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Full-length review

Synchronous Gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia

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Abstract

Synchronous high frequency (Gamma band) activity has been proposed as a candidate mechanism for the integration or 'binding' of distributed brain activities. Since the first descriptions of schizophrenia, attempts to characterize this disorder have focused on disturbances in such integrative processing. Here, we review both micro- and macroscopic neuroscience research into Gamma synchrony, and its application to understanding schizophrenia. The review encompasses evidence from both animal and human studies for the functional significance of Gamma activity, the association between Gamma dysfunction and information processing disturbances, and the relevance of specific Gamma dysfunctions to the integration and extension of previous disconnection models of schizophrenia. Attention is given to the relationship between Gamma activity and the heterogeneous symptoms of schizophrenia. Existing studies show that measures of Gamma activity have the potential to explain far more of the variance in schizophrenia performance than previous neurophysiological measures. It is concluded that measures of Gamma synchrony offer a valuable window into the core integrative disturbance in schizophrenia cognition.

Theme: Disorders of the nervous system

Topic: Neuropsychiatric disorders

Keywords: Schizophrenia; Gamma synchrony; 40 Hz; Binding; Neural connection

Contents

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1. Introduction

One of the fundamental questions in neuroscience is the 'binding problem': how the brain codes and integrates its disparate network activities, including perception, cognition, and memory. Attention has focused recently on the candidate binding mechanism of 'Gamma synchrony' [180]—high frequency oscillations in electrical brain activity (typically 40 Hz, but varying from 30 to 90 Hz) that occur synchronously (in-cycle) across brain regions. The synchronous cycling of Gamma activity is purported to underlie the integration of diverse brain activities and associated neuronal networks [44].

The phenomenology of schizophrenia points to a core disturbance in the integration of brain activities. Indeed, the clinical history of this disorder shows a focus on deficits in integrative processing since Kraepelin's [93] earliest attempts to describe schizophrenia as a 'loss of the inner unity' and 'intrapsychic coordination'. Similarly, subsequent models of schizophrenia have postulated that the core pathophysiology of schizophrenia is one of abnormal integration of sensory input with stored information [63,75]. Andreasen et al. [7] emphasized in particular the abnormal *temporal* integration of brain networks, referred to as 'cognitive dysmetria'. Animal and human evidence from both microscopic and macroscopic neuroscience concerning the mechanisms and functional significance of synchronous Gamma oscillations has direct implications for understanding the failure of integration in schizophrenia. The tens of milliseconds temporal resolution of Gamma activity corresponds with the time scale at which human cognition is thought to occur. Indices of synchronous Gamma activity therefore offer a window onto cognitive dysfunction, not readily provided within the spectrum of brain imaging measures applied in previous schizophrenia research (including electroencephalography, event-related potentials, magnetoencephalography, rCBF, PET, SPECT, and fMRI) [57].

To date, the relevance of Gamma research in relation to schizophrenia pathophysiology has not been the focus of a critical review. Previous reviews have provided an excellent coverage of the contribution of psychopharmacological agents [215], and specific functional correlates of Gamma activity, including perception [194], motor responses [46], language [146] and consciousness [108,178]. This review first outlines the theoretical models and empirical definitions of synchronous Gamma activity, followed by evidence for the functional significance of Gamma activity in terms of cognitive constructs. Coverage of the proposed neurophysiological mechanisms of Gamma activity includes the contribution of gamma-aminobutyric acid (GABA)-ergic interneuron activity described in synaptic scale neuroscience research [217], as well as the whole-brain association of Gamma oscillations with the thalamo-cortical modulation of arousal [188]. Studies on abnormal Gamma activity and its mechanisms may provide an interpretive framework for understanding schizophrenia-specific breakdowns in integrative function. Finally, we review current hypotheses, and preliminary evidence, that dysfunctions in Gamma mechanisms might account for the heterogeneity of symptoms in schizophrenia. This review provides a platform for sketching the beginnings of an integrative neuroscience account of schizophrenia that brings together emerging evidence from different scales and fields of neuroscience and from both the animal and human research domains.

2. Models and measurements of synchronous gamma activity

2.1. The binding problem and synchronization of neural activities

Over the past few decades, neuroscientists have proposed two primary, yet fundamentally different, theories to account for the 'binding problem' of how the brain codes and represents disparate network activities, such as perception, emotion, cognition, and memory—known as the 'distributed coding' and 'grandfather cell' theories. Synchronous Gamma activity provides empirical support for the latter account.

The theory of distributed coding, advocated by von der Malsburg and Schneider [213], states that neurons involved in the processing of a single object will tend to synchronize their firing with each other, while simul-

taneously desynchronizing their firing from the remaining neurons not involved in the processing of that object. Thus, the same neurons can be used in different sensory contexts, in that different *combinations* of these neurons represent different sensory objects. Rather than a 'limited capacity' account of the brain, this theory of distributed synchronized networks allows for a 'flexibility' in capacity. It was suggested that this synchronization might represent the integration of perceptions into a coherent output [180]. By contrast, the 'grandmother cell' (also called 'cardinal' or 'gnostic' cell [15,64]) theory states that the brain contains a raft of single cells that represent distinct unitary perceptions. When a particular cell 'fires', it triggers a set of synapses relevant to the particular perception. For example, these Grandmother cells can respond to specific conjunctions of features that identify a particular object [12]. Such a strategy would provide a rigid and hard-wired network in which the path of information flow and its destination is predetermined and unambiguously channelled [15,177].

Observations by Singer's group [59,61], that the occurrence of synchronous Gamma activity in the visual cortex of cats and primates is closely linked to the features of external visual stimuli (e.g. movement), provided the first direct support for the distributed account of brain coding and representation. In these animals, spatially separated neurons (within and between columns, and more globally between different hemispheres) synchronized their activity to the stimuli, within the Gamma band range and with near zero time lag (see Refs. [44,180] for reviews). Subsequently, such synchronized neuronal activities have also been found to contribute to the selection and formation of interconnected circuits in the early developing brain [87,211], and to the long term potentiation (LTP) and depression (LTD) mechanisms that play a crucial role in learning and memory [172,204]. Evidence concerning the specific contribution of Gamma synchronization to these processes is outlined in detail in Section 4.4 below. The Gamma research outlined in this review has been conducted within a distributed coding theory framework.

Whilst the majority of research on feature binding has focused on synchronous Gamma activity, there is some evidence that synchronous activities in other frequency bands, and across a broad range of frequencies (e.g. Ref. [25]), may also contribute to functional integration. In this review we focus on synchronous activity in the Gamma band in particular, given that this high frequency activity is likely to underlie the fundamental cognitive disturbances in schizophrenia. However, the role of synchronous activity in other frequency bands warrants an independent review and analysis.

2.2. Empirical measurements of Gamma activity

Gamma activity can be observed at the various levels of analysis from microscopic (single neuron) to macroscopic, by the use of intracellular recording, extracellular recording, and non-invasive recording (EEG and MEG): see summary of each method in Table 1. These methods are typically used to measure either 'Gamma oscillation' ('amplitude' or 'power') or synchronous Gamma oscillations. In single cell recordings, Gamma oscillation usually refers to the magnitude of Gamma activity at a given neuron(s). By contrast, Gamma 'synchrony' refers specifically to the extent to which Gamma activity is *in phase* between pairs of individual neurons.

It has been proposed that the distinction between Gamma activity and Gamma synchrony is less clear in EEG recording (and other extracellular methods), because these methods measure aggregated electrical activity that is generated by a large number of neurons in the first place [176]. One of the most complex issues concerns the relative importance of Gamma oscillations versus Gamma synchrony between pairs of recording sites. It has been suggested that Gamma oscillation may be the modulator for the more focused and specific integration of information, subserved by Gamma synchrony [30,40]. For example, Konig et al. [92] proposed that neuronal firing within the Gamma frequency (oscillation) may act as the 'carrier signal' to establish the synchronization that binds widely distributed neuronal activities. This suggestion was based on the finding that Gamma synchrony measured by multi-unit activity (MUA) for regions separated by greater than two millimeters (or between hemispheres) was also concomitant with neuronal firing in the Gamma frequency range.

