001).
112. Stellwagen, D. & Shatz, C. J. An instructive role for retinal waves in the development of retinogeniculate connectivity. *Neuron* **33**, 357–367 (2002).
113. Cang, J. *et al.* Development of precise maps in visual cortex requires patterned spontaneous activity in the retina. *Neuron* **48**, 797–809 (2005).
114. Yang, J. W., Hanganu-Opatz, I. L., Sun, J. J. & Luhmann, H. J. Three patterns of oscillatory activity differentially synchronize developing neocortical networks *in vivo*. *J. Neurosci.* **29**, 9011–9025 (2009).

115. Hebb, D. O. *The Organization of Behavior: A Neuropsychological Theory* (Wiley, New York, 1949).
116. Markram, H., Lubke, J., Frotscher, M. & Sakmann, B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* **275**, 213–215 (1997).  
**An important paper showing that modifications in synaptic connections between neurons in the neocortex are dependent on the precise temporal relation between postsynaptic action potentials and unitary excitatory postsynaptic potentials.**
117. Uhlhaas, P. J. *et al.* The development of neural synchrony reflects late maturation and restructuring functional networks in humans. *Proc. Natl Acad. Sci. USA* **106**, 9866–9871 (2009).  
**The first study to comprehensively examine the development of task-related neural synchrony in humans, highlighting the role of late brain maturation for the shaping and reorganization of functional networks.**
118. Yakovlev, P. I. & Lecours, A. R. in *In Regional Development of the Brain in Early Life* (ed. Minkowski, A.) 3–70 (Blackwell Scientific, Oxford, 1967).
119. Perrin, J. S. *et al.* Sex differences in the growth of white matter during adolescence. *Neuroimage* **45**, 1055–1066 (2009).
120. Salami, M., Itami, C., Tsumoto, T. & Kimura, F. Change of conduction velocity by regional myelination yields constant latency irrespective of distance between thalamus and cortex. *Proc. Natl Acad. Sci. USA* **100**, 6174–6179 (2003).
121. Takahashi, T. *et al.* Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. *Arch. Gen. Psychiatry* **66**, 366–376 (2009).
122. Vidal, C. N. *et al.* Dynamically spreading frontal and cingulate deficits mapped in adolescents with schizophrenia. *Arch. Gen. Psychiatry* **63**, 25–34 (2006).
123. Hashimoto, T. *et al.* Protracted developmental trajectories of GABA<sub>A</sub> receptor  $\alpha 1$  and  $\alpha 2$  subunit expression in primate prefrontal cortex. *Biol. Psychiatry* **65**, 1015–1023 (2009).
124. Klausberger, T., Roberts, J. D. & Somogyi, P. Cell type- and input-specific differences in the number and subtypes of synaptic GABA<sub>A</sub> receptors in the hippocampus. *J. Neurosci.* **22**, 2513–2521 (2002).
125. Doischer, D. *et al.* Postnatal differentiation of basket cells from slow to fast signaling devices. *J. Neurosci.* **28**, 12956–12968 (2008).
126. Fisahn, A., Neddens, J., Yan, L. & Buonanno, A. Neuregulin-1 modulates hippocampal gamma oscillations: implications for schizophrenia. *Cereb. Cortex* **19**, 612–618 (2009).
127. Demiralp, T. *et al.* DRD4 and DAT1 polymorphisms modulate human gamma band responses. *Cereb. Cortex* **17**, 1007–1019 (2007).
128. Schoffelen, J. M. & Gross, J. Source connectivity analysis with MEG and EEG. *Hum. Brain. Mapp.* **30**, 1857–1865 (2009).
129. Meyer-Lindenberg, A. & Weinberger, D. R. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nature Rev. Neurosci.* **7**, 818–827 (2006).
130. Uhlhaas, P. J. & Singer, W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron* **52**, 155–168 (2006).
131. O'Donnell, B. F. *et al.* Neural synchronization deficits to auditory stimulation in bipolar disorder. *Neuroreport* **15**, 1369–1372 (2004).
132. Uhlhaas, P. J. *et al.* Gamma-band oscillations during perceptual integration in autism spectrum disorders. *Soc. Neurosci. Abstr.* 411.8 (2008).
133. Lakatos, P. *et al.* An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. *J. Neurophysiol.* **94**, 1904–1911 (2005).
134. Sirota, A. *et al.* Entrainment of neocortical neurons and gamma oscillations by the hippocampal theta rhythm. *Neuron* **60**, 683–697 (2008).
135. Tognoli, E. & Kelso, J. A. Brain coordination dynamics: true and false faces of phase synchrony and metastability. *Prog. Neurobiol.* **87**, 31–40 (2009).
136. van Vugt, M. K., Sederberg, P. B. & Kahana, M. J. Comparison of spectral analysis methods for characterizing brain oscillations. *J. Neurosci. Methods* **162**, 49–63 (2007).
137. Fries, P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn. Sci.* **9**, 474–480 (2005).
138. Woo, T. U., Miller, J. L. & Lewis, D. A. Schizophrenia and the parvalbumin-containing class of cortical local circuit neurons. *Am. J. Psychiatry* **154**, 1013–1015 (1997).
