Exploring intermediate phenotypes with EEG: Working memory dysfunction in schizophrenia

Corinna Haenschel and David Linden

Corinna Haenschel and David Linden

Wales Institute of Cognitive Neuroscience,

School of Psychology

Adeilad Brigantia

Bangor University,

Gwynedd LL57 2AS, UK.

Tel: + 44 (0) 1248 388835

Fax: + 44 (0) 1248 382599

Email: c.haenschel@bangor.ac.uk

Abstract: 135 words
Article: 10789 words
Figures: 4

1. Introduction
2. Perceptual and encoding deficits
3. Synchronous oscillatory activity during working memory
4. Abnormal neural Synchronisation in Schizophrenia and Working Memory
5. Neuropharmacological mechanisms underlying WM and oscillatory activity
6. Summary and Outlook

Abstract:

This review brings together two strands of investigation in the neuropsychology and neurophysiology of schizophrenia that have been particularly productive over the last 20 years. We review the literature on working memory deficits, particularly in the visual domain, and changes in oscillatory neural activity as measured with electroencephalography (EEG) and magnetoencephalography (MEG). We argue that recent results suggest a link between these two phenomena, in that altered oscillations underlie some of the working memory deficits. We furthermore argue that early sensory mechanisms contribute more to working memory (and other) deficits than previously thought. The final part of our review suggests links between working memory, oscillations, and their alterations in schizophrenia and the dopamine, GABA, glutamate and acetylcholine system. These links have already resulted in the development of new remediation strategies, which have some translational potential.

Introduction

Schizophrenia is a severe mental disorder affecting approximately 1% of the population with an equal gender distribution. The typical age of onset is between 16 and 35 years, but retrospective studies have shown milder cognitive and psychopathological abnormalities during a prodromal period, which lasts on average for five years before the fully fledged clinical picture. Minor neurological and behavioural abnormalities can occur even earlier [129]. Core clinical symptoms include auditory hallucinations and bizarre delusions, illogical thinking and incoherent conversation, affective flattening, poverty of speech and lack of drive. The heritability has been estimated at around 50%, and genome-wide association studies have yielded the first replicated genetic risk variants [154]. Treatment with antipsychotic agents is often effective but only brings symptomatic relief. The observation that all antipsychotic agents are dopamine receptor antagonists has led to the dopamine hypothesis of schizophrenia. However, negative symptoms and cognitive deficits do not respond well, and therefore more research is needed into their mechanisms.

Many current models ascribe schizophrenia to cortical circuit abnormalities resulting from the interplay of genetic risk factors and environmental influences [82, 134]. The models generally propose that dysfunctional coordination of distributed neural activity leads to the psychopathology and neuropsychology of schizophrenia. Cognitive deficits are often present before the onset of clinical symptoms. Working memory impairments, particularly in the visuospatial and verbal domain, are amongst the most consistent cognitive deficits in the schizophrenia prodrome. Prodromal patients perform about one standard deviation below the norm on standardised tests of working memory [193]. Furthermore, the magnitude of cognitive impairments following disease onset is associated with poor functioning and lower quality of life [72, 122]. Working memory deficits may in themselves lead to poorer outcome (for example because patients are cognitively less able to cope with psychotic symptoms) or they may reflect neurophysiological processes that lead to a more chronic course of schizophrenia. In either case, it will be important to identify the underlying neurophysiological mechanisms, and the hope is that these will inform future prevention and rehabilitation programmes.

Working memory encompasses processes that form, maintain, and manipulate short-term representations, which are crucial for comprehension, learning, reasoning and many everyday

tasks [9]. The content of WM stores can be derived from sensory (e.g. visual, auditory, tactile etc.) information or internal processes (e.g. retrieving information from long-term memory). Due to its ubiquity WM has been selected as a promising measure to improve quality of life in schizophrenia (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia, CNTRICS). WM spans a variety of processing levels (perceptual to cognitive) and is comprised of a number of component tasks. First, the information needs to be accurately perceived and encoded, second, the internal representation needs to be precisely maintained and defended against interference, and third it needs accurately to be compared with the relevant information in the probe. Additionally tasks may also involve the manipulation of items in WM (reordering of letters, spatial or object transformations) [e.g. 146].

Deficits in WM task performance can potentially arise from impairments in any of these phases irrespective of sensory modality or information source. In fact, patients with schizophrenia show deficits in fundamental processes during the early stages of sensory processing (e.g., lateral inhibition) up to deficits in higher cognitive processing in prefrontal areas. Nonetheless, many studies of WM impairments in schizophrenia have focussed on the later stages of processing (i.e. memory maintenance and retrieval) and particularly the contribution of prefrontal cortex (PFC) dysfunction. This bias is attributable both to the well documented physiological effects of schizophrenia on PFC function and Goldman-Rakic' [66] highly influential theory regarding the importance of the DLPFC in WM, which suggests that the sustained delay-period activity of neurons in PFC provides a neurophysiological substrate of the storage buffer proposed by the standard WM cognitive model [9]. Although this approach has been extremely fruitful it is becoming increasingly apparent that it cannot account for all empirical findings and that other approaches are needed [164]. Indeed, due to the traditional disciplinary divisions, executive and perceptual dysfunctions in patients with schizophrenia have largely been studied separately. In this review we argue that the study of *visual* working memory (WM) provides a natural opportunity for bridging the gap between these approaches because it inherently involves basic sensory and higher strategic processes. However, it is important to emphasise that WM deficits in schizophrenia have been reported from a wide variety of tasks that span across modalities some of the mechanisms described within the current review may apply quite generally across domains.

Neurophysiological and functional neuroimaging studies of visual WM in normal participants emphasise its dependence upon an extended network of neural areas including the prefrontal, parietal, primary and higher sensory cortices [133, 242]. For example, Pasternak and Greenlee [159] emphasise the nature of early (visual) areas contributing to WM. Importantly, areas within the WM network may be differentially associated with the various components of WM processing, but there may also be considerable interactions between areas contributing to these component processes. For example, top-down processes may contribute to the fidelity of visual representation during encoding.

In recent years there has been considerable interest in the dynamics of network interactions through analysis of functional connectivity and the time course of network activity. One proposed mechanism is that functional networks are created transiently by the synchronisation of periodic firing of groups of neurons (termed oscillatory activity) within and between cortical areas [194, 195, 225]. Oscillatory activity has been shown to occur at a wide range of temporal frequencies (3 to over 100 Hz) and associated with a variety of cognitive functions [194]. These include a number of processes likely to be critical for WM performance including visual perception, object recognition, attention and memory maintenance [98, 208].

This raises the possibility that abnormalities in synchronous oscillatory activity [121, 218] may provide a parsimonious account for many of the cognitive deficits observed in schizophrenia [163]. This is in line with the observation that the pathological process in schizophrenia does not respect regional (and functional) boundaries. For example, Selemon et al. [188] reported post-mortem changes in regions as widespread and functionally diverse as the primary visual and prefrontal cortices in schizophrenia [188]. As a consequence a number of researcher propose that core aspects of the pathophysiology of the disorder arise from a dysfunction in the integration and coordination of distributed neural activity [4, 57, 163]. This disconnection hypothesis is supported by reports of altered functional connectivity in schizophrenia during WM particularly between prefrontal and parietal areas [104, 144, 212] which indicates that perceptual deficits may in part result from impairments in reciprocal interactions between sensory and higher cortical areas [54]. Our own recent results confirm the important contribution of early visual processes to successful WM performance in healthy subjects and deficits in patients with schizophrenia [76, 77].

Nonetheless, only a few studies investigating WM impairment in schizophrenia have addressed the effects of early perceptual encoding problems or the interaction between sensory and prefrontal processing. This is surprising given the evidence (i) for patients' deficits in basic sensory processing [27, 28, 34, 94] for review), (ii) impaired encoding as a major contributor to WM deficits [120] and (iii) the link between WM and sensory processes [159]. Additionally, impairments in both perception and WM have been associated with deficits in synchronous oscillatory activity [14, 29, 76, 115, 132, 200, 219, 239] and at the neurochemical level both are associated with an imbalance between excitatory and inhibitory transmitters (glutamate and GABA) [130, 134]. The fractionation of working memory functions in the study of neurocognitive mechanisms of schizophrenia is also important for the molecular genetics approach. Working memory, like schizophrenia, has a heritability of about 50%, and some genetic variants have been implicated as risk factors for both schizophrenia and working memory dysfunction. Examples include genes for proteins involved in neurodevelopment, neurotransmission and neuroplasticity such as catechol-O-methyltransferase, dysbindin-1 and neuregulin-1. Any genetic variant, unless it affected neuronal functioning so severely as to lead to global cognitive impairment, will only act on one or several of the component processes of WM, but not affect them indiscriminately. Thus, a better understanding of the physiology of the perceptual and executive processes needed for working memory will also aid the translation of genetic research. Studies on perceptual [43] and working memory [42, 233] effects of variations in the dysbindin-1 gene are a case in point.

Figure 1 about here

The current review will argue that WM deficits in schizophrenia can be best understood by considering the interactions of distributed neural populations associated with a variety of underlying cognitive processes. A distinctive pattern of molecular changes in subpopulations

of neurotransmitter receptors and other synaptic proteins create abnormalities in cortical networks that underlie the core perceptual and cognitive deficits contributing to WM dysfunctions (Fig. 1). We will argue that synchronous oscillatory activity dynamically instantiates networks of neural activity and provides a substrate for linking WM deficits in schizophrenia across behavioural, neurophysiological, neurochemical and genetic levels. Synchronous oscillatory activity may be considered an intermediate phenotype or endophenotype, which are more closely correlated with the fundamental abnormalities underlying schizophrenia than the cognitive and behavioural symptoms themselves.

Perceptual and encoding deficits contributing to WM in schizophrenia

The earliest stages of WM involve extracting the critical information from a transient sensory input to form a more durable WM representation. This necessitates a variety of processes, collectively described under the term encoding, which if impaired can potentially contribute to impaired WM performance. Since the first evidence of WM impairments in patients with schizophrenia [158], several behavioural studies have shown impairments associated with WM encoding performance [60, 95, 120, 123], but the underlying causes remain to be fully understood.

A WM encoding deficit may be attributable to documented disturbances in basic visual processing in schizophrenia. In a number of studies Butler et al. [25, 27, 94 for review] have provided evidence for a specific impairment in the magnocellular pathway. This is a visual pathway which specialises in the processing of luminance information, while chromatic information is subserved by parvo- and koniocellular pathways [112]. Interestingly, the rapid and transient signal transmission in the magnocellular pathway makes it ideal for quick links between early visual and higher cognitive areas. In fact, recent models of visual perception posit that the efficiency and speed of everyday vision largely rely on early bottom-up/top-down interactions between occipital and prefrontal areas of the cortex which are driven by magnocellular projections from early visual areas [12, 114]. As a consequence magnocellular pathway deficits might contribute to encoding problems by causing basic difficulties in perceptual discriminability or top-down enhancement of earlier representations. Further fundamental perceptual difficulties that might affect WM have been reported by Dakin et al [34]. They showed that individuals with schizophrenia are less prone to the visual ‘contrast–contrast’ illusion (Fig. 2), which suggests that they have weaker visual contextual suppression

resulting from impaired lateral inhibition. This might result in difficulties encoding stimuli into WM due to either reduced perceptual salience or increased interference from competing stimuli. However, the consequences of these very basic effects on WM encoding have not been considered.

Figure 2 about here

Patients' WM performance may improve with increasing stimulus presentation duration or decreasing sensory discrimination thresholds, which points to an underlying encoding problem [8, 83, 123, 213]. Tek et al. [213] demonstrated that impaired perceptual processing in schizophrenia patients contributes to visuospatial working memory deficits. Patients showed impaired performance compared to controls for both an object and spatial perceptual discrimination task. The authors then adjusted the target exposure duration for participants to reach 80-90% performance on the task and used these stimuli in a working memory task where either the object or location had to be matched. After controlling for the perceptual performance patients still showed impaired performance for the spatial but not the object working memory task. These results suggest that both perceptual impairments and maintenance processes contribute to WM impairments in patients. Hartman et al. [83] asked participants to encode a set of 3 colours as part of a delayed match to sample task. They first adjusted stimulus presentation time to reach 80% correct performance level under a 0-delay condition for all participants. Patients needed longer stimulus presentation times to achieve such a performance level. However, there was no group difference in the delay conditions. These studies support the view that slowed or impaired visual processing may contribute to WM deficits, and that they can be remediated by longer presentation times or presentation at higher contrast.

Visual WM is generally considered to comprise an initial iconic representation [202], from which critical information is extracted and consolidated for longer durations [100] into a low-capacity visual short-term memory [137, 162, see 196 for an intermediate vSTM]. Visual

iconic memory is a high-capacity, but rapidly decaying (after approx. 100 ms) memory trace, more or less like a fleeting (and degraded) internal snapshot [202]. In contrast, short-term visual memory contains a more abstract representation [162] held for a brief time span and either consolidated for retention [165] or not retained. Elements seem to be transferred from this store sequentially [162], and its limited capacity of around four [137] means that many details are not encoded. Importantly, both iconic and short-term memory can be driven by low level perceptual processes as well being subject to the effects of strategic and other attentional factors [64, 120].

Results from studies investigating iconic and short-term memory in patients with schizophrenia have been mixed. Backward masking tasks have been used to investigate iconic memory formation. Presenting a mask within the first 100 ms following stimulus presentation supposedly interrupts processing within iconic memory, whereas presenting masks at longer intervals affects short-term memory. Patients typically show deficits in backward masking with mask presentations within 100 ms of stimulus presentation [20, 70, 176]. This has usually been interpreted as an indication of a slow transfer from iconic to vSTM under the assumption that stimulus duration without a mask would be unchanged [153]. Knight et al. [107] have questioned the specificity of masks used to probe iconic memory. They argue that patients may impose meaning upon random pattern masks and consequently their disruptive effects may not be restricted to iconic processing, but instead may be found in more cognitive processing of representations into short-term memory. The authors compared patients' and controls' performance for masks that were either meaningless random patterns or real world photographs (cognitive mask). Although controls showed greatest interference for the cognitive mask, patients were equally affected by both, and the magnitude of the effect was similar to that of the cognitive mask in controls. In addition, Green and Walker [71] suggested that masking interrupts stimulus classification processes and that the masking deficit in patients with schizophrenia may reflect a slowing in the classification process. Hahn et al. [81] investigated whether patients' iconic memory was subject to a faster decay rate than that of controls. The authors used a partial report procedure, where patients had to memorise up to six letters arranged in a circle with a variable delay interval until a cue appeared indicating the target. Patients showed a similar decay rate to controls and the speed of cue processing and attention shifting was also unimpaired. Consequently Hahn et al [81] concluded that although the decay of iconic memory is normal

with patients with schizophrenia, it remains to be investigated whether there is a deficit in the formation of iconic memory.