For each of above methods, examination of the time course of Gamma activity in response to sensory stimuli reveals two distinct Gamma components, which may subserve two different information processing functions [54]. 'Evoked' early Gamma activity tends to be time-locked to the stimulus and may primarily be an index of integrative sensory processing with modulation from attention [201]. By contrast, the later 'induced' Gamma response tends to be only loosely time-locked [134,194] and serves a context processing and integration role [139]. Pantev [134] proposed that early Gamma represents a general mechanism for perception by synchronizing 'within sensory cortex' and late Gamma indicates the presence of cognitive processing with more 'global cortical synchronization.' More specifically, Phillips and Singer [139] described that upon 'Receptor Field' (RF) inputs, reflecting isolated sensory inputs, into a neural network, 'Contextual Field' (CF) fibres (long range pyramidal cells) might operate to achieve synchrony or coordination between separate sites of RF inputs. That is, the ascending connections could provide much of the RF input, and both the descending and the lateral connections could include CF input. Furthermore, within cortical regions there are many distinct streams of processing, that are linked by long-range horizontal collaterals that could transmit synchronizing information. Thus, in this manner, sensory

Table 1
Measurements of Gamma activity

Spatial summation of neuronal activity		Gamma frequency oscillations (power)	Gamma synchrony
~1 μm ↓	**Intracellular recording**: Single cell recordings	Firing rate or membrane potentials of individual neurons at about 40 cycles/s	Correlated firings of a pair of neurons in Gamma frequency range. Difficult to detect Gamma synchrony in this measure, due to cell sampling problems and non-stationarity of the time series [176]
	Extracellular recording: Local field potentials (LEP) and multi-unit spike density (multi-unit activity: MUA)—both signals can be recorded from a single electrode, but different signal filtering methods are applied (LEP: 1–100 Hz; MUA: 0.5–3.0 kHz, followed by a spike event counting) [210]	The distinction between Gamma power and synchrony is obscure in LEP and MUA, because Gamma frequency activity in these measures is indicative not only of oscillatory firing patterns but also of response synchrony among local groups of neurons. This level of activation has been called coherence within an assembly of neurons (i.e. meso-scopic scale [50])	Large-scale interaction is optimally studied at this level by the use of cross-correlation between pairs of electrodes. The relationship between Gamma power and synchrony in this type of measure was studied by Konig et al. [92] who showed in MUA recordings that short range (<2 mm) Gamma synchrony can occur in the relative absence of Gamma oscillations, but long range (>2 mm or between hemispheres) Gamma synchrony always accompanies Gamma frequency oscillations (see [175] for more detailed discussion)
↓ >2 cm	**EEG and MEG recording**	Macroscopic Gamma activity recorded with EEG or MEG signals can be regarded as spatially integrated LFPs or a synthetic measure of local circuitry [209]	It is only in the last few years that the first methods for evaluating Gamma phase synchronization using human EEG recordings have emerged [71,156]

There are two important factors in understanding the relationship between LFPs in the cortex and macroscopic field potentials, as measured in scalp EEG [131]. The first relates to the length scales of LFPs and the macroscopic potentials that give rise to the EEG, which differ in magnitude by an order of two to three. It is helpful to recall that in-phase fluctuations in LFPs will summate, whereas out-of-phase fluctuations will cancel. Thus, macroscopic field potentials will tend to arise from the summation of in-phase LFPs present in several centimetres-squared of underlying cortex. Gamma oscillations in surface EEG already reflect the coherent activity from microscopic sources in underlying cortical networks. Synchronous Gamma oscillations in the scalp EEG therefore reflect a second order synchronization between these coherent microscopic sources. The second factor relates to the effect of the scalp on the macroscopic field potentials, as they propagate outwards from the cortex. The scalp tends to 'smear' much of the spatial information in the sources, and reduces the root-mean-square of their amplitude by a factor of approximately five [131]. However, the transfer of signal through the scalp is independent of frequency, so that changes in scalp EEG truly reflect proportional changes in cortical sources [131]. Because of these factors, caution is required when making the transition to human EEG studies. This transition requires validation of the cognitive and psychological correlates of synchronous Gamma oscillations in scalp EEG, independently of the research outcomes already achieved in invasive animal studies. However, it is argued that much of this independent validation research has already been achieved. This research is outlined in Section 3.

inputs could be amplified or diminished depending on synchrony mechanism (by CF input), possibly resulting in late, internally generated Gamma response.

2.3. Methods for the study of synchronous Gamma activity

A variety of methodological approaches have been employed in the study of synchronous neural activity. Terms such as 'synchronous oscillations' and 'coherent activity' are among those used to describe neural inter-dependence. However these terms are derived using a variety of different methods and may refer to quite different types of interdependences between distributed systems.

The traditional methods of detecting interdependence between bivariate signals derive from the linear analysis of random processes and thus depend upon the 'spectral representation' of a time series. The cross-spectral density function is obtained by taking the cross-products of the Fourier components of each of the individual time series. The coherence function is obtained by normalizing the cross-spectral density by division with the product of each individual spectra. The coherence equals 0 when the two time series are completely independent and 1 when the two time series are identical. The coherence function has been used very widely in EEG studies and has the advantage of

permitting the analysis of interdependence in discrete frequency bins. There are some methodological problems for this approach such as the choice of reference electrode [47] and the problem of volume conduction (the direct electromagnetic spread of the electric fields from their neural sources to distant recording electrodes). When restricted to the analysis of high frequency (Gamma band) neural activity, the application of this term is best described as Gamma band coherence [121]. A variety of papers have investigated the structure and role of Gamma coherence in neurophysiological recordings (e.g. [28,137]). Variations on this method allow for the analysis of non-stationary signals, through the employment of Kalmann filters [122] and wavelets [90] rather then the Fourier transform.

However, using the coherence function alone, it is not possible to distinguish between the relative contributions of phase and amplitude covariance [53]. Using conventional linear techniques, it is necessary to calculate three indices, such as the coherence, phase and cross-amplitude, to exactly determine these relative contributions [32]. Recently there have appeared several alternative techniques for the exclusive analysis of phase. In each of these the phase is extracted from the time series by either (1) the Hilbert transform, (2) the Fourier transform or (3) a wavelet transform. These indices produced by these techniques are best referred to as Gamma phase synchronization.

(1) Using the Hilbert transform, it is possible to separate any signal into a unique amplitude and phase component. Once the phase has been determined for each time series, a statistic quantifying the degree of phase coherence between each time series, such as the entropy, is then applied [160]. This method is most suited to the study of systems which produce large-amplitude oscillations. For the analysis of noisy signals, such as EEG and MEG, it is necessary to subject the time series to band-pass filtering [24,198]. The method has only recently been employed to examine Gamma phase synchronization in human EEG data [19].

(2) It is also possible to quantify the degree of phase synchronization by extracting the phase component using the Fourier transform. This has the advantage over the Hilbert transform in allowing the examination of narrow-band phase synchrony without the need for band-pass filtering. Haig et al. [70,71] from our group developed a measure of Gamma phase synchronization between time series using the Fourier transform applied to two or more time series. A sliding Welch window is applied to each time series. A Fourier transform is taken from each window. The phase is extracted from the Fourier components and the circular variance is calculated from the two or more phase values (the 'circular variance' is not biased by the apparent jump of phase between 0 and 2π). This method confers the distinct advantage of permitting the calculation of a single estimate of Gamma phase synchronization between many concurrent EEG channels.

(3) Another method of Gamma phase synchronization was provided by Rodriguez et al. [156]. The time series are first band-pass filtered into the Gamma frequency range. The convolution of the time series with a Gabor wavelet centered at Gamma band frequency is then calculated. This once again permits determination of the phase of each signal and hence a statistic estimating the degree of phase synchronization (a complete description of this technique is presented in [99]).

Each of these methods of measuring Gamma phase synchronization confers certain advantages and disadvantages in comparison to the others. For example, the use of band pass-filtering ((1) and (3)) is problematic as filtering induces correlations within and between time series. This must be overcome by comparing the experimental signals to surrogate data that have also been filtered, but do not share other properties of the original signal. Inverting the signal in the time domain is one method of producing surrogate data. Care must also be taken in choosing a filter that has minimal effect on the phase of the original signal. On the other hand, both the Hilbert and wavelet approaches permit the extraction of phase on shorter time domains than the Fourier transform (2) and do not require the use of periodic windows to control for 'end-point mismatch'. The ability to calculate a single index of phase synchrony from multiple concurrent inputs (2) can also be seen as beneficial. This can be overcome to some extent by analyzing electrode pairs in all possible combinations [156], although this then requires statistical adjustment to account for multiple measurements.

In summary, there are several different techniques for measuring Gamma phase synchronization, each of which has both advantages and disadvantages. The differences present in each of the approaches may in fact lead to contradictory results. On the other hand, the converging results revealed in studies to date speak further to the validity of synchronous Gamma activity as an electrophysiological measure of cognitive processes.

In this review, we focus in particular on the phase synchronization of neuronal activity to distinguish Gamma synchrony (phase synchrony across regions) from Gamma oscillation (neuronal firing at a given region, without attention to phase across regions), although the vast majority of human EEG (scalp recording) studies have focused on Gamma oscillations, and have not specifically measured Gamma phase synchrony across diverse cortical regions. It should be noted that some studies (most notably, Lamme and Spekreije [101]) have failed to reveal an association between Gamma synchrony and perceptual binding. This null finding has raised some doubt in relation to the proposed role of neural synchrony in binding [208]. However, in the Lamme and Spekreije study, 'synchrony' was indexed by the correlation coefficient of the measured local field potentials, rather than the *phase synchronization* of these signals. It is possible therefore, that the phase synchronization in these signals could have been obscured

by the presence of uncorrelated activity in other frequency bands. However, our primary aim in this review was to outline a body of neuroscience research into Gamma synchrony to understand schizophrenia abnormalities in brain function, rather than to focus on specific and contentious methodological issues in the literature. The next section considers the evidence for the functional significance of Gamma activity (both power and synchrony), encompassing perception, arousal and attention, motor responses, language and learning. This evidence is derived from the full spectrum of experimental protocols, from microscopic scale studies with experimental animals to human EEG and MEG recording.