139. Lodge, D. J. & Grace, A. A. Gestational methylazoxymethanol acetate administration: a developmental disruption model of schizophrenia. *Behav. Brain Res.* **204**, 306–312 (2009).
140. Raghavachari, S. *et al.* Theta oscillations in human cortex during a working-memory task: evidence for local generators. *J. Neurophysiol.* **95**, 1630–1638 (2006).
141. Tsujimoto, T., Shimazu, H. & Isomura, Y. Direct recording of theta oscillations in primate prefrontal and anterior cingulate cortices. *J. Neurophysiol.* **95**, 2987–3000 (2006).
142. Vertes, R. P. Hippocampal theta rhythm: a tag for short-term memory. *Hippocampus* **15**, 923–935 (2005).
143. Gevins, A., Smith, M. E., McEvoy, L. & Yu, D. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. *Cereb. Cortex* **7**, 374–385 (1997).
144. Andersen, P. & Andersson, S. A. *Physiological Basis of the Alpha Rhythm* (Appelton Century Crofts, New York, 1968).
145. Schürmann, M., Başar-Eroglu, C. & Başar, E. A possible role of evoked alpha in primary sensory processing: common properties of cat intracranial recordings and human EEG and MEG. *Int. J. Psychophysiol.* **26**, 149–170 (1997).
146. Berger, H. Über das elektroencephalogramm des menschen. *Arch. Psychiatr. Nervenkr.* **87**, 527–570 (1929).
147. Pfurtscheller, G., Neuper, C., Andrew, C. & Edlinger, G. Foot and hand area mu rhythms. *Int. J. Psychophysiol.* **26**, 121–135 (1997).
148. Klimesch, W., Sauseng, P. & Hanslmayr, S. EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res. Rev.* **53**, 63–88 (2007).
149. Thut, G., Nietzel, A., Brandt, S. A. & Pascual-Leone, A. Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *J. Neurosci.* **26**, 9494–9502 (2006).
150. Palva, S., Linkenkaer-Hansen, K., Naatanen, R. & Palva, J. M. Early neural correlates of conscious somatosensory perception. *J. Neurosci.* **25**, 5248–5258 (2005).
151. Doesburg, S. M., Green, J. J., McDonald, J. J. & Ward, L. M. From local inhibition to long-range integration: a functional dissociation of alpha-band synchronization across cortical scales in visuospatial attention. *Brain Res.* **1303**, 97–110 (2009).
152. Marco-Pallares, J. *et al.* Human oscillatory activity associated to reward processing in a gambling task. *Neuropsychologia* **46**, 241–248 (2008).
153. Martin, C., Gervais, R., Hugues, E., Messaoudi, B. & Ravel, N. Learning modulation of odor-induced oscillatory responses in the rat olfactory bulb: a correlate of odor recognition? *J. Neurosci.* **24**, 389–397 (2004).
154. Hong, L. E., Buchanan, R. W., Thaker, G. K., Shepard, P. D. & Summerfelt, A. Beta (~ 16 Hz) frequency neural oscillations mediate auditory sensory gating in humans. *Psychophysiology* **45**, 197–204 (2008).
155. Gross, J. *et al.* Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. *Proc. Natl Acad. Sci. USA* **101**, 13050–13055 (2004).
156. Kilner, J. M., Baker, S. N., Salenius, S., Hari, R. & Lemon, R. N. Human cortical muscle coherence is directly related to specific motor parameters. *J. Neurosci.* **20**, 8838–8845 (2000).
157. Kopell, N., Ermentrout, G. B., Whittington, M. A. & Traub, R. D. Gamma and beta rhythms have different synchronization properties. *Proc. Natl Acad. Sci. USA* **97**, 1867–1872 (2000).
158. Neuenschwander, S. & Singer, W. Long-range synchronization of oscillatory light responses in the cat retina and lateral geniculate nucleus. *Nature* **379**, 728–732 (1996).
159. Stopfer, M., Bhagavan, S., Smith, B. H. & Laurent, G. Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. *Nature* **390**, 70–74 (1997).
160. Fries, P., Reynolds, J. H., Rorie, A. E. & Desimone, R. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* **291**, 1560–1563 (2001).
161. Tallon-Baudry, C., Bertrand, O., Peronnet, F. & Pernier, J. Induced gamma-band activity during the delay of a visual short-term memory task in humans. *J. Neurosci.* **18**, 4244–4254 (1998).
162. Melloni, L. *et al.* Synchronization of neural activity across cortical areas correlates with conscious perception. *J. Neurosci.* **27**, 2858–2865 (2007).
163. Berlucchi, G. Anatomical and physiological aspects of visual fuctions of corpus callosum. *Brain Res.* **37**, 371–392 (1972).

**Competing interests statement**

The authors declare no competing financial interests

**DATABASES**

Entrez Gene: <http://www.ncbi.nlm.nih.gov/gene>  
 CHRNA7 | DRD4 | dysbindin | GAD1 | neuregulin1 | SLC6A3  
 UniProtKB: <http://www.uniprot.org>  
 GAD67 | GAT1

**FURTHER INFORMATION**

Peter J. Uhlhaas's homepage: [http://www.mpih-frankfurt.mpg.de/global/Np/Staff/uhlhaas\\_eindex.htm](http://www.mpih-frankfurt.mpg.de/global/Np/Staff/uhlhaas_eindex.htm)  
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