Several studies have argued that patients have a deficit in short term visual memory, but not in the iconic store [107, 168, 238]. One argument is that patients' performance is more disrupted than that of controls by masks presented at longer intervals [59, 60]. In these studies patients with schizophrenia were vulnerable to interference from mask for an abnormally prolonged duration, providing evidence for impaired WM consolidation into a more durable representation. Wynn et al. [238] used the attentional blink (AB) paradigm to dissociate masking effects at early (iconic) and later (STM) stages. They found that patients exhibited prolonged AB compared to controls, but that varying the mask strength specifically to target iconic representations had little effect on the patients' performance (no interaction between the groups). Thus the authors concluded that the abnormalities are specifically owed to deficits in short-term memory. However, the extent to which AB changes in schizophrenia are owed to perceptual masking or problems in selective attention has not been determined.

WM encoding deficits may in principle arise from impairments in attention. Specifically, attention is important for the selection and transfer of task-relevant perceptual representations into WM. In particular patients may find it difficult to selectively encode task-relevant information and gate access to WM storage [64, 136]. However, attentional modulation of WM seems to be at least partially preserved in patients. In five change detection task experiments Gold et al. [64] demonstrated that patients with schizophrenia are able to use selective attention to guide WM encoding (this included both bottom-up and top-down cues for a subset of the stimuli and the ability to select these for WM encoding). These findings do not support a generalised attentional deficit, but there may still be specific impairments, e.g. whenever tasks require a high degree of top down control and rule selection. Patients with schizophrenia are consistently impaired in cognitive control (i.e. the ability to adjust strategies flexibly in accordance with one's intentions and goals) and n-back paradigms [see for instance 65, 136 for reviews]. In a N-back task participants are typically required to monitor a series of numbers or letters and to respond whenever a stimulus occurs that is the same as the one presented 1 or 2 trials previously (1 or 2 N-back). However, these tasks conflate the different stages of WM and thus make it difficult to assess their specific affects on encoding.

In summary, patients with schizophrenia exhibit fundamental perceptual deficits as well as higher level cognitive impairments. As a consequence patients exhibit deficits in encoding sensory information into WM. It is unclear whether initial iconic representations are affected, but there is good evidence for impairment in short-term memory. Furthermore, studies have indicated that although not generally impaired, bottom-up and top-down attentional processes can modulate (both positively and negatively) the encoding process in patients. To further understand the nature of these encoding deficits it is necessary to elucidate the underlying neurophysiological mechanisms. The available evidence for both perceptual and higher level contribution to WM encoding processes suggests that they are likely to require coordinated contribution from a network of processing areas. In the next section we will review whether impaired neural synchrony (as an index of network activity) may provide a parsimonious explanation for deficits during WM encoding.

Synchronous oscillatory activity during cognitive tasks

To form networks for any cognitive task it is necessary to link together the activity of groups of neurons involved in that particular task. There is a considerable body of evidence supporting the hypothesis that functional networks may be instantiated by groups of neurons repeatedly synchronising their firing at different frequencies in time [195, 225]. This elegant proposal enables neurons to flexibly contribute to many different networks implementing a variety of cognitive tasks. Synchronous oscillatory activity can be measured in a broad range of frequencies (theta: 3-7 Hz; alpha: 8-12 Hz, beta: 12-30 Hz, gamma: >30 Hz) by examining power and phase on a trial by trial basis. The last decade has demonstrated that such measures are related to a multitude of cognitive tasks including working memory and a variety of processes which may contribute to WM, e.g. feature binding in perception, object representation and attention [e.g. 6, 23, 38, 39, 52, 53, 74, 86, 90, 97, 99, 101, 105, 116, 138, 140, 156, 157, 171, 194, 208-210, 220]. There is considerable evidence that synchronous oscillatory activity is impaired in schizophrenia and its widespread functional significance may provide a neurophysiological mechanism to help explain the range of deficits demonstrated by patients in WM tasks.

Theorists distinguish between three main forms of synchronized oscillatory activity: evoked activity, induced activity and long-range synchrony. Evoked oscillatory activity is tightly time and phase-locked to the onset of the stimulus and has been especially related to early,

stimulus-driven encoding processes, which is commonly measured by averaging the response across all trials and then examining power in a specific frequency band. It can also be measured by examining the variability in the phase of a stimulus elicited response at a specific electrode across individual trials (termed inter-trial phase locking or inter-trial coherence (ITC)).

Although induced activity is also elicited in direct response to the appearance of the stimulus its timing reflects internal network processes and is therefore less tightly linked to stimulus onset, which is commonly measured by examining the power in each frequency band for individual trials and then averaging this power across trials[1]. Finally, long-range synchrony measures phase coupling between electrodes, which reflects the degree to which activity at those sites form part of a common functional network of activity. In general long-rang synchrony is considered to depend upon coordination in the lower frequency ranges (theta, alpha, beta) [185, 226] because synchronization at lower frequencies tolerates longer conduction delays [108] necessary for forming temporal synchronised networks over large distances. All these forms of synchronised oscillatory activity provide mechanisms to integrate neural activities that instantiate the stable, salient and coherent representations required for WM even when information is no longer available in the environment [98]. Additionally, they provide mechanisms for understanding the fundamental basis of WM processes.

The relationship between synchronised oscillations at different frequencies has been proposed to explain WM capacity limitations. More specifically, Lisman and Idiart [135] used computer simulations to demonstrate that working memory capacity can in principle be explained by the number of gamma cycles (where each cycle represents an individual memory item) per theta cycle. Subsequent physiological studies provided evidence to support such a relationship between memory capacity and activity in the gamma and theta frequency range [5, 182]. Axmacher et al [5] showed that cross-frequency coupling between the phase of the theta activity and gamma band amplitude in the human hippocampus accompanies

[1] Following the recent report of Yuval-Greenberg et al ([243] S. Yuval-Greenberg, O. Tomer, A. Keren, I. Nelken, L. Deouell, Transient induced gamma-band response in EEG as a manifestation of miniature saccades., Neuron 58 (2008) 429-441. see also [142] L. Melloni, C. Schwiedrzik, M. Wibral, E. Rodriguez, W. Singer, Response to: Yuval-Greenberg et al., "Transient Induced Gamma-Band Response in EEG as a Manifestation of Miniature Saccades." Neuron 58, 429-441., Neuron 62 (2009) 8-10; author reply 10-12.), the possibility of a relationship between induced gamma band activity and microsaccades should also be considered.

WM maintenance of multiple items. Importantly, a recent physiological study has demonstrated that the order and segregation of items may be encoded by the phase of the theta wave in relation to each gamma peak [189, see 223 for comment].

A recent study has attempted to understand the dynamic functions of the entire WM network by examining synchronised oscillatory activity across the whole of the cortex during the performance of a delayed discrimination task, which enabled segregation of the distinct processes underlying WM [156]. They concluded that the maintenance of object representations in WM is implemented by interareal phase synchrony in the alpha, beta and gamma band -frequency bands within and between fronto-parietal and visual areas.

In summary, synchronized oscillatory activity provides a mechanism for dynamic formation of networks during cognitive tasks. More specifically, the interaction of oscillatory activity across different frequencies may be the missing (physiological) link between the processes underlying WM and may explain the limitations in WM capacity. In the next section we review the evidence that patients with schizophrenia exhibit impairments in oscillatory activity during a variety of cognitive tasks associated with WM.

Abnormal Neural Synchronisation in Schizophrenia and Working Memory

Recent models of cognitive deficits and a substantial body of findings from EEG studies have emphasized the potential role of neural synchrony as a pathophysiological mechanism underlying impaired perceptual [e.g. 132, 200, 219] and cognitive processes [e.g. 7, 14, 29, 76, 184], which may consequently explain deficits across processes associated with WM [79].

Evidence for early visual deficits in synchronised oscillatory activity have been provided by studies investigating steady-state response, visual binding and object representation and backward masking [see 218 for a recent review]. Visual steady-state evoked potential (SSVEP) paradigms are used to probe the ability of cortical networks to generate and maintain oscillatory activity in patients with schizophrenia. A stimulus is flickered at a specific temporal frequency and modulates neural activity in early visual areas to produce the SSVEPs. These are synchronized to the flicker in frequency and phase. Krishnan et al. [111] showed significantly reduced SSVEPs in patients with schizophrenia compared to controls at high (17 Hz, 23 Hz, and 30 Hz) but not at low flicker frequencies. This result is consistent with the large number of studies reporting that patients with

schizophrenia have a specific deficit in the magnocellular pathway [e.g. 26, 183, but see Skottun BC, Skoyles J. for an alternative view], which is associated with high temporal frequency visual responses. Furthermore, Butler et al. [25, 28] demonstrated a correlation between impaired SSVEP generation and reduced integrity of the optic radiation in patients with schizophrenia.

There is also evidence for reduced evoked oscillatory activity in response to stable non-flickering visual stimuli [200, 201, 219]. Spencer et al. [200] examined responses to illusory Kanizsa triangles, which evoked gamma frequency oscillations and a high-degree of inter-trial phase locking at electrodes associated with visual processing in healthy participants, but these responses were considerably attenuated in patients. Finally, patients show reduced evoked [239] and induced [73] gamma band oscillations in response to backward visual masking. In comparison to controls patients showed a specific deficit in evoked gamma-band activity for masked targets but not unmasked targets.

Steady-state evoked potentials can also be elicited by periodic auditory stimulation. Light et al. [132] showed impairments at 30 and 40 Hz for the auditory steady state response and demonstrated and an association with reduced working memory performance (measured with the Letter-Number Sequencing test). This suggests that deficits at early sensory-perceptual stages of processing may contribute to WM encoding difficulties across sensory modalities. A more global deficit in thalamocortical projections, perhaps mediated through dysfunction in one of the key neurotransmitter systems (glutamatergic, GABAergic, cholinergic) may thus underlie these impairments in stimulus-driven oscillations. However, reduced gamma oscillations in schizophrenia are not confined to situations where the oscillations are driven by external stimuli (and reduced power could thus be an effect of impaired sensory input channels), but also occurred with direct transcranial cortical stimulation [50].

In a recent series of studies we have directly examined the effects of WM encoding deficits in schizophrenia, which are assumed to arise in large part due to the visual processing difficulties described above. We first measured neural activity with event-related potentials (ERPs) during WM encoding of up to three abstract test shapes that were presented sequentially and followed by a probe shape, which was either drawn from the test shapes (50%) or was a non match (a visual delayed discrimination task). For control participants, but not patients, a prominent early P100 (related to stimulus encoding) increased with WM load and predicted performance (Fig. 3A). Furthermore, the P100 reduction in patients was

mirrored by reduced activation of visual areas in fMRI [77]. A reduced P100 during WM encoding has recently also been reported in participants with high schizotypy compared to low schizoptypy [109]. Together with the P100 reduction observed in relatives of patients with schizophrenia these results point to a role of such neurophysiological changes as trait markers of schizophrenia, or indeed of a psychosis spectrum [32], considering that similar effects have also been reported in bipolar disorder [240].

Figure 3 about here

One possible explanation for this P100 deficit is an increase in neuronal response variability ("cortical noise") in patients. This would lead to a higher trial to trial variation of the P100 response and thus the average would be reduced compared to controls. In a subsequent paper we examined these deficits in patients with schizophrenia in greater detail by looking at the effects of oscillatory activity in a broad frequency range. We demonstrated that patients show reduced evoked theta, alpha, and beta oscillatory activity during WM encoding [76] (Fig.3B). Importantly, in contrast to ERPs and evoked oscillatory activity, induced oscillatory activity can be used to assess directly the processes occurring during the maintenance period. In our study, induced gamma activity increased monotonically across all tested loads in controls, but reached an asymptote at load 2 in patients, reflecting a greater impact of task difficulty in patients.

Although most neurophysiological studies of cognitive tasks in patient groups focus on the mechanisms of cognitive deficit, it is of equal interest to investigate the mechanisms that support the cognitive abilities that are preserved or provide some compensation. One possibility is that patients use selective attention to enhance the salience of items to be encoded into WM, because this function is largely unaffected in patients with schizophrenia [64, 65]. Consistent with this proposal we recently demonstrated that alpha phase-locking during encoding correlates with working memory performance in patients (but not controls) [78]; activity in this frequency band has been linked to selective visual attention [214, 234].

Interestingly, physiological evidence from animal models indicates that attention can directly enhance the temporal precision with which networks of oscillatory activity are formed [117] and suggests a physiological mechanism for its putative compensatory role in the above studies. Furthermore, Lakatos et al [117] link the specific pattern of evoked and phase reset responses to the specific (parvalbumin-expressing neurons) and nonspecific (calbindin expressing neurons) thalamocortical pathways, respectively. Given that mainly the former have been related to deficits in oscillatory activity in schizophrenia [130], this may further support the notion that some subprocesses of WM are preserved (see below for details). In summary, oscillatory activity can be used to identify both the impaired components of the WM network and the compensatory mechanisms.

Several studies have now shown abnormal oscillatory activity in response to working memory and executive function in schizophrenia [14, 29]. There is also evidence from animal models of schizophrenia for reduced prefrontal-hippocampal synchronization as a substrate for impaired working memory [190].