3. Functional significance of synchronous gamma activity

3.1. Perception

Eckhorn, Singer, and colleagues [42,59] were the first to demonstrate a direct link between visual perception and Gamma synchrony in the cat visual cortex, thereby initiating the current resurgence of interest in Gamma activity. For example, Gray and Singer [61] recorded multiunit neuronal activity (MUA) from two spatially separated (7 mm) fields in the visual cortex of anaesthetized cats. The critical observation was that Gamma activity (35–50 Hz) in the two receptive fields was synchronized only in response to a single stimulus (continuous light bar) moving simultaneously across *both* fields. Synchronization was reduced or absent when these fields were stimulated independently by two light bars moving in the same direction or the same two bars moving in opposite directions. A subsequent study by Singer's group reproduced the properties of Gamma synchrony in alert cats, indicating that the initial observation of Gamma could not be explained by the anaesthetized state of the experimental cats [62]. Singer and colleagues have since demonstrated Gamma synchrony in the middle temporal area (related to motion perception) in response to the moving light stimulus in awake macaques [95]. Similarly, Prechtl [145] reported synchronous Gamma activity in the visual cortex of turtles in response to this stimulus. Together, these animal studies support the proposal that synchronous Gamma is critical to the binding of stimulus information for coherent perception.

In humans, a growing body of studies provides convergent evidence for the role of Gamma activity in the coherent perception of both visual and auditory stimuli. In the visual modality, Lutzenberger et al. [112] reported that Gamma activity was enhanced over the occipital electrodes for bars that were moving with a regular rather than irregular frequency. Similarly, EEG Gamma activity is also greater at occipito-temporal electrode sites when subjects are presented a single bar that moves across these sites, compared to two incoherently moving bars [127,128]. These studies have addressed only Gamma amplitude, but have used equivalent paradigms and achieved similar results to Singer's initial animal research. One might therefore extrapolate from these results to suggest that the synchronization of Gamma across neuronal assemblies may also be involved in coherent human perception.

Perception of an ambiguous visual stimulus as a gestalt is associated with enhanced Gamma activity, highlighting the role of Gamma activity in perceptual binding. Tallon-Baudry et al. [196] examined both early and late peak Gamma activity, while subjects counted distractor stimuli, presented amongst illusory and real triangles, and a non-triangle shape. The late Gamma peak (200–300 ms, 30–40 Hz) was enhanced only in response to real and illusory triangles, consistent with the notion that Gamma activity underlies the binding of stimulus features into a coherent percept. By contrast, while early Gamma activity (70–120 ms, 40 Hz) was phase-locked to the stimuli, it did not vary with stimulus type (percept). In a subsequent study, Tallon-Baudry et al. [195] compared the Gamma activity for a condition in which subjects were trained to perceive an initially meaningless stimulus as a coherent Dalmation dog to that for an 'untrained perception' condition. Consistent with their previous finding, the trained 'coherent perception' condition showed a comparatively increased late (280 ms) Gamma response. Additional support for the role of Gamma in fluent perception comes from a stereoscopic fusion task in which random dots are perceived as a single gestalt (three-dimensional object) are compared to those that do not produce a gestalt perception [152]. Increased Gamma activity was observed in occipital and right posterior areas shortly before subjects reported perceiving the gestalt object, but not for the non-gestalt stimulus. Klemm et al. [90] reported coherent Gamma band activity in a study of an ambiguous figure task in which subjects were asked to press a button when they perceived an alternative ('hidden') image in the stimulus. Increased Gamma coherence was observed among diverse regions (frontal, parietal, central, occipital regions of both hemispheres). This increase particularly strong between distal (compared to adjacent) electrode sites, suggesting that cognitive binding is subserved by high frequency coordination among widespread brain networks.

Several studies have also used biologically meaningful stimuli (e.g. faces) to examine Gamma activity in relation to gestalt perception. Rodriguez et al. [156] demonstrated enhanced Gamma phase synchrony (as well as Gamma power) between occipito-temporal and parietal regions, during the point at which ambiguous stimuli were identified as faces. Keil et al. [88] presented subjects with a rotating face stimulus that could be perceived as either sad or happy in expression, depending on its orientation. Gamma responses were enhanced when both the happy or sad expressions were in the typically upright (vertical) orientation, compared with a horizontal orientation. Addi-

tional evidence from facial emotion stimuli suggests that increases in Gamma activity may be lateralized, depending on the emotional valence. Muller et al. [126] observed enhanced right (frontal and temporal areas) relative to left hemisphere Gamma activity when subjects were viewing positive emotional pictures. Right Gamma activity was also generally increased for emotional relative to neutral pictures.

Gamma studies using auditory stimuli also support the role of Gamma activity in perceptual binding. Joliot et al. [86] observed two successive Gamma peaks in response to two corresponding click stimuli, but the second Gamma response was present at inter-stimulus intervals of greater than 15 ms, when subjects could *perceive* the second click. Knief et al. [91] developed an auditory version of the gestalt perception task (the 'Kanizsa experiment') to determine if coherent auditory stimuli would produce whether different EEG/MEG Gamma responses to incoherent auditory stimuli. While Gamma activity was unexpectedly no different in amplitude for coherent stimuli, Knief et al. did observe longer Gamma response latencies for these coherent stimuli. It was suggested that coherent auditory perception requires a longer time due to the gestalt recognition process. As an example of the specialized instance of gestalt perception, Bhattacharya and Petsche [18] examined Gamma phase synchrony in musicians and non musicians, while listening to music versus a short neutral story. They observed comparatively enhanced synchrony in musicians during music listening (especially in the left hemisphere), but no group differences for the neutral text. Bhattacharya and Petsche suggested that enhanced Gamma synchrony in musicians might represent various perceptual and working memory processes that are coordinated, as well as the retrieval of musical patterns from memory.

Taken together, these studies suggest that both a localized increase in Gamma power as well as a widespread cortical increase in Gamma synchrony is crucial for the perceptual grouping or binding processes involved in both the visual and auditory perception of complex stimuli. Studies of arousal and attention provide a further demonstration of the role of Gamma synchrony in the active state of perception.

3.2. Arousal and attention

The association between arousal and high frequency (e.g. Gamma) activity can be traced back to the early finding of Moruzzi and Magoun [125], that direct stimulation of the brain stem ascending reticular activation system (ARAS) has the effect of replacing high-voltage slow waves with low-voltage fast-wave activity. More recently, Steriade et al. [191] showed subsequently that stimulation of the ARAS is associated with enhanced Gamma activity in the cat cortex. This observation was extended to Gamma synchrony by Munk et al. [130] who demonstrated that stimulation of the ARAS facilitates Gamma synchrony as well as power in the cat visual cortex. In this study, synchronous activity remained dependent on the simultaneous stimulation of spatially diverse receptive fields.

The stimulus-specific nature of Gamma synchrony in relation to arousal modulation was examined in a study of both spontaneous changes in arousal state and ARAS stimulation in response to visual stimuli in cats [76]. During a state of low arousal there was a lack of precise Gamma synchronization, whereas the magnitude of Gamma synchrony in the visual cortex increased in a linear fashion with increased ARAS activation. This effect could not simply be explained by changes in neuronal firing rate. Such 'stimulus-specific' Gamma synchrony under the modulation of arousal suggests that enhanced synchrony is not simply due to non-specific arousal, but that the effect of arousal may be to facilitate particular aspects of information processing that are the focus of synchronous activity.

Further support for the stimulus specific effect of Gamma activity in relation to arousal comes from the behavior of experimental animals, which is associated with enhanced Gamma activity only when they are in an actively vigilant state. For example, using multiple electrode recording in the somatosensory and parietal cat cortex, Bouyer et al. [23] showed that Gamma activity (35–45 Hz) characterizes a cat's gaze toward a given target (mouse), suggesting that Gamma activity reflects the intense vigilance involved in hunting and prey-catching strategies. More recently, Roelfsema et al. [157] trained cats to respond to visual stimuli for subsequent food rewards. Cats who were waiting attentively for a stimulus-related reward showed strong Gamma synchrony, in which there was no time lag between visual and parietal, and motor and parietal cortices (by contrast, alpha-band activity was not synchronized in this reward period). Moreover, the strength of synchrony was found to reflect functional relationships, rather that the spatial distance between these cortices (for instance, increases in visual-parietal synchrony occurred without affecting the synchrony between parietal and motor cortices). These findings suggest that Gamma synchrony is specific to behavioral situations, as well as associated states of alertness.

Human vigilance and sleep studies have provided converging evidence for the association between Gamma activity and states of arousal or alertness. Makeig and Jung [114] demonstrated that enhanced Gamma activity was associated with higher arousal/alertness and preceded correct responses in a target detection task, whereas decreased Gamma activity was associated with drowsiness/lower arousal and poor performance in this task situation. Both EEG and MEG sleep studies have observed that Gamma activity is high during the REM stage of sleep (associated with higher arousal), but markedly reduced during the non-REM stage (associated with relatively lower arousal) [206]. However, REM states were still

differentiated from awake states by responses to external stimuli. When responses to auditory stimuli were examined, Gamma activity was elicited only during wakefulness, and not during either REM or non-REM sleep [107]. It was concluded that Gamma activity is modulated by different levels of cognitive processing in the awake (greater alertness to external stimuli) and the REM dream ('internal' stimulus processing) states. Using intracranial EEG recordings in presurgical epilepsy patients, Gross and Gotman [65] provided further evidence that Gamma activity varies in accordance with the sleep–wake cycle (through wakefulness, REM, and slow-wave sleep) and associated degree of cognitive processing. It has been proposed, on the basis of sleep evidence, that both the alert awake state and REM dream mentation are associated with a core level of activation (reflected in some degree of parallel Gamma activity), but that the bizarre, hallucinatory, and disoriented REM state is linked only to uncoordinated activation in limbic structures and certain posterior association areas [77], whereas the qualitatively different state of waking consciousness is associated with additional frontal and sensorimotor activities.

A number of animal studies have suggested that Gamma synchrony in particular is augmented by selective attention, feasibly to enhance the perception and representation of relevant stimuli. For instance, Steinmetz et al. [187] reported that neurons in the monkey somatosensory cortex showed stronger synchrony during a tactile versus visual stimulus switching task, when the monkeys were trained to focus attention on the tactile stimulus. They suggested that the enhanced synchrony, produced by selective attention to the tactile stimulus might serve to increase synaptic efficacy in the somatosensory (relevant) brain region. Similarly, Fries et al. [51] observed a rapid increase in Gamma synchrony (35–90 Hz) of V4 neurons, together with reduced synchrony in lower frequencies ($<$17 Hz), in monkeys trained to discriminate particular luminance contrasts from 'distractor' contrasts. By contrast, V4 neurons did not fire in synchrony to distractor stimuli, but showed only a similar rate of firing. These findings suggest that Gamma synchrony may represent focused attention on a relevant stimulus, making perception and representation of the stimulus more prominent.

Converging evidence for the modulating role of attention in Gamma activity also comes from studies that show a gradual reduction (habituation) of Gamma with repeated presentation of the same stimulus [68,200]. This laboratory evidence for a direct association between Gamma and arousal is supported by findings from the numerical simulation of whole-brain neurophysiology developed in our group [151] in that increasing of gain related parameters in the cortico-thalamic feedback loop and therefore high activation of cortex is related to enhanced Gamma activity. Similarly, in a modeling study, Wright et al. [223] who found that synchronous neuronal activity provides a definition of a single object under *increasing cortical activation* suggested that ''any spatially synchronous pattern of activity in the brain is an object—either the representation of a physical object via sensory input, or a coherent pattern partly internally generated'' (p. 349).

Human studies have also demonstrated that Gamma activity is modulated by selective attention. In a dichotic listening task, Tiitinen et al. [201] observed that stimuli presented to the attended ear produced greater Gamma activity in EEG recordings than stimuli presented to the unattended ear. Sokolov et al. [184] reported similarly enhanced MEG Gamma activity in response to moving visual stimuli presented without an auditory distractor, relative to the same stimuli presented with a distractor stimulus. Evidence from a visuo-spatial task in which a cue predicts targets presented in either the left or right visual field, indicates that Gamma activity is enhanced specifically in the contralateral parietal-occipital brain region [66]. Selective attention tasks have also revealed *faster* Gamma responses; in the Go/No-Go task, Shibata et al. [170] reported shorter Gamma peak latency to an initial attended versus unattended visual stimulus.

In summary, the modulation of Gamma activity by arousal and selective attention is consistent with the view that Gamma activity represents a focused state of cortical arousal ''to achieve maximum sensitivity to stimulus input'' ([169], p. 73). Focused arousal refers here to the phasic arousal of specific cortical areas, in contrast to the tonic arousal associated with diffuse desynchronization (activation) across the cortex. In this regard, demonstration of stimulus-specific Gamma synchrony is important, because enhanced Gamma activity might instead reflect background electrical activity during activated brain states. Whilst synchronous Gamma activity has been studied primarily in sensory systems, there is converging evidence for the role of Gamma synchrony in the binding of distributed activities within the motor system.

3.3. Motor response

The significance of Gamma synchrony in motor systems was reviewed recently by Farmer [46], who suggested that the phenomena operating during the components of movement (preparation to move, movement, and maintenance of posture) might be the same as that observed in visual-perception experiments. In this regard, both animal and human studies reviewed by Farmer have reported an association between Gamma activity and components of movement. For instance, Hamada et al. [72] observed that Gamma power from the LFP of the primary somatosensory cortex was maximal about 100 ms before exploratory whisking onset in the rat, which might reflect an efference copy of the motor command to prepare actual movement.

Behavioural reaction time studies in humans show a robust relationship between simple reaction response and peak Gamma latency (earlier peak with faster reaction time) [96,138,156,171]. Furthermore, Jokeit and Makeig

[85] showed that Gamma responses occurring around reaction time were higher in fast responders than in slow responders. While a number of EEG and MEG studies using diverse paradigms have observed a transient increase of Gamma activity around the onset of hand movements [35,143], Gamma activity is not only the simple concomitant of movement in motor system, but higher cognitive functions that are operated in parallel in the brain. For example, De Pascalis and Ray [38] showed a phasic increase of Gamma activity in a movement condition (Go), compared with that of without movement (No-Go). More importantly, they found that the pattern of Gamma activity was modulated by working memory load—with pronounced Gamma activity in high memory load, compared with low memory load condition.

Several studies have now confirmed the presence of Synchronized Gamma oscillations during muscle contraction. For example, during multiple single neuron recordings in the primary motor cortex of monkeys performing a precision grip task, widespread Gamma synchrony (among pairs of neurons) was observed, especially during the steady hold period [10]. These activities may in turn be synchronized with the electromyographic (EMG) activity of muscle contractions (i.e. the Piper rhythm). Brown et al. [26] reported that human muscle activity is linearly correlated with focal MEG activity in the contralateral motor cortex at about 40 Hz during strong voluntary contractions. From a similar observation using EEG and EMG signals, Mima et al. [123] suggested that one of the functional roles of cortical Gamma activity is to drive muscle activity.

3.4. Learning and language

In view of the converging evidence for the role of the Gamma synchrony in perception and action, and the modulation of active attention by arousal, one might consider it's the further implications of mechanism for learning. Some studies in this regard have focused on learning in terms of classical conditioning. Bauer and Jones [16] were able to condition cats to increase their Gamma activity (36–44 Hz) in the left visual cortex and hippocampus, after 20–30 training sessions (with 60 milk-related reinforcements in each). Increased Gamma activity in the visual cortex was associated with a behavioral pattern of staring intently at an area within test chamber, suggesting that the cats learned the association between staring response and milk reinforcement. Similarly, Amzica et al. [4] conditioned cats to increase Gamma activity in the motor cortex by water reward. The conditioned increase in Gamma amplitude as well as synchrony returned to baseline level after extinction sessions. Interestingly, Gamma activity showed differential changes during conditioning in the motor and visual cortices, indicating the cats may learn to increase Gamma activity in selected cortical areas.

In humans learning-related Gamma synchrony was first reported by Miltner et al. [122]. In this study, an increase in Gamma synchrony and Gamma power was observed between visual and somatosensory areas when subjects were conditioned to associate visual and tactile stimuli. By contrast, there was no synchrony for non-conditioned stimuli, and a parallel loss of synchrony when the conditioned association was extinguished. These results are in accord with the notion that, in learning, synchronous Gamma activity between specific cortical areas may represent a 'signature of relatedness' [179].

The involvement of Gamma activity in semantic processing has also been reported (e.g. Refs. [94,148,149]), although only the Krause et al. study used the same key Gamma frequency range as the other studies outlined above (the others used a somewhat lower range of about 30 Hz). Enhanced Gamma activity for words (particularly in the left hemisphere), compared with pseudo-words, has been observed for both auditory [94,148] and visual [150] modalities, whereas alpha activity does not differ with word type [150]. Furthermore, Pulvermuller et al. [147] revealed a differential topography of Gamma activity between nouns (enhanced at O1 and O2) and verbs (enhanced at C3 and C4), demonstrating the sensitivity of Gamma activity as an index of cortical information processing, even when recorded from the scalp.

In summary, the significance of synchronous Gamma activity has been demonstrated in various recording techniques (from single cell recording in animals to EEG and MEG in humans) and diverse signal processing methods. Gamma synchrony is achieved when visual and auditory perceptual binding occurs. The same phenomenon of synchrony is observed when sub-components within the motor system bind in order to move or to maintain a posture. Moreover, in response to both the external and internal environment, there is an over-arching parallel synchronization of Gamma activity that occurs within each modality (e.g. Ref. [157]). This multi-modal synchrony is modulated by arousal and attention, such that different states of awareness are facilitated, and consciousness awareness of the relevant perceptual and motor events is achieved. The experimental evidence discussed above is in keeping with the proposal that Gamma activity is the 'universal functional building block' of information processing in the brain [14]. Gamma activity has also been examined in pathological conditions, and these studies may provide different insights into the functional significance of Gamma activity.