In addition to the delayed discrimination studies described above that looked at the different component processes separately, there are a few studies that investigated the relationship between reduced oscillatory activity and tasks that require a high degree of top down control [136] such as N-back paradigms and other tasks involving executive function [14, 29, 184]. For example, Cho et al. [29] used a stimulus-response compatibility task where patients with schizophrenia showed a higher behavioral cost for incongruent compared to congruent trials. Controls, but not patients, showed increased induced gamma band activity for the incongruent condition, which correlated with performance. The authors linked this induced gamma band activity to the need to override the automatic pre-potent response. This aspect of cognitive control was impaired in the patients, which could be explained by the reduced oscillatory activity.

Basar-Eroglu et al. [14] and Schmiedt et al. [184] used an N-back task in which the stimuli were selected from three possible numbers. In addition they manipulated demands on executive function by having one number require a response with the opposing hand. In conditions requiring high cognitive control (respond with opposing hand) they found evoked frontal theta (not apparent in other conditions) and evoked gamma activity that increased with WM load in the healthy participants. In contrast, patients with schizophrenia showed

attenuated evoked theta activity and high gamma band activity but neither increased with WM load.

In addition to these studies, which focused on impairments in measures of power, there is also EEG and some MEG evidence for impairments in functional connectivity during WM tasks. Measures of functional connectivity in neural networks can be obtained through correlation analysis [160] or graph theory [15, 36, 145, 155]. Networks with "small-world properties" are characterised by a combination of local clustering of activity and a short characteristic path length as an index of global integration and cost efficiency. Patients with schizophrenia exhibited dysfunctional organization of neuronal networks during WM. Bassett et al [15] used small-world properties to demonstrate that working memory performance in the N-back task was associated with greater cost efficiency in the beta frequency band in controls than in patients with schizophrenia, indicating cortical inefficiency within these networks. In addition to reduced efficiency, De Vico Fallani et al. [36] also reported an increase in cortical synchronization in the high alpha (11-13 Hz) frequency range in a group of high functioning patients with schizophrenia who were able to perform the N-back task as well as controls, which was interpreted as a compensatory mechanism (see also Haenschel et al., 2010 for findings of relationship between alpha phase locking and performance in patients with schizophrenia).

In summary, the reviewed studies suggest a relationship between impairments in synchronized oscillatory activity and perceptual and higher-level cognitive processing contributing to WM deficits in schizophrenia. Additionally, correlations in synchronized activity and performance may also indicate the use of compensatory mechanisms to perform the task, e.g. increased alpha phase locking as an indicator of increased attention. In the next section we review the evidence for a link between impairments in oscillatory activity and neurotransmitter dysfunctions.

Neuropharmacological mechanisms underlying WM and oscillatory activity

Contemporary models understand WM dysfunctions as a result of cortical circuit abnormalities. One way of gaining insights into the neural circuits in which the WM dysfunction is embedded it to investigate the actions and interaction of neurotransmitters involved in the disorder [16, 134]. The relationship between the dopaminergic, GABAergic, glutamatergic and cholinergic systems and WM has long been established. Both animal and

human studies [170] also point to effects on WM-related brain activation. However, we only start to understand the relationship between these neurotransmitters and impaired oscillatory activity contributing to WM deficits.

Dopamine

First evidence for a relationship between neuromodulators and WM came from a study showing that dopamine depletion in the monkey DLPFC markedly impaired WM [22]. Sawaguchi & Goldman-Rakic [179] reported selective impairment of working memory (delayed saccades) after local infusion of D1, but not D2 antagonists; further studies showed that response-related but not mnemonic activation is D2 receptor-dependent [228], which provides insight into the specific pharmacology of WM subprocesses. [179, 180]. Because administration of dopaminergic drugs in humans has not consistently resulted in memory improvement, it is likely that any WM-enhancing effects of dopamine will depend on the specific receptor and postsynaptic signaling cascade and/or the homoestatic state of dopamine. Regarding the latter, it has been proposed that dopamine promotes cognitive function during hypodopaminergic states but can disrupt it during hyperdopaminergic states. Functional polymorphisms of genes related to the dopamine system may provide a non-invasive way of measuring these states. For example, the Val(108/158)Met polymorphism on the gene for catechol-O-methyltransferase (COMT), a dopamine-degrading enzyme, influences dopamine concentration. Val-carriers, who have reduced prefrontal dopamine levels, show slightly reduced performance on the n-back WM task [211] and higher noise levels in prefrontal activity, measured by ERPs [232]. These effects may interact with genetic variants that influence the concentration of postsynaptic dopamine receptors [203]. Such interactions may explain why low intrinsic dopamine levels alone are not sufficient for dopaminergic medication to enhance working memory. A recent study on emotional face working memory in Parkinson's disease found changing emotion biases (from sad to angry) after dopaminergic medication, but no overall improvement [206in revision]. Furthermore, recent evidence for epistatic effects between variants on the genes for the dopamine D2 receptor and the alpha-4 subunit of the nicotinic acetylcholine receptor on WM capacity at higher WM loads suggests an interplay of multiple neuromodulatory systems [139].

It has further been suggested that dopamine/D1 signaling modulates the cortical signal-to-noise ratio by enhancing selective inputs to both pyramidal cells and inhibitory interneurons

[67] and it has been shown that reduced D1-receptor signaling on prefrontal pyramidal cells attenuates $GABA_A$ and NMDA- receptor induced currents [45, 186, 187]. Dopamine may thus modulate frequency-dependent signal transmission and thereby adjust oscillations in cortical networks [91]. Recent evidence for the importance of dopaminergic modulation of parietal in addition to prefrontal areas [141] suggests that similar mechanisms may also apply to other parts of the cortical WM. Dopaminergic input can have inhibitory or excitatory effects on pyramidal neurons, depending on which group of dopamine receptors (D2, D3, D4 or D1, D5) are activated, and thus may reduce or enhance oscillatory activity. A study of the effects of functional polymorphisms in the dopamine transporter and D4 receptor genes has provided first EEG evidence for such divergence [40], but further receptor-specific studies are needed to determine the direction of the effects of dopamine on gamma oscillations.

Dopamine modulates glutamatergic and GABAergic transmission, and is also under the influence of the same synaptic proteins. Dystrobrevin-binding protein-1 (dysbindin-1) regulates both dopamine and glutamate release and trafficking. Genetic variability in *dysbindin-1* contributed to interindividual differences in spatial working memory in schizophrenia patients [42] and in working memory for emotional faces in healthy controls [233]. The neurophysiological effects of *dysbindin-1* variants have been investigated with both early/ perceptual ERPs (P100) [43] and indices of (prefrontal) cognitive control [48]. These findings underline the importance of looking beyond the classical neurotransmitter pathways of synthesis, release, receptor binding, transport and degradation and assess functional differences in the synaptic apparatus, which is likely to be crucial for the maintenance of oscillatory activity as well.

GABA

The work on the link between dopamine and WM was later complemented by studies showing that in monkeys' activity of gamma-aminobutyric acid (GABA) neurons in DLPFC are essential for normal WM function [169, 181]. Interestingly, this work was based on previous results showing that $GABA_A$ mediated inhibition plays an important role in the generation of spatial selectivity in the primary sensory areas of cortex. For instance, in the primary visual cortex both broadening of orientation tuning [47, 178, 191] and reduction of directional selectivity [151] have been observed with the application of bicuculline methiodide, a $GABA_A$ receptor antagonist. Rao et al. [169] showed that $GABA_A$ mediated inhibition plays an important role at the cellular level in the processes underlying spatial

working memory in the dPFC as well, improving spatial selectivity and possibly playing critical roles in the attentional control mechanisms of central executive function. Interestingly, Yoon et al. [241] showed a reduced GABA concentration in visual cortex in patients with schizophrenia. They found a correlation with GABA concentration and orientation-specific surround suppression as further evidence for impaired lateral inhibition [34] and thus a deficit in early visual processing.

GABAergic inhibition has also been functionally linked to the generation of cortical oscillations within different frequency bands [130, 134, 217, 231]. For instance, gamma band oscillations can be produced and propagated intracortically by network interactions among large groups of inhibitory and excitatory neurons. These networks consist of interconnected inhibitory interneurons that are coupled to each other and shaped into a rhythmic pattern through their mutual connections. When this network of inhibitory neurons is tonically excited by excitatory pyramidal neurons, the interneurons entrain each other and impose a synchronised inhibition across the population. When the synchronised inhibition decays, the neurons will enable and determine when a pyramidal cell to which they project will fire [231]. In summary the inhibitory network receives a steady tonic drive, which makes the network oscillate. It is thus providing a clock, which determines when pyramidal cells can fire, if they receive suprathreshold, excitatory afferent inputs (Jefferys, Traub & Whittington, 1996) and thus generates oscillation in different frequency bands.

Inhibition from subclasses of GABA neurons has been shown to be important for synchronised oscillatory activity. For instance, whereas selective activation of the interneurons containing the Ca^{2+}-binding protein parvalbumin (PV) is sufficient to generate gamma oscillations in mice in vivo [197], the multipolar GABA neurons that express both PV and calbindin may give rise to theta frequency (4–7 Hz) oscillations [19]. Muthukumaraswamy et al. [152] provided further support for a relationship between GABA concentration and gamma band frequency. The authors showed a correlation between the individual gamma frequency and the GABA concentration measured in visual cortex with MR-spectroscopy [46, 152].

PV neurons are characterized by a fast-spiking pattern and control the excitability of pyramidal neurons [58]. The release of GABA from PV neurons is controlled by the growth factor neuregulin 1 (NRG1) through its ErbB4 receptor. Selective ablation of these receptors in mice resulted in a phenotype with schizophrenia-like features, including impaired working memory, reduced pre-pulse inhibition and hyperactivity. Some of these features normalized

after treatment with diazepam, a positive allosteric modulator of the $GABA_A$ receptor. Thus, reduced GABAergic activity can lead to schizophrenia-like phenotypes in experimental animals. It is interesting that both the NRG1 and the ErbB4 gene have been suggested to be susceptibility genes for schizophrenia [13, 229].

In ErbB4 knockout mice both the number of PV-interneurons and induced gamma oscillations have been shown to be reduced [51]. Furthermore, blocking $GABA_A$ receptors alters the dynamic profile of gamma oscillatory activity to changes in the network drive [216, 231]. Genetically modified mice, in which $GABA_A$ receptor-mediated synaptic inhibition onto PV-interneurons was removed exclusively, exhibited altered theta oscillations and altered coupling between theta and gamma oscillations [235]. In contrast, gamma oscillations were not changed, indicating that mutual inhibition between PV interneurons is not necessary for the generation of oscillations in this frequency range [68 for review, 235].

However, a direct link between alterations in glutamatergic (using ketamine) onto GABAergic neurotransmission and gamma oscillatory activity has been found in animal models of schizophrenia [33, 174], demonstrating a deficit in rhythmogenesis. It has therefore been suggested that the abnormalities of GABAergic networks in schizophrenic patients may lead to reduced oscillatory activity and thus to WM deficits.

Thus it is not surprising that alterations in the GABA system have been suggested to underlie WM deficits. Several studies have suggested alterations of the GABA system in the brains of patients with schizophrenia [17, 126, 130] providing evidence of a dysfunction of inhibitory interneurons in schizophrenia (Fig. 4). Postmortem studies have shown that the 67-kiloDalton isoform of glutamic acid decarboxylase (GAD67) responsible for the synthesis of GABA is reduced in patients with schizophrenia [224]. In general, the GABAergic system is vulnerable to changes and can be modified by a variety of factors [246]. For instance, there is some evidence that GAD67 can be reduced by sensory deprivation [31, 84].

Using network simulation Vierling-Classen et al. [222] showed that increasing the time the decay time at the $GABA_A$ synapse from interneuron to pyramidal neuron can model the gamma band deficits found in schizophrenia. Increasing the decay time of the extended inhibitory postsynaptic current (IPSCs) resulted in longer inhibition and a reduced probability of pyramidal cell spiking for a longer duration. As expected from these simulations, patients showed pronounced 20 Hz (beta band), but reduced 40 Hz activity in an auditory steady state paradigm. Interestingly, these authors noted that the fidelity of the networks is not only dependent on the GABAergic interneurons, but also on the strength of the drive of the input

to the network. If the drive is too strong, it will overrule any extended inhibition. This raises the question whether a sufficiently salient or motivating stimulus may also be enough to overcome extended inhibition and enhance weak synchronization, in this instance the diminished gamma activity.

Finally, it has been proposed that WM impairments in schizophrenia might be improved with $GABA_A$ agonists [130]. The suggestion is that these drugs may alleviate WM dysfunctions by increasing the synchronization of pyramidal cell firing at gamma frequencies attributable to an enhancement of the chandelier neuron inhibition of DLPFC pyramidal neurons [131]. Indeed, there is now some evidence that MK-0777, a relatively selective agonist at $GABA_A$ receptors containing α2 subunits, improves performance in a cognitive control task and increases the power of gamma band oscillations in individuals with schizophrenia [127]. Lewis et al. note that "the adverse cognitive effects and sedation associated with the benzodiazepines currently available (which are attributable to their activity at $GABA_A$ receptors containing alpha1 and alpha5 subunits) are likely to mask the hypothesized cognitive benefits associated with alpha2 selectivity".

In addition $GABA_B$ receptor activity may also be impaired in schizophrenia. $GABA_B$ receptor agonists such as baclofen had ameliorating effects in several animal models of schizophrenia. Using a paired pulse TMS paradigm Daskalakis et al. [35] combined interleaved transcranial magnetic stimulation and EEG to measure long interval cortical inhibition, which has been suggested to be related to $GABA_B$ receptor mediated neutransmission [177]. They first reported a selective inhibition of DLPFC (middle frontal gyrus) but not of motor cortex in healthy participants and now extended this finding by reporting that patients with schizophrenia exhibit deficits in inhibition of DLPFC [49, see also 50]. In summary, both deficits in inhibition (both $GABA_A$ & $_B$) may result in a lack of precision that is necessary to ensure multiple item coding by specific phase codes and thus disrupt the functional connectivity necessary to ensure functioning of the WM network.