4. Mechanisms of Gamma activity

Although the exact mechanisms of synchronous Gamma activity have not yet been fully elucidated, several mechanisms has been proposed. This review focuses on the two main proposals concerning mechanisms of Gamma

synchrony, including cellular scale neuroscience studies that highlight the contributions of GABA-ergic interneuron activity [217] and the whole-brain evidence for thalamo-cortical modulation of arousal [188]. These proposed mechanisms, together with the converging evidence for the role of Gamma synchrony in information processing, provide an interpretive framework for evaluating Gamma disturbance in a number of brain pathologies.

4.1. GABA-ergic interneuron network model

One of the predominant models of Gamma synchrony is the network model put forward by Traub, Whittington and colleagues [202]. This model proposes two different Gamma synchronization mechanisms. The first mechanism is termed the 'local interneuron network Gamma synchrony' and describes short-range or local (<2 mm) synchrony. Local Gamma synchrony occurs when metabotropic glutamate receptors activate GABA-ergic interneurons ($GABA_A$ receptor mediated). When activated, the postsynaptic interneuron potentials engage in ongoing mutual inhibition, which occurs synchronously at 40 cycles per second. Thus, the fundamental mechanism of Gamma synchrony is the recurrent feedback loop produced by the ongoing synchronous mutual inhibition of interneurons [217]. In this mechanism, cortical interneurons themselves alone can produce synchronous Gamma activity, without the need of the excitatory input from pyramidal cells.

In Traub et al.'s model, long-range (>2 mm) Gamma synchrony occurs when there is simultaneous firing of multiple interneuron networks in precise in-phase synchrony with the firing of pyramidal cells [205]. The resulting cycle of excitation and inhibition from the synchronous interaction between long-range pyramidal cells and the interneuron networks, forms the recurrent feedback loop of long-range Gamma synchrony. It was demonstrated experimentally that long-range Gamma synchrony emerged when interneurons fire in rapid succession (i.e. produce pairs of spikes) by tetanic (repetitive) stimulation [205]. It has been proposed that Gamma activity within the inhibitory interneuron network may therefore be the 'clock signal for timing' or 'context' which determines when pyramidal cells can fire [30]. It has been suggested that the first interneuron spike might signal the timing, and that the second interneuron spike may determine the synchronous interaction of interneuron and pyramidal cell firing, and thereby the mechanism of effective information processing [83,205].

Pharmacological intervention studies in both animals and humans have provided converging evidence for Traub et al.'s [202] 'GABA-ergic interneuron network model' of the mechanisms underlying Gamma synchrony. The most critical condition for maintaining Gamma synchrony in this model is the tonic excitation of GABA-ergic interneurons via G-protein coupled metabotropic receptors to produce 'in cycle' Gamma oscillations. Gamma activity should therefore be slowed when pharmacological agents are applied to retard the decay of inhibitory postsynaptic potentials [83]. The effect of $GABA_A$ receptor antagonists such as bicuculline, was shown to abolish Gamma activity robustly in experimental animals [21,34,193,216,217]. Stopfer et al. [192] demonstrated that picrotoxin (which blocks GABA-ergic inhibitory interneuron activity) produced a specific disruption to Gamma synchrony in honey bees, while the firing rate of neurons remained intact, consistent with the proposed central role of mutual interneuron inhibition in producing Gamma synchrony. More importantly, honey bees (previously trained to recognize odors associated with a sugar water reward) were also impaired in their ability to discriminate similar odors after administration of picrotoxin, further highlighting the role of Gamma synchrony in effective perception.

4.2. Thalamo-cortical arousal model

The thalamocortical model of Gamma synchrony suggests that resonance between the thalamus and cortex is primarily responsible for Gamma synchrony, and therefore the brain activity that underlies information processing [108,189,190]. Sheer [169] has proposed a similar thalamo-cortical model of Gamma synchrony that highlights the role of arousal in modulating thalamo-cortical activity.

The thalamus is a sensory processing/relay centre for all sensory input, with the exception of olfactory input. To date, the synaptic properties of the relay neurons between the thalamus and cortex are not fully understood. However, it is likely that some thalamo-cortical neurons may have distinct properties that make them sensitive to the facilitation of Gamma oscillations. Indeed, several types of neurons in the thalamus and cortex have been identified as 'intrinsic oscillators' which produce recurrent Gamma activity. For example, Gray and McCormick [60] identified a type of pyramidal cells in the superficial layers of the cat visual cortex which exhibits 'intrinsic' repetitive bursts (or discharges) of activity at the Gamma frequency range. These cells were referred to as 'chattering cells' since they appear to act as a pacemaker for synchronous Gamma activity by affecting synaptically connected neighbouring cells.

Complementary support for the view that resonance in thalamo-cortical neuron activity underlies Gamma synchrony comes from extra- and intracellular recordings. Steriade et al. [189,190] observed that thalamic oscillations in the Gamma band range become synchronized with oscillations in the cortex. It has also been reported that electrical stimulation of the acoustic thalamus is associated with Gamma activity in the auditory cortex [13], suggesting that 'stimulus-specific' cortical Gamma synchrony is associated directly with thalamic activity. From these observations, it might also be expected that damage to either the thalamus or cortex would have equivalent effects

on Gamma synchronization [108]. In this regard, thalamic (but not temporal lobe) lesions have been associated with a phase delay in the Gamma response to tones delivered at 40 Hz [186].

Sheer [169] highlighted the role of arousal in the thalamo-cortical generation of Gamma synchrony. It is argued that arousal makes a critical contribution to the generation of Gamma synchrony via the modulatory effects of the ascending reticular activation system (ARAS) and associated cholinergic activity on the intrinsic oscillation of thalamocortical neurons [169,188]. Consistent with this proposal, pharmacological studies have shown that the cholinergic agonist, carbachol, increases Gamma activity, whereas cholinergic receptor antagonists (such as atropine) abolish Gamma activity [27,49].

To date, it is unclear as to whether different mechanisms for neuronal communication underlie Gamma synchronization in different brain regions, or whether the GABA-ergic interneuron and thalamo-cortical mechanisms function in a synergistic manner across the brain [155]. It is feasible that these mechanisms are complementary, whereby more global integrative thalamo-cortical mechanisms operate to modulate Gamma activity in parallel across multiple brain networks, and more localized GABA-ergic mechanisms subserve Gamma activity in each of these networks. A third model has been proposed to account specifically for inter-hemispheric Gamma activity.

4.3. Corpus callosum model of inter-hemispheric Gamma activity

At the whole brain scale, animal evidence suggests that relay via the corpus callosum is primarily responsible for effective inter-hemispheric Gamma activity. Engel et al. [43] observed that neurons in both the left and right hemisphere of the cat visual cortex tended to fire in synchrony to visual stimuli. However, when the corpus callosum was severed, Gamma activity remained strongly synchronized *within* the left and right hemispheres, but not between hemispheres. Converging evidence was reported by Munk et al. [129] who used sections of the cat brain to demonstrate that all types of inter-hemispheric synchrony (synchrony peaks differing in frequency, width and strength in cross-correlation histograms) in the visual cortex require an intact corpus callosum. Notably, spontaneously occurring inter-hemispheric Gamma activity is one and a half times more frequent than ipsilateral (within hemisphere) Gamma activity [172]. It has been suggested that inter-hemisphere synchrony may therefore provide a basis for the simultaneous processing of information arriving in parallel to the two hemispheres [172].

4.4. Gamma activity, synaptic plasticity and long-term potentiation and depression

As outlined in Section 3, the specific dependence of Gamma activity on sensory perception and performance supports the view that this activity underlies the binding of diverse brain functions to permit coherent perception and action [44,212]. Studies in developmental neuroscience have revealed that synchronized synaptic activity is also important in brain development. For example, correlated or synchronized firing of cells is an important factor in cell survival and the formation of interconnected networks during early development, while neurons that are not engaged in synchronized activity have been shown to die earlier [211].

Hebb [74] postulated that a plastic change would occur in the synapse between neurons when the neurons fire simultaneously. This mechanism of 'synaptic plasticity' produces either an increase or a decrease in the efficacy of synaptic transmission, depending on the type of neuronal stimulation. Long-term potentiation (LTP) refers to the activity-dependent, long-lasting enhancement in the strength of synaptic connections between neurons, which is usually induced experimentally by applying short, high-frequency bursts of stimulation. By contrast, long-term depression (LTD) typically refers to a reduction in synaptic efficacy induced by low-frequency stimulation (for a comprehensive review, see [116]). LTP has been proposed as a candidate memory mechanism, since it exhibits the characteristics of associativity, co-operativity, and input specificity [115]. The mechanism of LTP has been shown to depend upon the activation of NMDA receptors [78]. It has been proposed that LTP and NMDA receptors are involved in the mechanisms of epilepsy, Alzheimer's disease, and schizophrenia [154].

Experimental evidence from animal studies shows that Gamma activity is closely related to the synaptic plasticity mechanism of LTP. Using local field potential recording, Izaki et al. [79] observed increased Gamma power 500 ms after LTP was induced in the rat hippocampus by high frequency stimulation. By contrast, simple increments of stimulation intensity that did not induce LTP also failed to produce an increase in Gamma power.