NMDA

Evidence for an involvement of N-methyl-d-aspartate (NMDA) receptor activity in WM has come from studies with NMDA receptor antagonists in rats [221]. A study that applied an NMDA receptor antagonist directly to the DLPFC also reported impaired working memory performance in monkeys [44]. A role for NMDA receptor activity in schizophrenia is based on the finding that NMDA antagonists, such as ketamine or Phencyclidine (PCP), mimic both

positive and negative symptoms of schizophrenia [96]. The NMDA receptor has consistently been related to the cognitive symptoms of schizophrenia. Several studies investigated the effects of acute ketamine on different aspects of working memory tasks [147]. NMDA receptor antagonists have been shown to disrupt encoding processes [30] and to have an effect on manipulation but not on maintenance in frontal-parietal regions measured with fMRI [88]. Furthermore, in an N-back study ketamine was associated with decreased scores on the one-back and two-back, but not the zero-back condition [2, 148], indicating stronger effects with higher WM loads.

NMDA receptors play a crucial role in neuronal communication. Blocking NMDA does not only interfere with excitatory transmission and synaptic plasticity, but it also reduces the drive to inhibitory interneurons [230] (see Figure 3). Several recent studies demonstrate that altered GABA neurotransmission may be secondary to abnormalities in NMDA receptor functioning [87, 246]. This is based on the finding that ketamine reduces the activity of GABA interneurons and thus disinbibits pyramidal neurons [75]. In addition to the effect of acute intake, chronic ketamine intake has been shown to result in a reduction in the number of parvalbumin-containing axoaxonic cartridges (see Fig 4). These are synaptic terminals of inhibitory chandelier cells [149]. The reduced input on parvalbumin- containing interneurons (indicating low pyramidal activity) have been suggested to not only reduce parvalbumin, but to also downregulate GAD67, the principal synthesizing enzyme for GABA [149, 246]. This can be seen as an maladaptive attempt to restore pyramidal cell activity to the correct levels [134]. Taken together, these abnormalities may interfere with the generation of oscillatory activity and may lead to the observed changes in schizophrenia.

Figure 4 about here

There is evidence both from in vivo recordings from mouse hippocampus [119] and from human EEG [89] using the auditory paired-click gating paradigm that ketamine increases gamma oscillatory activity and reduces slow frequency activity. Interestingly, Hong et al. [89] showed that the increase in gamma and decrease in delta frequency predicted

withdrawal–retardation symptoms measured using the Brief Psychiatric Rating Scale (BPRS) directly following the EEG recording.

There is however in-vitro evidence for reduced oscillatory high-frequency activity in response to ketamine as well, which fits better with the cellular models of interneuron inhibition discussed above [33, 41, 174]. Roopun et al. [174] showed that ketamine can have region-specific effects with an increase in gamma in one region and reduced or no effect in a different region. They argued that reduced power in one region may lead to phase delays between oscillating networks across the cortex and as a consequence changes in long-range synchrony may occur. In addition, this would explain a reduction in lower frequencies, but also an increase in phase variability. Any of these changes may result or contribute to WM deficits in schizophrenia. These results emphasize the importance of understanding the time course of differential contributions of areas comprising the WM-network.

Alternatively, differential effects of acute or chronic ketamine have to be taken into account when using this as a model for schizophrenia [see 89, 166]. Whereas acute ketamine augments glutamate concentration measured with MR-spectroscopy in humans [175], it is the chronic use of ketamine that results in NMDA receptor hypofunction. Indeed, glutamate concentration has been shown to be higher in patients with recent onset of schizophrenia [24] but reduced in chronic schizophrenia [215].

Chrobak et al [30] tested the effects of ketamine on the encoding, retrieval and retention of memory in a delayed-match-to-place radial water maze task and showed impairment in encoding of new location information because of an increase of proactive interference. The authors suggested that the strength of the encoded representation is weakened with ketamine administration, which is in line with previous results of hippocampal place cells [103]. They also suggest that ketamine produces changes in theta and gamma power and coherence and that it decouples the phase relationship between the two frequencies, which may contribute to reduced WM capacity found in individuals with schizophrenia.

In addition to the abnormalities of excitatory NMDA-receptor transmission on shaping the inhibitory GABAergic transmission, these functional impairments may also interact with structural abnormalities [21], such as reductions in amount of cortical neuropil, axon terminals and dentritic spines density on cortical pyramidal neurons in schizophrenia [62, 126]. Dendritic spines are the principal targets of excitatory synapses to pyramidal neurons. These abnormalities have mainly been found in deep layer 3 pyramidal neurons in

DLPFC and other areas as well [126], which suggests an involvement in primarily intracortical circuits, and thus recurrent excitation [199]. This is in line with the dysconnection theory, according to which reduced synaptic connectivity results in abnormal functional integration of neural systems [57, see 204 for a recent review]. Furthermore, Friston (1999) suggested that this would be compatible with deficient backward modulatory connections given that backward (top-down) connections are slow, modulatory (voltage-sensitive NMDA receptor dependent) and divergent (less topographically specific) [10, see review in 56]. Reductions in spine density reflecting reduced network connectivity would provide an explanation for the impairments in long-range synchrony and could contribute to deficits in WM network functioning.

Cholinergic system

Finally, there is some suggestion that abnormalities in the cholinergic system may also contribute to the WM deficits [92, 113]. The involvement of the cholinergic system in schizophrenia has been suggested by the extremely high prevalence of smoking in patients with schizophrenia and by the clinical observation that patients use smoking as self-medication for symptom relief. Nicotine transiently improves ERP indices (the repetition positivity, [see 80] of stimulus encoding and sensory memory trace formation in a auditory roving oddball paradigm [11], performance and related fMRI activity in a rapid visual information processing task [118] and performance in the N-back task [113] in healthy smokers and nonsmokers. Furthermore, in patients with schizophrenia nicotine normalizes the auditory sensory gating (P50) deficit [3] that has been specifically related to alterations in the $\alpha 7$ nicotinic receptor, improves deficits in spatial WM [124], sustained attention [125] and performance in the N-back task [92]. Jacobsen et al. [92] also demonstrated that in line with performance improvement, nicotine also enhanced activity of and functional connectivity between brain regions involved in WM using fMRI in schizophrenia.

Evidence is starting to emerge that can explain these network functions. The $\alpha 7$ nicotinic receptors are concentrated on interneurons [110] and, by enhancing the excitation of the GABAergic interneurons, they may enhance their inhibitory output [134, 227]. Indeed, nicotine increases the gamma oscillations that are dependent on interneuron function in rat hippocampal slices [198]. Furthermore, cholinergic modulation (mainly via muscarinic

receptors) has also been shown to increase and to stabilize oscillatory activity [172, 173], which is not surprising given their role in attention [37].

Interestingly, animal studies have shown that oscillatory activity can be increased by stimulation of the mesencephalic reticular formation [85, 150], which triggers increased levels of ACh in the cortex [207], and by direct cholinergic stimulation [173]. In addition, stimulation of the nucleus basalis of Meynert, the main source of cortical ACh, also induced high-frequency oscillations [143]. Moreover, stimulation of the mesopontine cholinergic nuclei in the brainstem that activate processes in thalamocortical systems also facilitated oscillatory activity [205].

Thus alterations in the cholinergic system seem to contribute to deficits in oscillatory activity. It of interest to note that Gallinat et al. [61] tested the effect of smoking in patients and found higher early gamma activity in response to targets in an auditory oddball paradigm in smokers compared to non-smokers. Given that the $\alpha 7$ nicotinic receptor functioning has been shown to be impaired in schizophrenia; it is not surprising that patients can benefit from nicotine in some domains. Both the α7 and the α4/β2 receptor subtype are involved in working memory, at least in animal models [124].

Deco & Thiele [37] speculate that acetylcholine may increase the representation of stimuli that are within the current attentional focus, and protects it against interference from competing stimuli, thus resulting in reduced distractibility. In line with this there is some evidence that ACh can increase the signal-to-noise ratio of neural activity [192], reduce spike frequency adaptation (i.e., a gradual reduction of the firing frequency) and increase the efficacy of feedforward input [63] by acting on presynaptic nicotinic receptors located on thalamocortical synapses [167].

Conclusions and future research:

Working memory dysfunction is a core feature of schizophrenia, which many previous studies have linked to prefrontal cortex (PFC) dysfunction affecting memory maintenance and retrieval. In the current review we have argued that WM performance results from a range of processes implemented across many cortical areas, and that disturbances in any of these component processes or their interactions may contribute to impaired performance. Additionally, we have claimed that patients' residual performance may result from the recruitment of additional mechanisms to perform WM tasks. The review

has focused upon visual WM as an exemplar system, and we have emphasized the importance of early perceptual and encoding processes. We gave two main reasons for this: 1. the ability to encode stimuli into WM inherently acts as a limiting factor upon WM and, thus, impairments in this process will affect performance. 2. Understanding the links between impairments in neurochemical and system level processes in sensory areas is likely to contribute to understanding abnormalities at higher levels. Current models suggest that a distinctive pattern of molecular changes in neurotransmitter systems creates abnormalities in cortical network that underlie the core perceptual and cognitive deficits contributing to WM dysfunctions [for instance 134].

The review has focused upon the role of synchronized oscillatory activity as a bridge between basic neurochemical impairments and consequent performance deficits. The current evidence indicates that dysfunctional coordination of distributed neural activity associated with a variety of perceptual and cognitive functions leads to WM deficits in schizophrenia. These dysfunctions arise from impairments in a wide range of frequencies and associated processes. Importantly, correlations between WM performance and synchronous oscillatory activity can also identify the operation of compensatory mechanisms recruited by patients to perform tasks, e.g. the correlation between alpha phase locking and patients' performance indicating increased use of attention relative to controls. Recent methodological developments will help to further clarify the dynamic interactions of perceptual and executive processing areas contributing to working memory. For instance dynamic causal modeling (DCM) can be used to measure the strength and direction of connectivity between neural ensembles [55, 161], which will reveal the time-course of these interacting processes. Furthermore, combining measures of oscillatory activity and functional and structural fMRI [244, 245] will further elucidate the relationship between reductions in grey and white matter and impairments in oscillatory activity.

As noted earlier, synchronous oscillatory activity provides not only a window into working memory dysfunctions in schizophrenia but also a method by which in vivo, in vitro and computer simulation studies can be usefully combined. Measures of neuronal synchrony have been defined for both human and animal electrophysiology and can be studied at various levels of spatial analysis, from microscopic (e.g., single-unit recordings) to macroscopic (e.g., EEG) measurements [195, 220]. As a consequence they are uniquely suited for the testing of models of schizophrenia from molecular through to behavioural levels. Additionally,

oscillatory activity provides a powerful tool for examining the effects of translational research into the treatment of cognitive dysfunction in schizophrenia by illuminating the effects on the underlying neural mechanisms a basis for the development of biologically motivated animal models.

Understanding the relationship between neurochemical processes and oscillatory activity has resulted in the development of new pharmacological models developed in vitro. For instance, there is now some evidence that improving signaling through $GABA_A$ receptors containing an α2 subunit ameliorates working memory impairments and enhances gamma band oscillations associated with the specific cognitive task employed [127]. Furthermore, the link between oscillations and neurochemistry provides an important area for extending existing models. For example, the work by Javitt and colleagues demonstrating that deficits induced by NMDA antagonists can be reversed by compounds such as d-serine or glycine transport inhibitors that stimulate NMDA function [93, 102] is likely to be reflected in changes in oscillatory activity.

Recent methodological advances offer the opportunity to understand the relationship between neurochemical and neurophysiological processes in vivo. Specifically, measures of neurotransmitter concentration using magnetic resonance spectroscopy (MRS)[2] can be combined with EEG/MEG recordings of oscillatory activity. For instance, the specific frequency of oscillatory activity (measured using MEG) has been linked to the magnitude of GABA concentration in the visual cortex [46, 152]. Furthermore, the GABA concentration in visual cortex has now also been shown to be reduced in individuals with schizophrenia [241].

The links between neurochemical and system level processing, outlined in the studies above, offer an important potential future line of research for understanding very recent advances in the development of targeted behavioural therapies for cognitive deficits. Several studies have shown that WM can be improved by extensive adaptive training [106]. Training may target strategic processes, which the participant consciously adapts, or automatically induce plastic changes in the WM-network through repetitive activation. Furthermore, WM-training has

[2] MRS relies on detecting resonance properties of the hydrogen atoms in the molecule of interest (GABA, but also glutamate (Glu), glutamine) exposed to magnetic fields in a specific area measured in an MRI-scanner.

been linked to neurochemical changes in dopamine [141]. Of particular relevance for the current review, behavioural training programmes have been shown to produce improvements in WM for patients with schizophrenia. For instance, Adcock & Vinogradov [1] developed an adaptive auditory WM training programme demonstrating improvements in both early perceptual processing (perception and speech reception) and auditory working memory capacity [see also 18 for perceptual training effects on WM]. A broader cognitive remediation therapy (CRT) has also been associated with moderate improvements in digit span [236, 237]. Understanding the neural basis of the changes induced by these therapies using oscillatory activity may facilitate the development of further therapies that more effectively target the underlying impairments. Furthermore, the evidence for compensatory mechanisms in patients may open up new strategies for therapies for example by enhancing the compensatory mechanism utilized by patients rather than trying to restore deficient processes. Finally, understanding the links between neurochemical processes, oscillatory and behavioural impairments may enable us to differentiate between the underlying bases of cognitive problems in different disorders. Although WM deficits are common to many neurological and mental disorders, as well as healthy ageing, it is unlikely that the underlying pathology is the same. This is important because it affects the likely consequences of different treatment strategies.

In summary, WM is critical for many day to day activities and is comprised of a wide range of underlying processes which are instantiated by coordinated activity across the brain. Synchronous oscillatory activity provides a basis for studying the processes and linking behaviour to underlying neurophysiological and neurochemical mechanisms. Future improvements in techniques for measuring neurochemical changes and oscillatory activity offer considerable opportunities for targeting therapies to enhance WM performance in schizophrenia and other neuropsychiatric disorders.

Acknowledgment

CH was supported by the Wales Institute of Cognitive Neuroscience, funded by the Welsh Assembly Government. We would like to thank Dr. Andrew Parton for helpful discussions.

References

[1] R. Adcock, C. Dale, M. Fisher, S. Aldebot, A. Genevsky, G. Simpson, S. Nagarajan, S. Vinogradov, When top-down meets bottom-up: auditory training enhances verbal memory in schizophrenia., Schizophr Bull 35 (2009) 1132-1141.

[2] C.M. Adler, T.E. Goldberg, A.K. Malhotra, D. Pickar, A. Breier, Effects of ketamine on thought disorder, working memory, and semantic memory in healthy volunteers, Biological psychiatry 43 (1998) 811-816.

[3] L.E. Adler, L.D. Hoffer, A. Wiser, R. Freedman, Normalization of auditory physiology by cigarette smoking in schizophrenic patients, Am J Psychiatry 150 (1993) 1856-1861.

[4] N.C. Andreasen, A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly, Arch Gen Psychiatry 56 (1999) 781-787.

[5] N. Axmacher, M. Henseler, O. Jensen, I. Weinreich, C. Elger, J. Fell, Cross-frequency coupling supports multi-item working memory in the human hippocampus., Proc Natl Acad Sci U S A 107 (2010) 3228-3233.

[6] N. Axmacher, F. Mormann, G. Fernandez, M.X. Cohen, C.E. Elger, J. Fell, Sustained neural activity patterns during working memory in the human medial temporal lobe, J Neurosci 27 (2007) 7807-7816.

[7] P. Bachman, J. Kim, C. Yee, S. Therman, M. Manninen, J. Lönnqvist, J. Kaprio, M. Huttunen, R. Näätänen, T. Cannon, Abnormally high EEG alpha synchrony during working memory maintenance in twins discordant for schizophrenia., Schizophr Res 103 (2008) 293-297.

[8] J.C. Badcock, D.R. Badcock, C. Read, A. Jablensky, Examining encoding imprecision in spatial working memory in schizophrenia, Schizophr Res 100 (2008) 144-152.

[9] A.D. Baddeley, *Working Memory* Oxford University Press, London, 1986.

[10] T. Baldeweg, A. Klugman, J. Gruzelier, S. Hirsch, Mismatch negativity potentials and cognitive impairment in schizophrenia., Schizophr Res 69 (2004) 203-217.

[11] T. Baldeweg, D. Wong, K. Stephan, Nicotinic modulation of human auditory sensory memory: Evidence from mismatch negativity potentials., Int J Psychophysiol 59 (2006) 49-58.

[12] M. Bar, A cortical mechanism for triggering top-down facilitation in visual object recognition., J Cogn Neurosci 15 (2003) 600-609.

[13] C. Barros, B. Calabrese, P. Chamero, A. Roberts, E. Korzus, K. Lloyd, L. Stowers, M. Mayford, S. Halpain, U. Müller, Impaired maturation of dendritic spines without disorganization of cortical cell layers in mice lacking NRG1/ErbB signaling in the central nervous system., Proc Natl Acad Sci U S A 106 (2009) 4507-4512.

[14] C. Basar-Eroglu, A. Brand, H. Hildebrandt, K. Karolina Kedzior, B. Mathes, C. Schmiedt, Working memory related gamma oscillations in schizophrenia patients, Int J Psychophysiol 64 (2007) 39-45.

[15] D. Bassett, E. Bullmore, A. Meyer-Lindenberg, J. Apud, D. Weinberger, R. Coppola, Cognitive fitness of cost-efficient brain functional networks., Proc Natl Acad Sci U S A 106 (2009) 11747-11752.

[16] F. Benes, Neural circuitry models of schizophrenia: is it dopamine, GABA, glutamate, or something else?, Biol Psychiatry 65 (2009) 1003-1005.

[17] F.M. Benes, S. Berretta, GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder, Neuropsychopharmacology 25 (2001) 1-27.

[18] A. Berry, T. Zanto, W. Clapp, J. Hardy, P. Delahunt, H. Mahncke, A. Gazzaley, The influence of perceptual training on working memory in older adults., PLoS One 5 (2010) e11537.

[19] M. Blatow, A. Rozov, I. Katona, S. Hormuzdi, A. Meyer, M. Whittington, A. Caputi, H. Monyer, A novel network of multipolar bursting interneurons generates theta frequency oscillations in neocortex., Neuron 38 (2003) 805-817.

[20] S.D. Braff DL, Geyer MA, Information processing dysfunctions in schizophrenia: Studies of visual backward masking, sensorimotor gating, and habituation. In: G.J. Steinhauer SR, Zubin

J (Ed.), *Handbook of Schizophrenia: Neuropsychology, Psychophysiology, and Information* Processing, Vol. 5, Elsevier, Amsterdam, 1991, pp. 303-334.

[21] C. Brenner, G. Krishnan, J. Vohs, W. Ahn, W. Hetrick, S. Morzorati, B. O'Donnell, Steady state responses: electrophysiological assessment of sensory function in schizophrenia., Schizophr Bull 35 (2009) 1065-1077.

[22] T.J. Brozoski, R.M. Brown, H.E. Rosvold, P.S. Goldman, Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey, Science 205 (1979) 929-932.

[23] N.A. Busch, C.S. Herrmann, Object-load and feature-load modulate EEG in a short-term memory task, Neuroreport 14 (2003) 1721-1724.

[24] J. Bustillo, L. Rowland, P. Mullins, R. Jung, H. Chen, C. Qualls, R. Hammond, W. Brooks, J. Lauriello, 1H-MRS at 4 tesla in minimally treated early schizophrenia., Mol Psychiatry 15 (2010) 629-636.

[25] P. Butler, D. Javitt, Early-stage visual processing deficits in schizophrenia., Curr Opin Psychiatry 18 (2005) 151-157.

[26] P. Butler, I. Schechter, V. Zemon, S. Schwartz, V. Greenstein, J. Gordon, C. Schroeder, D. Javitt, Dysfunction of early-stage visual processing in schizophrenia., Am J Psychiatry 158 (2001) 1126-1133.

[27] P. Butler, S. Silverstein, S. Dakin, Visual perception and its impairment in schizophrenia., Biol Psychiatry 64 (2008) 40-47.

[28] P. Butler, V. Zemon, I. Schechter, A. Saperstein, M. Hoptman, K. Lim, N. Revheim, G. Silipo, D. Javitt, Early-stage visual processing and cortical amplification deficits in schizophrenia., Arch Gen Psychiatry 62 (2005) 495-504.

[29] R.Y. Cho, R.O. Konecky, C.S. Carter, Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia, Proc Natl Acad Sci U S A 103 (2006) 19878-19883.

[30] J. Chrobak, J. Hinman, H. Sabolek, Revealing past memories: proactive interference and ketamine-induced memory deficits., J Neurosci 28 (2008) 4512-4520.

[31] T. Cotrufo, A. Viegi, N. Berardi, Y. Bozzi, L. Mascia, L. Maffei, Effects of neurotrophins on synaptic protein expression in the visual cortex of dark-reared rats., J Neurosci 23 (2003) 3566-3571.

[32] N. Craddock, M. O'Donovan, M. Owen, Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology., Schizophr Bull 32 (2006) 9-16.

[33] M. Cunningham, J. Hunt, S. Middleton, F. LeBeau, M. Gillies, M. Gillies, C. Davies, P. Maycox, M. Whittington, C. Racca, Region-specific reduction in entorhinal gamma oscillations and parvalbumin-immunoreactive neurons in animal models of psychiatric illness., J Neurosci 26 (2006) 2767-2776.

[34] S. Dakin, P. Carlin, D. Hemsley, Weak suppression of visual context in chronic schizophrenia., Curr Biol 15 (2005) R822-824.

[35] Z. Daskalakis, F. Farzan, M. Barr, P. Rusjan, G. Favalli, A. Levinson, P. Fitzgerald, Evaluating the relationship between long interval cortical inhibition, working memory and gamma band activity in the dorsolateral prefrontal cortex., Clin EEG Neurosci 39 (2008) 150-155.

[36] F. De Vico Fallani, A. Maglione, F. Babiloni, D. Mattia, L. Astolfi, G. Vecchiato, A. De Rinaldis, S. Salinari, E. Pachou, S. Micheloyannis, Cortical network analysis in patients affected by schizophrenia., Brain Topogr 23 (2010) 214-220.

[37] G. Deco, A. Thiele, Attention: oscillations and neuropharmacology., Eur J Neurosci 30 (2009) 347-354.

[38] M.P. Deiber, P. Missonnier, O. Bertrand, G. Gold, L. Fazio-Costa, V. Ibanez, P. Giannakopoulos, Distinction between perceptual and attentional processing in working memory tasks: a study of phase-locked and induced oscillatory brain dynamics, Journal of cognitive neuroscience 19 (2007) 158-172.

[39] T. Demiralp, Z. Bayraktaroglu, D. Lenz, S. Junge, N.A. Busch, B. Maess, M. Ergen, C.S. Herrmann, Gamma amplitudes are coupled to theta phase in human EEG during visual perception, Int J Psychophysiol (2006).

[40] T. Demiralp, C.S. Herrmann, M.E. Erdal, T. Ergenoglu, Y.H. Keskin, M. Ergen, H. Beydagi, DRD4 and DAT1 polymorphisms modulate human gamma band responses, Cereb Cortex 17 (2007) 1007-1019.

[41] H.C. Doheny, H.J. Faulkner, J.H. Gruzelier, T. Baldeweg, M.A. Whittington, Pathway-specific habituation of induced gamma oscillations in the hippocampal slice, Neuroreport 11 (2000) 2629-2633.

[42] G. Donohoe, D. Morris, S. Clarke, K. McGhee, S. Schwaiger, J. Nangle, H. Garavan, I. Robertson, M. Gill, A. Corvin, Variance in neurocognitive performance is associated with dysbindin-1 in schizophrenia: a preliminary study., Neuropsychologia 45 (2007) 454-458.

[43] G. Donohoe, D. Morris, P. De Sanctis, E. Magno, J. Montesi, H. Garavan, I. Robertson, D. Javitt, M. Gill, A. Corvin, J. Foxe, Early visual processing deficits in dysbindin-associated schizophrenia., Biol Psychiatry 63 (2008) 484-489.

[44] K. Dudkin, V. Kruchinin, I. Chueva, Neurophysiological correlates of delayed visual differentiation tasks in monkeys: the effects of the site of intracortical blockade of NMDA receptors., Neurosci Behav Physiol 31 (2001) 207-218.

[45] D. Durstewitz, J.K. Seamans, The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyltransferase genotypes and schizophrenia, Biol Psychiatry 64 (2008) 739-749.

[46] R. Edden, S. Muthukumaraswamy, T. Freeman, K. Singh, Orientation discrimination performance is predicted by GABA concentration and gamma oscillation frequency in human primary visual cortex., J Neurosci 29 (2009) 15721-15726.

[47] U. Eysel, J. Crook, H. Machemer, GABA-induced remote inactivation reveals cross-orientation inhibition in the cat striate cortex., Exp Brain Res 80 (1990) 626-630.

[48] A. Fallgatter, M. Herrmann, C. Hohoff, A. Ehlis, T. Jarczok, C. Freitag, J. Deckert, DTNBP1 (dysbindin) gene variants modulate prefrontal brain function in healthy individuals., Neuropsychopharmacology 31 (2006) 2002-2010.

[49] F. Farzan, M. Barr, W. Wong, R. Chen, P. Fitzgerald, Z. Daskalakis, Suppression of gamma-oscillations in the dorsolateral prefrontal cortex following long interval cortical inhibition: a TMS-EEG study., Neuropsychopharmacology 34 (2009) 1543-1551.

[50] F. Ferrarelli, M. Massimini, M. Peterson, B. Riedner, M. Lazar, M. Murphy, R. Huber, M. Rosanova, A. Alexander, N. Kalin, G. Tononi, Reduced evoked gamma oscillations in the frontal cortex in schizophrenia patients: a TMS/EEG study., Am J Psychiatry 165 (2008) 996-1005.

[51] A. Fisahn, J. Neddens, L. Yan, A. Buonanno, Neuregulin-1 modulates hippocampal gamma oscillations: implications for schizophrenia., Cereb Cortex 19 (2009) 612-618.

[52] P. Fries, A mechanism for cognitive dynamics: neuronal communication through neuronal coherence., Trends Cogn Sci 9 (2005) 474-480.

[53] P. Fries, J.H. Reynolds, A.E. Rorie, R. Desimone, Modulation of oscillatory neuronal synchronization by selective visual attention, Science 291 (2001) 1560-1563.

[54] K. Friston, Disconnection and cognitive dysmetria in schizophrenia, Am J Psychiatry 162 (2005) 429-432.

[55] K. Friston, L. Harrison, W. Penny, Dynamic causal modelling., Neuroimage 19 (2003) 1273-1302.

[56] K. Friston, C. Price, Dynamic representations and generative models of brain function., Brain Res Bull 54 (2001) 275-285.

[57] K.J. Friston, Schizophrenia and the disconnection hypothesis, Acta Psychiatr Scand Suppl 395 (1999) 68-79.

[58] E. Fuchs, A. Zivkovic, M. Cunningham, S. Middleton, F. Lebeau, D. Bannerman, A. Rozov, M. Whittington, R. Traub, J. Rawlins, H. Monyer, Recruitment of parvalbumin-positive interneurons determines hippocampal function and associated behavior., Neuron 53 (2007) 591-604.

[59] R.L. Fuller, S.J. Luck, E.L. Braun, B.M. Robinson, R.P. McMahon, J.M. Gold, Impaired visual working memory consolidation in schizophrenia, Neuropsychology 23 (2009) 71-80.

[60] R.L. Fuller, S.J. Luck, R.P. McMahon, J.M. Gold, Working memory consolidation is abnormally slow in schizophrenia, J Abnorm Psychol 114 (2005) 279-290.

[61] J. Gallinat, G. Winterer, C.S. Herrmann, D. Senkowski, Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing, Clin Neurophysiol 115 (2004) 1863-1874.

[62] L. Garey, W. Ong, T. Patel, M. Kanani, A. Davis, A. Mortimer, T. Barnes, S. Hirsch, Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia., J Neurol Neurosurg Psychiatry 65 (1998) 446-453.

[63] Z. Gil, B. Connors, Y. Amitai, Differential regulation of neocortical synapses by neuromodulators and activity., Neuron 19 (1997) 679-686.