Experimental evidence for disturbances in Gamma activity in a number of pathological conditions has the potential to provide further insights into both the functional significance of Gamma activity and the underlying mechanisms. To date, only a few studies into Gamma and pathology have been conducted. These studies are reviewed in the next section as an introduction to the special focus on Gamma activity and schizophrenia psychosis.

5. Gamma activity and psychopathology: a focus on schizophrenia

5.1. Gamma activity and psychopathology

The emerging evidence from research into dysfunctional Gamma activity in pathological conditions has encompas-

sed both neurological and neuropsychiatric disorders, and provides a complementary window onto the functional role of Gamma activity in relation to perception, attention and arousal, and interhemispheric communication.

Disturbances in Gamma activity have been observed in patients with Alzheimer type dementia (AD). While healthy controls show a relative increase in left hemisphere Gamma activity during verbal problem solving, and in right hemisphere Gamma during an arithmetic task, AD patients were reported to show a disruption to this task-dependent lateralization of Gamma activity, as well as an overall *reduction* in Gamma [111]. Decreased Gamma (as well as alpha and beta) activity has also been observed in AD patients in response to visual flash and auditory stimulation [141,142,153]. In a source localization study of MEG signals, Ribary et al. [153] reported that Gamma activity in patients with AD was particularly reduced and distorted at cortical rather than thalamic sources. It was suggested that this finding might reflect synaptic losses in AD patients.

Lateralized disturbances in Gamma activity have also been observed in attention-deficit hyperactivity disorder (ADHD), which is characterized by symptoms of inattention, hyperactivity and impulsivity. Yordanova et al. [224] reported increased early Gamma activity in unmedicated children with ADHD. The increase in Gamma activity was particularly pronounced in the left hemisphere in response to auditory stimuli presented to right ear, suggesting that ADHD may be associated with an abnormal enhancement of arousal responses to sensory stimuli, or an abnormal pattern of habituation produced by over-reactivity to novel sensory stimuli. These suggestion draws on evidence for the modulatory role of arousal and attention in Gamma activity [169]. Direct evidence for a disturbance in the modulation of Gamma activity by autonomic arousal in ADHD was revealed in a recent study by our group in which abnormally enhanced early Gamma activity in ADHD adolescents was associated specifically with large increases in phasic arousal responses to auditory target stimuli [56].

Gamma activity has also been examined in relation to the neurological disorder of epilepsy. Le Van et al. [102] undertook subdural EEG recordings from a patient with ictal symptoms of visual hallucinations and speech disturbance. Stable and long lasting epileptic discharges were produced from recording sites in the left temporal-occipital region. A simultaneous increase in Gamma power was also observed at these recording sites (and surrounding sites) in response to task-relevant compared with task-irrelevant stimuli. It was suggested that cognitive activities associated with Gamma activity might also be involved in the induction of seizures. Moreover, Aoki et al. [8] observed that Gamma synchrony was most widespread in a subject with severe seizure activity and suggested that the extend of synchronous activity might be a consequence of the sustained facilitation of synaptic connections by incessant seizure activity. Traub et al. [203] noted that while repetitive stimulation in brain slices can induce both Gamma synchrony and epileptic activity, epileptic activity is distinguished by being 'incomprehensible' to the brain.

Llinas et al. [109] tested nine patients with heterogeneous neurological and psychiatric disorders, using MEG recording during 10 min of 'eyes closed' relaxation. A consistent finding was that observable, positive clinical symptoms were associated with increased Gamma activity compared to controls. They suggested that the core thalamo-cortical dysfunction forced the brain to generate Gamma frequencies in a continuous and stereotyped manner in these patients with positive neurological symptoms. Therefore, the symptoms may reflect the generation of cognitive experiences and motor behavior, in the absence of context with the external world and without the intentionality the normally characterizes human function.

In summary, while there has been relatively little research to date on Gamma activity and psychopathology, the findings suggest that a dysfunctional mental state can be produced by both increases and decreases in Gamma activity. Given that schizophrenia is defined by a fundamental breakdown in integrative processing, a growing number of studies have examined Gamma activity in this disorder. The contributions of Gamma disturbances to schizophrenia are considered in detail in the next section.

5.2. Gamma activity in schizophrenia

The defining symptoms of schizophrenia have been grouped into positive (hallucinations, delusions, thought disorder, odd behaviour) and negative (lack of content of speech, blunted affect, social withdrawal, and lack of motivation and goal-directed behaviour) symptoms [182]. These diverse symptoms form three primary symptom factors [6,105,110,218]: Psychomotor poverty (deficit negative symptoms), Disorganization (thought disorder and odd behaviour), and Reality distortion (hallucinations and delusions). The pattern of cognitive and neuropsychological dysfunctions across the three syndromes suggests that Psychomotor poverty reflects a slowing of mental activity and global cognitive deficits, whereas Disorganization might reflect language processing and an impaired ability to inhibit irrelevant mental activity [106,132]. While cognitive and neuropsychological abnormalities in Reality distortion is less pronounced than the two other syndromes, impairments in memory performance has been indicated [166].

Disturbances of integrative processing have been recognized in schizophrenia since the earliest descriptions of this disorder as a 'loss of the inner unity' and a disturbance in 'intrapsychic coordination' [20,93]. Current models of schizophrenia postulate that the core pathophysiology of schizophrenia is one of abnormal integration of sensory input with stored information [63,75]. Andreasen et al. [7] emphasize in particular the abnormal *temporal* integration

of brain networks for smooth coordination of cognitive processes or 'cognitive dysmetria'. These models point to the possibility that schizophrenia may involve a fundamental disruption in synchronous Gamma activity, given the proposal that Gamma synchrony is the mechanism for integration or 'binding' of brain functions across diverse networks, to provide a temporal coherence to perceptions and actions [139]. From this view, schizophrenia may reflect various 'binding errors' in the integration of cognitive activities across diverse brain regions.

Evidence for impaired perceptual binding in schizophrenia has come from psychological experiments. For example, Silverstein et al. [173] observed that schizophrenia subjects (particularly those with Disorganization symptoms) were comparatively unable to perceive spatially separated elements as the contours of a single object, when the elements were widely spaced. This task required the binding of perceptual elements into a 'whole' to form an object. It was proposed that schizophrenia reflects and impairment in the long-range interactions of cortical areas that subserve the perceptual binding processes. 'Binding errors' in schizophrenia may be present not only in perceptual processing, but also in motor performance, such as reaction time. Previous studies have demonstrated a relationship between Gamma activity and reaction time, such that Gamma response is occurring around reaction time. A substantial number of studies have reported reaction time abnormalities in patients with schizophrenia, especially in relation to the reaction time crossover phenomenon (the inability to benefit from the predictability of regular preparatory intervals) [161]. This 'preparatory set' dysfunction in schizophrenia might reflect an abnormal movement preparation due to an attentional abnormality in context processing (see Section 3.3 and Ref. [173]). Thus, it might be proposed that disturbances in context-related Gamma activity in schizophrenia are reflected in subsequent performance, such as abnormal reaction times. In addition, as noted in Section 3.3 muscle contractions are associated with widespread Gamma synchrony, especially during the steady hold period [10]. The reduced ability to maintain 'consistency' in grip strength (precise levels of tension) during a grip-induced muscle tension maintenance task in patients with schizophrenia [159] might also reflect the motor-related consequence of Gamma synchrony abnormalities in this disorder.

Several recent studies have directly examined Gamma activity in schizophrenia. These studies have focused primarily on Gamma power. Clementz et al. [33] reported that Gamma responses differentiated schizophrenia from normal control subjects within a P50 (paired click stimuli) paradigm, and suggested that poor suppression of P50 sensory gating responses might be due to the abnormal generation of Gamma activity in schizophrenia. A study by Kwon et al. [98] reported decreased and delayed Gamma responses to auditory click trains presented at 40 times a second in patients with schizophrenia.

Reduced Gamma activity in patients with schizophrenia has also be reported in response to target stimuli in an auditory oddball paradigm [69]. In this study, significant differences were observed between these groups in the amplitude of late Gamma (decreased in frontal and left hemisphere sites and increased in parieto-occipital and right hemisphere sites in patients with schizophrenia). A subsequent study by our group [103], in which Gamma activity was recorded simultaneously with autonomic arousal showed that reductions in early Gamma power were most pronounced in the right hemisphere in response to novel stimuli that are associated with increased phasic arousal. That is, the lack of lateralized early Gamma activity in the schizophrenia compared to control group occurred under conditions of novelty (high arousal) rather than routinization (low arousal) processing. More importantly, these sub-averaged results suggest that the lack of lateralization observed in patients with schizophrenia may result from a specific failure to achieve a dynamical balance or adaptation across trials, in response to the type of processing required. Similarly, Kissler et al. [89] reported that a lack of laterality in Gamma response in schizophrenia, possibly due to an imbalance in cerebral activations.