[64] J. Gold, R. Fuller, B. Robinson, R. McMahon, E. Braun, S. Luck, Intact attentional control of working memory encoding in schizophrenia., J Abnorm Psychol 115 (2006) 658-673.

[65] J. Gold, B. Hahn, G. Strauss, J. Waltz, Turning it upside down: areas of preserved cognitive function in schizophrenia., Neuropsychol Rev 19 (2009) 294-311.

[66] P. Goldman-Rakic, Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates., Prog Brain Res 85 (1990) 325-335; discussion 335-326.

[67] P.S. Goldman-Rakic, E.C. Muly, 3rd, G.V. Williams, D(1) receptors in prefrontal cells and circuits, Brain Res Brain Res Rev 31 (2000) 295-301.

[68] G. Gonzalez-Burgos, T. Hashimoto, D. Lewis, Alterations of cortical GABA neurons and network oscillations in schizophrenia., Curr Psychiatry Rep 12 (2010) 335-344.

[69] J. Gordon, Testing the glutamate hypothesis of schizophrenia., Nat Neurosci 13 (2010) 2-4.

[70] M. Green, K. Nuechterlein, J. Mintz, Backward masking in schizophrenia and mania. II. Specifying the visual channels., Arch Gen Psychiatry 51 (1994) 945-951.

[71] M. Green, E. Walker, Susceptibility to backward masking in schizophrenic patients with positive or negative symptoms., Am J Psychiatry 141 (1984) 1273-1275.

[72] M.F. Green, What are the functional consequences of neurocognitive deficits in schizophrenia?, Am J Psychiatry 153 (1996) 321-330.

[73] M.F. Green, J. Mintz, D. Salveson, K.H. Nuechterlein, B. Breitmeyer, G.A. Light, D.L. Braff, Visual masking as a probe for abnormal gamma range activity in schizophrenia, Biol Psychiatry 53 (2003) 1113-1119.

[74] T. Gruber, M.M. Muller, Oscillatory brain activity dissociates between associative stimulus content in a repetition priming task in the human EEG, Cereb Cortex 15 (2005) 109-116.

[75] H. Grunze, D. Rainnie, M. Hasselmo, E. Barkai, E. Hearn, R. McCarley, R. Greene, NMDA-dependent modulation of CA1 local circuit inhibition., J Neurosci 16 (1996) 2034-2043.

[76] C. Haenschel, R. Bittner, J. Waltz, F. Haertling, M. Wibral, W. Singer, D. Linden, E. Rodriguez, Cortical oscillatory activity is critical for working memory as revealed by deficits in early-onset schizophrenia., J Neurosci 29 (2009) 9481-9489.

[77] C. Haenschel, R.A. Bittner, F. Haertling, A. Rotarska-Jagiela, K. Maurer, W. Singer, D.E. Linden, Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia: a study with event-related potentials and functional magnetic resonance imaging, Arch Gen Psychiatry 64 (2007) 1229-1240.

[78] C. Haenschel, D. Linden, R. Bittner, W. Singer, S. Hanslmayr, Alpha Phase Locking Predicts Residual Working Memory Performance in Schizophrenia., Biol Psychiatry (2010).

[79] C. Haenschel, P. Uhlhaas, W. Singer, Synchronous oscillatory activity and working memory in schizophrenia., Pharmacopsychiatry 40 (2007) 54–61.
[80] C. Haenschel, D. Vernon, P. Dwivedi, J. Gruzelier, T. Baldeweg, Event-related brain potential correlates of human auditory sensory memory-trace formation., J Neurosci 25 (2005) 10494-10501.
[81] B. Hahn, E. Kappenman, B. Robinson, R. Fuller, S. Luck, J. Gold, Iconic Decay in Schizophrenia., Schizophr Bull (2010).
[82] P. Harrison, D. Weinberger, Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence., Mol Psychiatry 10 (2005) 40-68; image 45.
[83] M. Hartman, M. Steketee, S. Silva, K. Lanning, H. McCann, Working memory and schizophrenia: evidence for slowed encoding., Schizophr Res 59 (2003) 99-113.
[84] S. Hendry, E. Jones, Activity-dependent regulation of GABA expression in the visual cortex of adult monkeys., Neuron 1 (1988) 701-712.
[85] S. Herculano-Houzel, M. Munk, S. Neuenschwander, W. Singer, Precisely synchronized oscillatory firing patterns require electroencephalographic activation., J Neurosci 19 (1999) 3992-4010.
[86] C.S. Herrmann, A. Mecklinger, E. Pfeifer, Gamma responses and ERPs in a visual classification task, Clin Neurophysiol 110 (1999) 636-642.
[87] H. Homayoun, B. Moghaddam, NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons., J Neurosci 27 (2007) 11496-11500.
[88] R.A. Honey, G.D. Honey, C. O'Loughlin, S.R. Sharar, D. Kumaran, E.T. Bullmore, D.K. Menon, T. Donovan, V.C. Lupson, R. Bisbrown-Chippendale, P.C. Fletcher, Acute ketamine administration alters the brain responses to executive demands in a verbal working memory task: an FMRI study, Neuropsychopharmacology 29 (2004) 1203-1214.
[89] L. Hong, A. Summerfelt, R. Buchanan, P. O'Donnell, G. Thaker, M. Weiler, A. Lahti, Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine., Neuropsychopharmacology 35 (2010) 632-640.
[90] M.W. Howard, D.S. Rizzuto, J.B. Caplan, J.R. Madsen, J. Lisman, R. Aschenbrenner-Scheibe, A. Schulze-Bonhage, M.J. Kahana, Gamma oscillations correlate with working memory load in humans, Cereb Cortex 13 (2003) 1369-1374.
[91] H. Ito, E. Schuman, Frequency-dependent gating of synaptic transmission and plasticity by dopamine., Front Neural Circuits 1 (2007) 1.
[92] L.K. Jacobsen, D.C. D'Souza, W.E. Mencl, K.R. Pugh, P. Skudlarski, J.H. Krystal, Nicotine effects on brain function and functional connectivity in schizophrenia, Biol Psychiatry 55 (2004) 850-858.
[93] D. Javitt, Glycine transport inhibitors for the treatment of schizophrenia: symptom and disease modification., Curr Opin Drug Discov Devel 12 (2009) 468-478.
[94] D. Javitt, When doors of perception close: bottom-up models of disrupted cognition in schizophrenia., Annu Rev Clin Psychol 5 (2009) 249-275.
[95] D.C. Javitt, R.D. Strous, S. Grochowski, W. Ritter, N. Cowan, Impaired precision, but normal retention, of auditory sensory ("echoic") memory information in schizophrenia, J Abnorm Psychol 106 (1997) 315-324.
[96] D.C. Javitt, S.R. Zukin, Recent advances in the phencyclidine model of schizophrenia, The American journal of psychiatry 148 (1991) 1301-1308.
[97] O. Jensen, J. Gelfand, J. Kounios, J.E. Lisman, Oscillations in the alpha band (9-12 Hz) increase with memory load during retention in a short-term memory task, Cereb Cortex 12 (2002) 877-882.
[98] O. Jensen, J. Kaiser, J. Lachaux, Human gamma-frequency oscillations associated with attention and memory., Trends Neurosci 30 (2007) 317-324.

[99] D. Jokisch, O. Jensen, Modulation of gamma and alpha activity during a working memory task engaging the dorsal or ventral stream, J Neurosci 27 (2007) 3244-3251.
[100] P. Jolicoeur, R. Dell'Acqua, The demonstration of short-term consolidation., Cogn Psychol 36 (1998) 138-202.
[101] J. Kaiser, B. Ripper, N. Birbaumer, W. Lutzenberger, Dynamics of gamma-band activity in human magnetoencephalogram during auditory pattern working memory, NeuroImage 20 (2003) 816-827.
[102] J. Kantrowitz, D. Javitt, N-methyl-d-aspartate (NMDA) receptor dysfunction or dysregulation: The final common pathway on the road to schizophrenia?, Brain Res Bull (2010).
[103] C. Kentros, E. Hargreaves, R. Hawkins, E. Kandel, M. Shapiro, R. Muller, Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade., Science 280 (1998) 2121-2126.
[104] J. Kim, J. Kwon, H. Park, T. Youn, D. Kang, M. Kim, D. Lee, M. Lee, Functional disconnection between the prefrontal and parietal cortices during working memory processing in schizophrenia: a[15(O)]H2O PET study., Am J Psychiatry 160 (2003) 919-923.
[105] W. Klimesch, B. Schack, M. Schabus, M. Doppelmayr, W. Gruber, P. Sauseng, Phase-locked alpha and theta oscillations generate the P1-N1 complex and are related to memory performance, Brain Res Cogn Brain Res 19 (2004) 302-316.
[106] T. Klingberg, Training and plasticity of working memory., Trends Cogn Sci 14 (2010) 317-324.
[107] R. Knight, D. Elliott, E. Freedman, Short-term visual memory in schizophrenics., J Abnorm Psychol 94 (1985) 427-442.
[108] N. Kopell, G.B. Ermentrout, M.A. Whittington, R.D. Traub, Gamma rhythms and beta rhythms have different synchronization properties, Proceedings of the National Academy of Sciences of the United States of America 97 (2000) 1867-1872.
[109] I. Koychev, W. El-Deredy, C. Haenschel, J. Deakin, Visual information processing deficits as biomarkers of vulnerability to schizophrenia: an event-related potential study in schizotypy., Neuropsychologia 48 (2010) 2205-2214.
[110] I. Krenz, D. Kalkan, A. Wevers, R. de Vos, E. Steur, J. Lindstrom, K. Pilz, S. Nowacki, U. Schütz, N. Moser, B. Witter, H. Schröder, Parvalbumin-containing interneurons of the human cerebral cortex express nicotinic acetylcholine receptor proteins., J Chem Neuroanat 21 (2001) 239-246.
[111] G.P. Krishnan, J.L. Vohs, W.P. Hetrick, C.A. Carroll, A. Shekhar, M.A. Bockbrader, B.F. O'Donnell, Steady state visual evoked potential abnormalities in schizophrenia, Clin Neurophysiol 116 (2005) 614-624.
[112] J. Kulikowski, Neural basis of fundamental filters in vision Vol. 334, NATO Science Series, 2003, pp. 3-68.
[113] V. Kumari, J. Gray, D. ffytche, M. Mitterschiffthaler, M. Das, E. Zachariah, G. Vythelingum, S. Williams, A. Simmons, T. Sharma, Cognitive effects of nicotine in humans: an fMRI study., Neuroimage 19 (2003) 1002-1013.
[114] K. Kveraga, J. Boshyan, M. Bar, Magnocellular projections as the trigger of top-down facilitation in recognition., J Neurosci 27 (2007) 13232-13240.
[115] J.S. Kwon, B.F. O'Donnell, G.V. Wallenstein, R.W. Greene, Y. Hirayasu, P.G. Nestor, M.E. Hasselmo, G.F. Potts, M.E. Shenton, R.W. McCarley, Gamma frequency-range abnormalities to auditory stimulation in schizophrenia, Arch Gen Psychiatry 56 (1999) 1001-1005.
[116] J.P. Lachaux, N. George, C. Tallon-Baudry, J. Martinerie, L. Hugueville, L. Minotti, P. Kahane, B. Renault, The many faces of the gamma band response to complex visual stimuli, Neuroimage 25 (2005) 491-501.
[117] P. Lakatos, M. O'Connell, A. Barczak, A. Mills, D. Javitt, C. Schroeder, The leading sense: supramodal control of neurophysiological context by attention., Neuron 64 (2009) 419-430.

[118] N. Lawrence, T. Ross, E. Stein, Cognitive mechanisms of nicotine on visual attention., Neuron 36 (2002) 539-548.
[119] M. Lazarewicz, R. Ehrlichman, C. Maxwell, M. Gandal, L. Finkel, S. Siegel, Ketamine modulates theta and gamma oscillations., J Cogn Neurosci 22 (2010) 1452-1464.
[120] J. Lee, S. Park, Working memory impairments in schizophrenia: a meta-analysis, J Abnorm Psychol 114 (2005) 599-611.
[121] K.H. Lee, L.M. Williams, M. Breakspear, E. Gordon, Synchronous gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia, Brain Res Brain Res Rev 41 (2003) 57-78.
[122] V. Leeson, T. Barnes, S. Hutton, M. Ron, E. Joyce, IQ as a predictor of functional outcome in schizophrenia: a longitudinal, four-year study of first-episode psychosis., Schizophr Res 107 (2009) 55-60.
[123] T. Lencz, R.M. Bilder, E. Turkel, R.S. Goldman, D. Robinson, J.M. Kane, J.A. Lieberman, Impairments in perceptual competency and maintenance on a visual delayed match-to-sample test in first-episode schizophrenia, Arch Gen Psychiatry 60 (2003) 238-243.
[124] E. Levin, Nicotinic receptor subtypes and cognitive function., J Neurobiol 53 (2002) 633-640.
[125] E. Levin, W. Wilson, J. Rose, J. McEvoy, Nicotine-haloperidol interactions and cognitive performance in schizophrenics., Neuropsychopharmacology 15 (1996) 429-436.
[126] D. Lewis, Neuroplasticity of excitatory and inhibitory cortical circuits in schizophrenia., Dialogues Clin Neurosci 11 (2009) 269-280.
[127] D. Lewis, R. Cho, C. Carter, K. Eklund, S. Forster, M. Kelly, D. Montrose, Subunit-selective modulation of GABA type A receptor neurotransmission and cognition in schizophrenia., Am J Psychiatry 165 (2008) 1585-1593.
[128] D. Lewis, G. González-Burgos, Neuroplasticity of neocortical circuits in schizophrenia., Neuropsychopharmacology 33 (2008) 141-165.
[129] D. Lewis, P. Levitt, Schizophrenia as a disorder of neurodevelopment., Annu Rev Neurosci 25 (2002) 409-432.
[130] D.A. Lewis, T. Hashimoto, D.W. Volk, Cortical inhibitory neurons and schizophrenia, Nat Rev Neurosci 6 (2005) 312-324.
[131] D.A. Lewis, D.W. Volk, T. Hashimoto, Selective alterations in prefrontal cortical GABA neurotransmission in schizophrenia: a novel target for the treatment of working memory dysfunction, Psychopharmacology 174 (2004) 143-150.
[132] G. Light, J. Hsu, M. Hsieh, K. Meyer-Gomes, J. Sprock, N. Swerdlow, D. Braff, Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients., Biol Psychiatry 60 (2006) 1231-1240.
[133] D.E. Linden, R.A. Bittner, L. Muckli, J.A. Waltz, N. Kriegeskorte, R. Goebel, W. Singer, M.H. Munk, Cortical capacity constraints for visual working memory: dissociation of fMRI load effects in a fronto-parietal network, Neuroimage 20 (2003) 1518-1530.
[134] J. Lisman, J. Coyle, R. Green, D. Javitt, F. Benes, S. Heckers, A. Grace, Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia., Trends Neurosci 31 (2008) 234-242.
[135] J.E. Lisman, M.A. Idiart, Storage of 7 +/- 2 short-term memories in oscillatory subcycles, Science (New York, N.Y 267 (1995) 1512-1515.
[136] S. Luck, J. Gold, The construct of attention in schizophrenia., Biol Psychiatry 64 (2008) 34-39.
[137] S. Luck, E. Vogel, The capacity of visual working memory for features and conjunctions., Nature 390 (1997) 279-281.
[138] N. Mainy, P. Kahane, L. Minotti, D. Hoffmann, O. Bertrand, J.P. Lachaux, Neural correlates of consolidation in working memory, Hum Brain Mapp 28 (2007) 183-193.