While the most studies of Gamma activity in schizophrenia reveal a general reduction in activity [181], studies of symptom profile reveal distinct patterns of disturbance in Gamma activity. Intense somatic hallucinations have been associated with excessively high (rather than reduced) Gamma power [11]. Our study of the three primary syndromes showed that Reality distortion was also associated with increased Gamma activity, whereas Psychomotor poverty was related to reduced Gamma [58]. These findings suggest that previous observations of reduced Gamma in schizophrenia as a group may be due to predominant contributions from subjects with symptoms of Psychomotor poverty and some aspects of Disorganization. The heterogeneous symptoms of schizophrenia may be accounted for by distinct reductions in binding (minimum cognitive activity underlying Psychomotor poverty and negative symptoms of Disorganization) or abnormal increases binding ('binding errors' or excessive information processing underlying Reality distortion and positive symptoms of Disorganization.

In our study of Gamma synchrony and clinical syndromes of schizophrenia [104], patients with schizophrenia, as a group, showed a decrease in frontal and left hemisphere Gamma synchrony, but increased posterior Gamma synchrony. Examination of the three syndromes of schizophrenia revealed markedly different and distinctive patterns of Gamma synchrony: Psychomotor poverty was associated with decreased left hemisphere synchrony and Reality distortion showed increased right hemisphere synchrony. Disorganization, on the other hand, was associated with a widespread (right hemisphere and posterior) increase in Gamma synchrony, and a delay in frontal

Gamma synchrony. These results provide support for the dimensional approach in explicating the biological dimensions of the disorder. The following sections outline possible mechanisms of abnormal (either reduced or excessive) Gamma activity in patients with schizophrenia.

5.3. The GABA system and Gamma activity in schizophrenia

As outlined in the section on proposed mechanisms of Gamma, the GABA-ergic interneuron network may have a primary role in synchronous Gamma activity. In patients with schizophrenia, both structural and functional abnormalities in GABA system have been reported. Recent postmortem tissue studies have reported that the density of axon terminals (cartridges) in chandelier neurons (which are the GABA-ergic neurons that synapse exclusively with pyramidal cells) is selectively decreased by 40% in patients with schizophrenia. This decrease could not be explained by medication effects [140,221]. Functionally, decreased $GABA_A$ receptor binding ability has also been observed in schizophrenia, particularly in the frontal cortex and in relation to the chronic or negative symptom form of schizophrenia [29,165,219].

Structural and functional GABA-ergic dysfunctions may cause decreased Gamma activity and a subsequent slowing of mental activity, which may be reflected in the widespread cognitive impairments that characterize the negative symptoms of schizophrenia. By contrast, positive schizophrenia symptoms (Reality distortion, Disorganization) may be associated with *increased* Gamma activity, as noted in the previous section on Gamma activity in schizophrenia. It has been reported that the rapid onset action of certain benzodiazepines, which are GABA-ergic agents, can alleviate positive psychotic symptoms in schizophrenia [39,220]. The efficacy of low doses of benzodiazepines (such as diazepam) has also been demonstrated with regard to treatment for the prodromal signs (disturbed sleep, increased anxiety, agitation and irritability, increased suspiciousness, and peculiar perceptual experiences) of symptom exacerbation in schizophrenia [31]. Since administration of benzodiazepines has been shown to decrease Gamma activity [80], it is plausible that the normalization (reduction) of Gamma activity is the mechanism by which these GABA-ergic agents act to reduce positive symptoms and associated cognitive disturbances in schizophrenia.

5.4. NMDA receptor hypofunction and dopamine models of schizophrenia and Gamma activity

Enhanced Gamma activity in schizophrenia (in relation to positive symptoms of Reality distortion and Disorganization) might also be considered in terms of both *N*-methyl-D-aspartate (NMDA) receptor hypofunction [133] and classical dopaminergic overactivity [36] models of schizophrenia.

Noncompetitive NMDA receptor antagonists such as phencyclidine and ketamine, produce schizophrenia-like psychosis [82]. NMDA receptors may provide an indirect modulation of Gamma activity via the action of non-NMDA receptors. Recent pharmacological studies in animals have demonstrated that administration of ketamine produces 'excessive activation' of glutamatergic neurotransmissions via non-NMDA receptors [1,5,124]. Glutamatergic neurotransmission, in turn, has been associated with enhanced Gamma activity (see Traub et al.'s model described in Section 4.1). From this model, abnormally increased Gamma activity in patients with Reality distortion and Disorganization symptoms of schizophrenia might reflect the glutamate overactivity on inhibitory interneurons (produced by hypofunction of NMDA receptors). Similarly, it is possible that the schizophrenia-like thought disorder and perceptual/cognitive impairments observed in healthy volunteers receiving ketamine [97] could be mediated by the increased glutamate transmission, and subsequent Gamma activity, produced by an hypofunction of NMDA receptors. Consistent with this interpretation, Lahti et al. [100] reported that an infusion of ketamine in schizophrenia subjects produced an increase in overt hallucinations, delusions, and thought disorder in a dose dependent manner. Blood flow was observed to be particularly increased in the anterior cingulate cortex.

Pharmacological studies have demonstrated that ketamine injection is closely associated with enhanced dopamine activity [84,183], suggesting that dopamine agents may also enhance Gamma activity. For example, Ma and Leung [113] undertook EEG recordings from the hippocampus in rats injected with two dopamine agents, phencyclidine (PCP) and methamphetamine (MAP). They observed that both PCP and (to a lesser extent) MAP produced specific increases in hippocampal Gamma activity (but not other frequency bands), and in concomitant behavioural activity, including rearing, walking, head-weaving and circling. By contrast, the dopamine D_2-receptor *antagonist,* haloperidol, was found to significantly *suppress* Gamma activity in a selective attention task [2]. These findings suggest that the modulation of Gamma activity by dopamine transmission may be an important mechanism by which antipsychotic medications (such as haloperidol) serve to lessen schizophrenia symptoms.

Taken together, the NMDA hypofunction and dopamine models of schizophrenia provide an account of how abnormal Gamma activity might be manifested in patients with schizophrenia and how the glutamatergic and dopaminergic actions of antipsychotic medications might impact on schizophrenia symptoms via the modulation of Gamma activity.

5.5. Cholinergic activity in schizophrenia and Gamma activity

As outlined in Section 4.2, in the whole brain, thalamocortical model of Gamma activity, the arousal of the

ascending reticular activating system (ARAS) makes a critical contribution to the generation of synchronous Gamma activity [169,188]. Sheer [169] referred in particular to the role of cholinergic activity in ARAS modulation of Gamma activity, which has been confirmed in recent pharmacological studies [27,49]. The extrapolation from abnormal cholinergic activity to Gamma findings in schizophrenia is difficult, because there is little information concerning the relationship between this activity and clinical profile. There is evidence that muscarinic cholinergic activity is increased in patients with positive symptoms [163], although this is controversial [136,164,197]. Nevertheless, it is noted that the use of anticholinergic agents such as scopolamine (a muscarinic receptor antagonist) produces both memory deficits and a decrease in Gamma (as well as beta), measured by EEG frequency changes [41]. One might speculate that the memory-impairing effects of anticholinergic medications in schizophrenia operate via a mechanism involving the suppression of Gamma activity. There is also some indirect evidence concerning the effects of clozapine (a partial muscarinic cholinergic agonist), improves cognitive deficiencies such as verbal fluency and graphomotor speed [3], which are most apparent in Psychomotor poverty. We might therefore speculate that the primary efficacy of clozapine may be to produce an increase in Gamma activity in negative symptoms in schizophrenia, rather than a decrease in Gamma activity in positive symptoms.

5.6. Structural abnormality in the corpus callosum and Gamma activity

As outlined in Section 4.3, the corpus callosum may play an important role in relaying synchronous brain activity at the whole brain scale [17]. In view of evidence that split brain patients often have passivity phenomena that are also observed in patients with schizophrenia, and that the corpus callosum may play an important role in inter-hemisphere communication, it might be suggested that abnormalities in the corpus callosum are an underlying factor in the pathophysiology of schizophrenia [37].

Direct investigations of corpus callosum abnormalities in schizophrenia have revealed both increases and decreases in corpus callosum size in the diagnostic group of schizophrenia [120], which could reflect distinct pathophysiological processes with regard to symptom subtype. Some studies have reported that larger total corpus callosum area is associated with earlier onset, poor outcome, and more positive symptoms in patients with schizophrenia [67,81,207], suggesting an excessive (and dysfunctional) degree of interhemispheric communication. The increase in corpus callosum size might be related to increased Gamma activity. Decreased corpus callosum size, in contrast, has been associated with negative symptoms [199,222], consistent with the view that these symptoms may involve reduced cortico-cortical communication and concomitant Gamma activity.

In summary, microscopic neuropathological studies in schizophrenia have shown that abnormal increases in Gamma activity in positive forms of schizophrenia may be modulated by NMDA and dopamine, whereas the reduction in Gamma associated with negative symptoms, may reflect the consequence of loss of function (e.g. loss of dendritic spines in pyramidal neurons) for glutamate synapses. The next section considers how the microscopic scale evidence might be integrated with connectivity models of schizophrenia, in accounting for Gamma dysfunctions in this disorder, and the relationship between these dysfunctions and symptom profile.