[139] S. Markett, C. Montag, M. Reuter, The association between dopamine DRD2 polymorphisms and working memory capacity is modulated by a functional polymorphism on the nicotinic receptor gene CHRNA4., J Cogn Neurosci 22 (2010) 1944-1954.
[140] J. Martinovic, T. Gruber, M. Müller, Coding of visual object features and feature conjunctions in the human brain., PLoS One 3 (2008) e3781.
[141] F. McNab, A. Varrone, L. Farde, A. Jucaite, P. Bystritsky, H. Forssberg, T. Klingberg, Changes in cortical dopamine D1 receptor binding associated with cognitive training, Science (New York, N.Y 323 (2009) 800-802.
[142] L. Melloni, C. Schwiedrzik, M. Wibral, E. Rodriguez, W. Singer, Response to: Yuval-Greenberg et al., "Transient Induced Gamma-Band Response in EEG as a Manifestation of Miniature Saccades." Neuron 58, 429-441., Neuron 62 (2009) 8-10; author reply 10-12.
[143] R. Metherate, C. Cox, J. Ashe, Cellular bases of neocortical activation: modulation of neural oscillations by the nucleus basalis and endogenous acetylcholine., J Neurosci 12 (1992) 4701-4711.
[144] A. Meyer-Lindenberg, J. Poline, P. Kohn, J. Holt, M. Egan, D. Weinberger, K. Berman, Evidence for abnormal cortical functional connectivity during working memory in schizophrenia., Am J Psychiatry 158 (2001) 1809-1817.
[145] S. Micheloyannis, E. Pachou, C. Stam, M. Breakspear, P. Bitsios, M. Vourkas, S. Erimaki, M. Zervakis, Small-world networks and disturbed functional connectivity in schizophrenia., Schizophr Res 87 (2006) 60-66.
[146] H. Mohr, D. Linden, Separation of the systems for color and spatial manipulation in working memory revealed by a dual-task procedure., J Cogn Neurosci 17 (2005) 355-366.
[147] C.J. Morgan, H.V. Curran, Acute and chronic effects of ketamine upon human memory: a review, Psychopharmacology 188 (2006) 408-424.
[148] C.J. Morgan, A. Mofeez, B. Brandner, L. Bromley, H.V. Curran, Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers, Neuropsychopharmacology 29 (2004) 208-218.
[149] B. Morrow, J. Elsworth, R. Roth, Repeated phencyclidine in monkeys results in loss of parvalbumin-containing axo-axonic projections in the prefrontal cortex., Psychopharmacology (Berl) 192 (2007) 283-290.
[150] M. Munk, P. Roelfsema, P. König, A. Engel, W. Singer, Role of reticular activation in the modulation of intracortical synchronization., Science 272 (1996) 271-274.
[151] A. Murthy, A. Humphrey, Inhibitory contributions to spatiotemporal receptive-field structure and direction selectivity in simple cells of cat area 17., J Neurophysiol 81 (1999) 1212-1224.
[152] S. Muthukumaraswamy, R. Edden, D. Jones, J. Swettenham, K. Singh, Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans., Proc Natl Acad Sci U S A 106 (2009) 8356-8361.
[153] K. Nuechterlein, M. Dawson, Information processing and attentional functioning in the developmental course of schizophrenic disorders., Schizophr Bull 10 (1984) 160-203.
[154] M. Owen, N. Craddock, M. O'Donovan, Suggestion of roles for both common and rare risk variants in genome-wide studies of schizophrenia., Arch Gen Psychiatry 67 (2010) 667-673.
[155] E. Pachou, M. Vourkas, P. Simos, D. Smit, C. Stam, V. Tsirka, S. Micheloyannis, Working memory in schizophrenia: an EEG study using power spectrum and coherence analysis to estimate cortical activation and network behavior., Brain Topogr 21 (2008) 128-137.
[156] J. Palva, S. Monto, S. Kulashekhar, S. Palva, Neuronal synchrony reveals working memory networks and predicts individual memory capacity., Proc Natl Acad Sci U S A 107 (2010) 7580-7585.
[157] C. Pantev, Evoked and induced gamma-band activity of the human cortex, Brain Topogr 7 (1995) 321-330.

[158] S. Park, P. Holzman, Schizophrenics show spatial working memory deficits., Arch Gen Psychiatry 49 (1992) 975-982.
[159] T. Pasternak, M. Greenlee, Working memory in primate sensory systems., Nat Rev Neurosci 6 (2005) 97-107.
[160] A. Peled, A. Geva, W. Kremen, H. Blankfeld, R. Esfandiarfard, T. Nordahl, Functional connectivity and working memory in schizophrenia: an EEG study., Int J Neurosci 106 (2001) 47-61.
[161] W. Penny, V. Litvak, L. Fuentemilla, E. Duzel, K. Friston, Dynamic Causal Models for phase coupling., J Neurosci Methods 183 (2009) 19-30.
[162] W.A. Phillips, On the distinction between sensory storage and short-term visual memory., Perception and Psychophysics 16 (1974) 283-290.
[163] W.A. Phillips, S.M. Silverstein, Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia, Behav Brain Sci 26 (2003) 65-82; discussion 82-137.
[164] B. Postle, Working memory as an emergent property of the mind and brain., Neuroscience 139 (2006) 23-38.
[165] M. Potter, Short-term conceptual memory for pictures., J Exp Psychol Hum Learn 2 (1976) 509-522.
[166] J. Pratt, C. Winchester, A. Egerton, S. Cochran, B. Morris, Modelling prefrontal cortex deficits in schizophrenia: implications for treatment., Br J Pharmacol 153 Suppl 1 (2008) S465-470.
[167] G. Prusky, C. Shaw, M. Cynader, Nicotine receptors are located on lateral geniculate nucleus terminals in cat visual cortex., Brain Res 412 (1987) 131-138.
[168] E. Rabinowicz, L. Opler, D. Owen, R. Knight, Dot Enumeration Perceptual Organization Task (DEPOT): evidence for a short-term visual memory deficit in schizophrenia., J Abnorm Psychol 105 (1996) 336-348.
[169] S. Rao, G. Williams, P. Goldman-Rakic, Destruction and creation of spatial tuning by disinhibition: GABA(A) blockade of prefrontal cortical neurons engaged by working memory., J Neurosci 20 (2000) 485-494.
[170] T. Robbins, A. Arnsten, The neuropsychopharmacology of fronto-executive function: monoaminergic modulation., Annu Rev Neurosci 32 (2009) 267-287.
[171] E. Rodriguez, N. George, J.P. Lachaux, J. Martinerie, B. Renault, F.J. Varela, Perception's shadow: long-distance synchronization of human brain activity, Nature 397 (1999) 430-433.
[172] R. Rodriguez, U. Kallenbach, W. Singer, M. Munk, Stabilization of visual responses through cholinergic activation., Neuroscience 165 (2010) 944-954.
[173] R. Rodriguez, U. Kallenbach, W. Singer, M.H. Munk, Short- and long-term effects of cholinergic modulation on gamma oscillations and response synchronization in the visual cortex, J Neurosci 24 (2004) 10369-10378.
[174] A. Roopun, M. Cunningham, C. Racca, K. Alter, R. Traub, M. Whittington, Region-specific changes in gamma and beta2 rhythms in NMDA receptor dysfunction models of schizophrenia., Schizophr Bull 34 (2008) 962-973.
[175] L. Rowland, J. Bustillo, P. Mullins, R. Jung, R. Lenroot, E. Landgraf, R. Barrow, R. Yeo, J. Lauriello, W. Brooks, Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: a 4-T proton MRS study., Am J Psychiatry 162 (2005) 394-396.
[176] D. Saccuzzo, D. Braff, Early information processing deficit in schizophrenia. New findings using schizophrenic subgroups and manic control subjects., Arch Gen Psychiatry 38 (1981) 175-179.
[177] T. Sanger, R. Garg, R. Chen, Interactions between two different inhibitory systems in the human motor cortex., J Physiol 530 (2001) 307-317.
[178] H. Sato, N. Katsuyama, H. Tamura, Y. Hata, T. Tsumoto, Mechanisms underlying orientation selectivity of neurons in the primary visual cortex of the macaque., J Physiol 494 (Pt 3) (1996) 757-771.

[179] T. Sawaguchi, P.S. Goldman-Rakic, D1 dopamine receptors in prefrontal cortex: involvement in working memory, Science 251 (1991) 947-950.
[180] T. Sawaguchi, P.S. Goldman-Rakic, The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task, J Neurophysiol 71 (1994) 515-528.
[181] T. Sawaguchi, M. Matsumura, K. Kubota, Delayed response deficits produced by local injection of bicuculline into the dorsolateral prefrontal cortex in Japanese macaque monkeys., Exp Brain Res 75 (1989) 457-469.
[182] B. Schack, N. Vath, H. Petsche, H. Geissler, E. Möller, Phase-coupling of theta-gamma EEG rhythms during short-term memory processing., Int J Psychophysiol 44 (2002) 143-163.
[183] I. Schechter, P. Butler, G. Silipo, V. Zemon, D. Javitt, Magnocellular and parvocellular contributions to backward masking dysfunction in schizophrenia., Schizophr Res 64 (2003) 91-101.
[184] C. Schmiedt, A. Brand, H. Hildebrandt, C. Basar-Eroglu, Event-related theta oscillations during working memory tasks in patients with schizophrenia and healthy controls, Brain Res Cogn Brain Res 25 (2005) 936-947.
[185] A. Schnitzler, J. Gross, Normal and pathological oscillatory communication in the brain, Nature reviews 6 (2005) 285-296.
[186] J.K. Seamans, D. Durstewitz, B.R. Christie, C.F. Stevens, T.J. Sejnowski, Dopamine D1/D5 receptor modulation of excitatory synaptic inputs to layer V prefrontal cortex neurons, Proc Natl Acad Sci U S A 98 (2001) 301-306.
[187] J.K. Seamans, N. Gorelova, D. Durstewitz, C.R. Yang, Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons, J Neurosci 21 (2001) 3628-3638.
[188] L. Selemon, G. Rajkowska, P. Goldman-Rakic, Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17., Arch Gen Psychiatry 52 (1995) 805-818; discussion 819-820.
[189] M. Siegel, M. Warden, E. Miller, Phase-dependent neuronal coding of objects in short-term memory., Proc Natl Acad Sci U S A 106 (2009) 21341-21346.
[190] T. Sigurdsson, K. Stark, M. Karayiorgou, J. Gogos, J. Gordon, Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia., Nature 464 (2010) 763-767.
[191] A. Sillito, Functional considerations of the operation of GABAergic inhibitory processes in the visual cortex., Cerebral cortex, Plenum, New York, 1984.
[192] A. Sillito, J. Kemp, Cholinergic modulation of the functional organization of the cat visual cortex., Brain Res 289 (1983) 143-155.
[193] A. Simon, K. Cattapan-Ludewig, S. Zmilacher, D. Arbach, K. Gruber, D. Dvorsky, B. Roth, E. Isler, A. Zimmer, D. Umbricht, Cognitive functioning in the schizophrenia prodrome., Schizophr Bull 33 (2007) 761-771.
[194] W. Singer, Neuronal synchrony: a versatile code for the definition of relations?, Neuron 24 (1999) 49-65, 111-125.
[195] W. Singer, C.M. Gray, Visual feature integration and the temporal correlation hypothesis, Annu Rev Neurosci 18 (1995) 555-586.
[196] I. Sligte, H. Scholte, V. Lamme, Are there multiple visual short-term memory stores?, PLoS One 3 (2008) e1699.
[197] V. Sohal, F. Zhang, O. Yizhar, K. Deisseroth, Parvalbumin neurons and gamma rhythms enhance cortical circuit performance., Nature 459 (2009) 698-702.
[198] C. Song, T. Murray, R. Kimura, M. Wakui, K. Ellsworth, S. Javedan, S. Marxer-Miller, R. Lukas, J. Wu, Role of alpha7-nicotinic acetylcholine receptors in tetanic stimulation-induced gamma oscillations in rat hippocampal slices., Neuropharmacology 48 (2005) 869-880.