6. Towards an integrative neuroscience model of schizophrenia

Recent ‘functional dysconnection’ models of schizophrenia have emerged from the limitations of the classic neuropsychological lesion model in explaining the diversity of symptoms in this disorder. The functional disconnection account instead highlights aberrations that occur in the dynamical process of neuronal development [9,48,55,214]. In this section, we consider diverse ‘dysconnectivity’ models of schizophrenia [9,73,117,144,162,167], with regard to how they might be extended and integrated in relation to synchronous brain activity. The proposed integration relies upon experimental evidence that synchronized neuronal activity contributes to the selection and formation of interconnected circuits in the early developing brain [87,211], and leads to plastic changes (such as LTP and LTD) in the synapse that are thought to be crucial for learning and memory [172,204]. For instance, increases in Gamma activity are closely related to the mechanism of LTP [79]. We focus on the possibility that Gamma activity may modulate the involvement of activity-dependent synaptic changes in the development of schizophrenia symptoms.

At the synaptic scale, Meehl [118,119] has suggested that the core element of schizophrenia is a deviation in the *neuron’s synaptic control parameter*, producing an ‘integrative neural defect’ known as ‘schizotaxia’. He considered thought disorder and anhedonia to be the core symptoms produced by this defect in integrative neural function. A subsequent review of the evidence for neuronal changes in schizophrenia indicated that the nature of the core defect is a reduction in the number of synaptic contacts, including both presynaptic and dendritic markers [73]. Harrison [73] suggested that this reduction might lead to an inability to undergo long-term normal plasticity in response to age-related and environmental factors, resulting in a ‘dysconnectivity’ or ‘misconnectivity’ in the normally precise organization of neural circuitry. Morphometric evidence from Selemon and Goldman-Rakic [167,168] showed that the impoverishment of neuronal connectivity (and associated breakdowns in synaptic, dendritic and axonal organization) occurs without detectable

neuronal loss. These findings are consistent with the view that the subsequent loss of functional communication between neurons across cortical regions is due to a neurodevelopmental rather than degenerative process.

Several researchers have suggested that distinct mechanisms may underlie the microscopic neurodevelopmental aberrations associated with different subgroups of schizophrenia symptoms. It has been proposed that an increased synaptic plasticity (producing erroneous and excessive growth of synapses) may underlie the positive symptoms of schizophrenia [144,162]. This proposal is consistent with the view that abnormally enhanced Gamma activity (reflecting excessive connectivity) has been observed in positive schizophrenia syndromes. Ruppin [162] has suggested that the excessive synaptic plasticity in positive symptom schizophrenia may, in turn, be due to a high proportion of immature NMDA receptors (NR2 subunit), and a consequently reduced threshold for the occurrence of Hebbian synaptic modification (see also Ref. [45]). As outlined in Section 5.4, NMDA hypofunction may provide an indirect modulation of Gamma activity in schizophrenia. Port and Seybold [144] suggested that enhanced synaptic modification (particularly, LTP) was most apparent in the limbic system of schizophrenia subjects with positive symptoms such as delusions and hallucinations. McGlashan and Hoffman [117], on the other hand, demonstrated by computer simulation that negative symptoms of schizophrenia are produced by a severe *reduction* in synaptic connectivity, which affects overall cerebral communication. This observation is consistent with the findings of reduced Gamma activity in negative symptom syndromes of Psychomotor poverty. Structural GABA system abnormalities and decreased cholinergic ARAS modulation may underlie the deficits.

Friston [52] has proposed that temporal cooperation (i.e. effective functional connectivity) in schizophrenia is also impaired at the macroscopic scale, both between and within brain regions. In this proposal, Friston postulated a disintegration of frontal-temporal connectivity in particular, and emphasized the role of dopamine in the modulation of cortico-cortical (dis)integration. Peled [135] elaborated the model of cortico-cortical disconnection in his 'multiple constraint organization' theory of schizophrenia, in which he suggested that either disconnectivity (segregation) or overconnectivity (overintegration) between and within interconnected systems may underlie the three syndromes of schizophrenia (Psychomotor poverty—prefrontal/frontal; Reality distortion—temporo-frontal and within the temporal lobe; Disorganization—most cortico-subcortical regions).

In this final section, we speculate as to how we might integrate both synaptic and large-scale disconnection models of schizophrenia, based on the notion of use-dependent modifications of synaptic efficacy (LTP and LTD). Impaired brain development in schizophrenia may result in disturbances of the microscopic scale neuronal connections that underlie cortico-cortical and cortical-limbic communications. We suggest there may be two extreme patterns of disconnectivity in schizophrenia. One form may reflect *reduced* connectivity so that the reduction may be reflected in decrease Gamma activity, which is associated with a decreased mental 'output', and a consequent slowing of psychomotor speed and general deficit in diverse cognitive functions. Existing evidence suggests that this pattern of synaptic dysfunction is associated with negative symptoms, including those that define the Psychomotor poverty syndrome. One might further speculate that reduced connectivity in Psychomotor poverty follows a course of 'disuse' of cognitive function, a subsequent progression of LTD, and an eventual loss of synaptic connection. Aetiological studies have suggested that environmental factors, such as birth complications, may contribute to the subsequent abnormality of neurodevelopment processes [158]. The observed decrease in Gamma activity and synchrony feasibly reflects the impoverishment of synaptic connectivity.

The other extreme condition may be *increased* connectivity that produces a poor signal to noise ratio in signal transmission, and therefore an excessive degree of simultaneous information processing. This pattern may produce the disturbances of selective attention, language (disturbed association and binding errors), sensory integration and perceptual binding, that underlie positive symptoms of schizophrenia. NMDA hypofunction (due to an inherited delay in NMDA maturation and concurrent increase in dopamine) [45,162] may be the mechanism that underlies increased connectivity and enhanced Gamma activity. The Disorganization syndrome (defined specifically by thought disorder) may reflect the abnormal increase of connectivity across diffuse brain regions, given that language processing feasibly involves a high level interaction of brain networks. Consistent with the proposal, a widespread increase in Gamma phase synchrony was evident in Disorganization. Reality distortion (defined by positive symptoms of hallucinations and delusions), on the other hand, may be associated with relatively localized enhancement of synaptic connectivity. Converging evidence from neuroimaging studies suggests that the temporal lobe may be the key site of disconnectivity in this syndrome [22].

Core constellation of factors that predispose to schizophrenia depends on the relative weighting of factors. The brain's homeostasis may be reflected in different forms of synaptic disconnectivity, namely reduced in Psychomotor poverty, and increased in Reality distortion and Disorganization. Future studies of high risk and first episode schizophrenia samples are required to clarify the point at which Gamma activity is disturbed in this disorder, to elucidate its role in this developmental course.

7. Conclusion

The evidence for the functional significance of Gamma activity and dysfunctional Gamma activity in a number of

pathological conditions provides a complementary window onto the functional role of Gamma activity. Our review suggests that Gamma synchrony represents 'stimulus-specific' neural communication between hemispheres (via the corpus callosum) and between cortico-subcortical networks (via the thalamus), under strong modulation from a 'focused' or 'phasic' state of arousal. Accordingly, Gamma synchrony has been associated with a number of cognitive functions in a highly task specific manner. Excitatory synapses between pyramidal cells, such as 'chattering cells', may play a central role in this communication function of Gamma activity. Within the inhibitory interneuron network, synchronous Gamma activity may provide a 'context or clock signal' which determines when pyramidal cells can fire, on the basis of interactions between GABA-ergic interneurons and pyramidal cells [83].

This review suggests that the core abnormality of schizophrenia is one of 'functional dysconnection', produced by dysregulation of the oscillatory Gamma activity that binds distributed local networks, and manifested in different patterns of disturbance across distinct schizophrenia syndromes. Furthermore, the underlying functional disconnection may produce two opposing processes: represented by Psychomotor poverty (structural GABA abnormalities, decreased cholinergic ARAS modulation) on the one hand, and Disorganization and Reality distortion on the other (neurotransmitter dysfunction in glutamate via NMDA hypofunction and/or dopamine). Consistent with this conclusion, Psychomotor poverty was associated with decreased Gamma synchrony, whereas Reality distortion and Disorganization showed increased Gamma synchrony.

Elucidation of the exact nature of Gamma synchrony requires a substantial amount of further research. While there is little controversy concerning the role of Gamma synchrony in information processing, to date little attention has been given to the relationship between dysfunctions in Gamma synchrony and specific cognitive/behavioral disorders. With regard to schizophrenia, future studies might include different tasks to examine the modulation of Gamma in relation to a range of cognitive functions. For example, concurrent measures of Gamma synchrony and semantic priming in patients with thought disorder may shed light on the mechanism underlying the enhanced priming effect commonly observed in these subjects [185]. It is also worth noting that the association between perceptual binding dysfunction (reflected in Gamma dysfunction) and poor premobid social functioning in patients with schizophrenia (particularly patients with symptoms of Disorganization) may provide a clue to bridging the gap between cognitive/brain and social domains in research into this disorder [174].

Our review of Gamma activity in schizophrenia suggests that the core disturbance in schizophrenia is abnormal temporal integration of brain networks that are widely distributed. Disturbances in Gamma activity can explain a broad range of schizophrenia symptoms. Future studies with high risk and first episode samples may shed light on the contribution of Gamma disturbances to the developmental course of this disorder. These studies might also include a range of samples across the course of schizophrenia to examine the temporal stability of Gamma dysfunctions in schizophrenia.

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