[199] K. Spencer, The functional consequences of cortical circuit abnormalities on gamma oscillations in schizophrenia: insights from computational modeling., Front Hum Neurosci 3 (2009) 33.
[200] K.M. Spencer, P.G. Nestor, M.A. Niznikiewicz, D.F. Salisbury, M.E. Shenton, R.W. McCarley, Abnormal neural synchrony in schizophrenia, J Neurosci 23 (2003) 7407-7411.
[201] K.M. Spencer, P.G. Nestor, R. Perlmutter, M.A. Niznikiewicz, M.C. Klump, M. Frumin, M.E. Shenton, R.W. McCarley, Neural synchrony indexes disordered perception and cognition in schizophrenia, Proc Natl Acad Sci U S A 101 (2004) 17288-17293.
[202] G. Sperling, The information available in brief visual presentations., *Psychological Monographs* 74 (1960) 1–29.
[203] C. Stelzel, U. Basten, C. Montag, M. Reuter, C. Fiebach, Effects of dopamine-related gene-gene interactions on working memory component processes., Eur J Neurosci 29 (2009) 1056-1063.
[204] K. Stephan, K. Friston, C. Frith, Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring., Schizophr Bull 35 (2009) 509-527.
[205] M. Steriade, R. Dossi, D. Paré, G. Oakson, Fast oscillations (20-40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat., Proc Natl Acad Sci U S A 88 (1991) 4396-4400.
[206] L. Subramanian, J. Hindle, M. Jackson, D. Linden, Dopamine Boosts Memory for Angry Faces in Parkinson's Disease, in revision.
[207] J. Szerb, Cortical acetylcholine release and electroencephalographic arousal., J Physiol 192 (1967) 329-343.
[208] C. Tallon-Baudry, O. Bertrand, Oscillatory gamma activity in humans and its role in object representation, Trends Cogn Sci 3 (1999) 151-162.
[209] C. Tallon-Baudry, O. Bertrand, F. Peronnet, J. Pernier, Induced gamma-band activity during the delay of a visual short-term memory task in humans, J Neurosci 18 (1998) 4244-4254.
[210] C. Tallon-Baudry, S. Mandon, W.A. Freiwald, A.K. Kreiter, Oscillatory synchrony in the monkey temporal lobe correlates with performance in a visual short-term memory task, Cereb Cortex 14 (2004) 713-720.
[211] H. Tan, J. Callicott, D. Weinberger, Prefrontal cognitive systems in schizophrenia: towards human genetic brain mechanisms., Cogn Neuropsychiatry 14 (2009) 277-298.
[212] H. Tan, S. Sust, J. Buckholtz, V. Mattay, A. Meyer-Lindenberg, M. Egan, D. Weinberger, J. Callicott, Dysfunctional prefrontal regional specialization and compensation in schizophrenia., Am J Psychiatry 163 (2006) 1969-1977.
[213] C. Tek, J. Gold, T. Blaxton, C. Wilk, R.P. McMahon, R.W. Buchanan, Visual perceptual and working memory impairments in schizophrenia, Arch Gen Psychiatry 59 (2002) 146-153.
[214] G. Thut, A. Nietzel, S. Brandt, A. Pascual-Leone, Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection., J Neurosci 26 (2006) 9494-9502.
[215] J. Théberge, Y. Al-Semaan, P. Williamson, R. Menon, R. Neufeld, N. Rajakumar, B. Schaefer, M. Densmore, D. Drost, Glutamate and glutamine in the anterior cingulate and thalamus of medicated patients with chronic schizophrenia and healthy comparison subjects measured with 4.0-T proton MRS., Am J Psychiatry 160 (2003) 2231-2233.
[216] S.K. Towers, T. Gloveli, R.D. Traub, J.E. Driver, D. Engel, R. Fradley, T.W. Rosahl, K. Maubach, E.H. Buhl, M.A. Whittington, Alpha 5 subunit-containing GABAA receptors affect the dynamic range of mouse hippocampal kainate-induced gamma frequency oscillations in vitro, The Journal of physiology 559 (2004) 721-728.
[217] J.J. Traub RD, Whittington MA., Fast oscillations in cortical circuits, MIT press., Cambridge, MA, 1999.

[218] P. Uhlhaas, C. Haenschel, D. Nikolić, W. Singer, The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia., Schizophr Bull 34 (2008) 927-943.
[219] P.J. Uhlhaas, D.E. Linden, W. Singer, C. Haenschel, M. Lindner, K. Maurer, E. Rodriguez, Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia, J Neurosci 26 (2006) 8168-8175.
[220] F. Varela, J.P. Lachaux, E. Rodriguez, J. Martinerie, The brainweb: phase synchronization and large-scale integration, Nature reviews 2 (2001) 229-239.
[221] A. Verma, B. Moghaddam, NMDA receptor antagonists impair prefrontal cortex function as assessed via spatial delayed alternation performance in rats: modulation by dopamine., J Neurosci 16 (1996) 373-379.
[222] D. Vierling-Claassen, P. Siekmeier, S. Stufflebeam, N. Kopell, Modeling GABA alterations in schizophrenia: a link between impaired inhibition and altered gamma and beta range auditory entrainment., J Neurophysiol 99 (2008) 2656-2671.
[223] E. Vogel, K. Fukuda, In mind and out of phase., Proc Natl Acad Sci U S A 106 (2009) 21017-21018.
[224] D. Volk, M. Austin, J. Pierri, A. Sampson, D. Lewis, 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 (2000) 237-245.
[225] C. *von der Malsburg*, The correlation theory of brain function., MPI biophysical chemistry, Internal report, 1981, pp. 81-82.
[226] A. von Stein, J. Sarnthein, Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization, Int J Psychophysiol 38 (2000) 301-313.
[227] N. Wanaverbecq, A. Semyanov, I. Pavlov, M. Walker, D. Kullmann, Cholinergic axons modulate GABAergic signaling among hippocampal interneurons via postsynaptic alpha 7 nicotinic receptors., J Neurosci 27 (2007) 5683-5693.
[228] M. Wang, S. Vijayraghavan, P. Goldman-Rakic, Selective D2 receptor actions on the functional circuitry of working memory., Science 303 (2004) 853-856.
[229] L. Wen, Y. Lu, X. Zhu, X. Li, R. Woo, Y. Chen, D. Yin, C. Lai, A.J. Terry, A. Vazdarjanova, W. Xiong, L. Mei, Neuregulin 1 regulates pyramidal neuron activity via ErbB4 in parvalbumin-positive interneurons., Proc Natl Acad Sci U S A 107 (2010) 1211-1216.
[230] M.A. Whittington, H.J. Faulkner, H.C. Doheny, R.D. Traub, Neuronal fast oscillations as a target site for psychoactive drugs, Pharmacology & therapeutics 86 (2000) 171-190.
[231] M.A. Whittington, R.D. Traub, J.G. Jefferys, Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation, Nature 373 (1995) 612-615.
[232] G. Winterer, M.F. Egan, B.S. Kolachana, T.E. Goldberg, R. Coppola, D.R. Weinberger, Prefrontal electrophysiologic "noise" and catechol-O-methyltransferase genotype in schizophrenia, Biol Psychiatry 60 (2006) 578-584.
[233] C. Wolf, M. Jackson, C. Kissling, J. Thome, D. Linden, Dysbindin-1 genotype effects on emotional working memory., Mol Psychiatry (2009).
[234] M. Worden, J. Foxe, N. Wang, G. Simpson, Anticipatory biasing of visuospatial attention indexed by retinotopically specific alpha-band electroencephalography increases over occipital cortex., J Neurosci 20 (2000) RC63.
[235] P. Wulff, A. Ponomarenko, M. Bartos, T. Korotkova, E. Fuchs, F. Bähner, M. Both, A. Tort, N. Kopell, W. Wisden, H. Monyer, Hippocampal theta rhythm and its coupling with gamma oscillations require fast inhibition onto parvalbumin-positive interneurons., Proc Natl Acad Sci U S A 106 (2009) 3561-3566.

[236] T. Wykes, E. Newton, S. Landau, C. Rice, N. Thompson, S. Frangou, Cognitive remediation therapy (CRT) for young early onset patients with schizophrenia: an exploratory randomized controlled trial, Schizophr Res 94 (2007) 221-230.
[237] T. Wykes, C. Reeder, S. Landau, B. Everitt, M. Knapp, A. Patel, R. Romeo, Cognitive remediation therapy in schizophrenia: randomised controlled trial, Br J Psychiatry 190 (2007) 421-427.
[238] J. Wynn, B. Breitmeyer, K. Nuechterlein, M. Green, Exploring the short term visual store in schizophrenia using the attentional blink., J Psychiatr Res 40 (2006) 599-605.
[239] J.K. Wynn, G.A. Light, B. Breitmeyer, K.H. Nuechterlein, M.F. Green, Event-related gamma activity in schizophrenia patients during a visual backward-masking task, Am J Psychiatry 162 (2005) 2330-2336.
[240] S. Yeap, S. Kelly, R. Reilly, J. Thakore, J. Foxe, Visual sensory processing deficits in patients with bipolar disorder revealed through high-density electrical mapping., J Psychiatry Neurosci 34 (2009) 459-464.
[241] J. Yoon, R. Maddock, A. Rokem, M. Silver, M. Minzenberg, J. Ragland, C. Carter, GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression., J Neurosci 30 (2010) 3777-3781.
[242] J.H. Yoon, C.E. Curtis, M. D'Esposito, Differential effects of distraction during working memory on delay-period activity in the prefrontal cortex and the visual association cortex, NeuroImage 29 (2006) 1117-1126.
[243] S. Yuval-Greenberg, O. Tomer, A. Keren, I. Nelken, L. Deouell, Transient induced gamma-band response in EEG as a manifestation of miniature saccades., Neuron 58 (2008) 429-441.
[244] T. Zaehle, I. Fründ, J. Schadow, S. Thärig, M. Schoenfeld, C. Herrmann, Inter- and intra-individual covariations of hemodynamic and oscillatory gamma responses in the human cortex., Front Hum Neurosci 3 (2009) 8.
[245] T. Zaehle, C. Herrmann, Neural synchrony and white matter variations in the human brain - Relation between evoked gamma frequency and corpus callosum morphology., Int J Psychophysiol (2010).
[246] Y. Zhang, M. Behrens, J. Lisman, Prolonged exposure to NMDAR antagonist suppresses inhibitory synaptic transmission in prefrontal cortex., J Neurophysiol 100 (2008) 959-965.

Legend

Figure 1. This figure illustrates the hierarchical relationship between different processing levels in the brain from genes to behaviour. Considerable insight into working memory and its dysfunction in disorders like schizophrenia can result from combining understanding gained at different levels in the processing hierarchy. The systems approach provides a bridge between behaviour and molecular mechanisms.

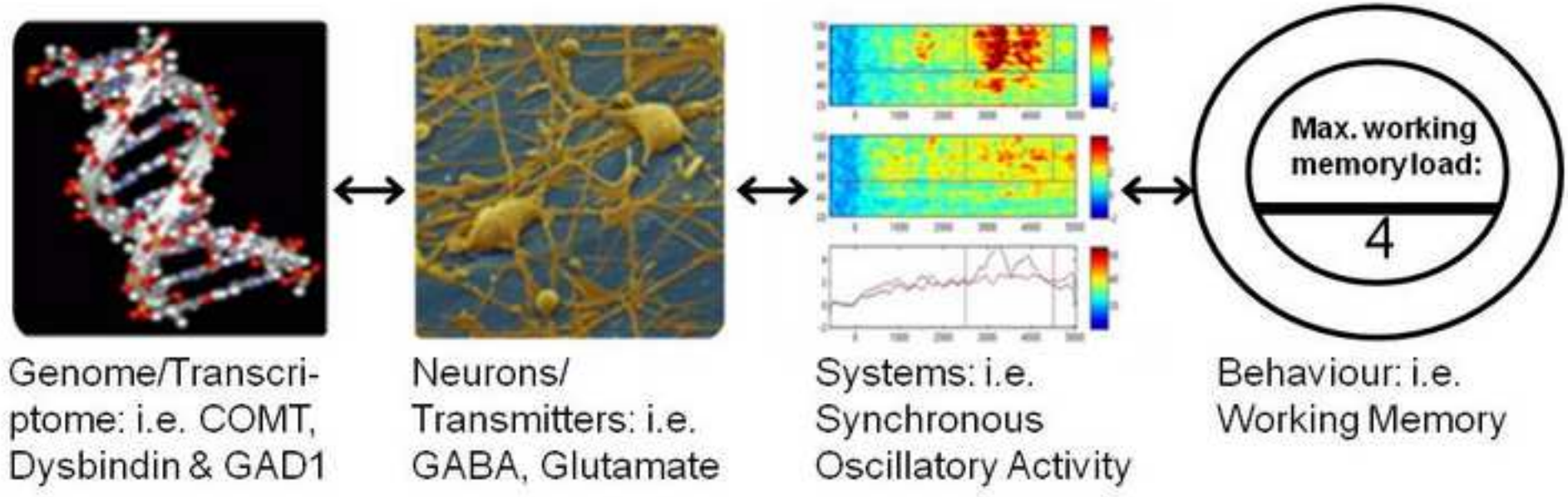
Figure 2. The medium-contrast disk in the centre of the figure is physically identical to the outer-disk at the bottom (labelled "True match"), but most normal participants are unable to ignore the high-contrast surround and match to a much lower contrast (e.g. the disk labelled "Typical match"). Dakin et al [34] showed in this experiment that patients with schizophrenia are generally much more accurate (i.e. immune to the illusion). Patients are more likely to match it to the "true match". With permission taken from http://www.ucl.ac.uk/~smgxscd/ClinicalResearch.html.

Figure 3. Fig. 3A depicts the P100 (P1) ERP component at the central occipital electrode (Oz) for each memory load for controls (CT, top) and patients with early-onset schizophrenia (SZ, bottom). The different WM loads are denoted by the line colour (black for load 1, green for load 2 and red for load 3). Fig. 3B shows the power of evoked oscillatory activity at theta (θ, top), alpha (α, middle), and beta (β, bottom) frequencies during working memory (WM) encoding for both groups at WM load 1. For each frequency the figure depicts the power for each group over time (up to 3s) and a line graph comparing the controls (blue) and patients (red). Modified from [76, 77].

Figure 4: Top: Parvalbumin (PV)-containing inhibitory interneurons modulate levels of excitatory activity via release of GABA to pyramidal neurons (excitatory neuron). The PV-containing neurons (for example chandelier cells) are themselves regulated by glutamatergic input, for example through NMDA receptors. In controls, the inhibitory neuron maintains sufficient GABA release and the excitatory neuron sufficient glutamate release to balance inhibition with excitation. The feedback inhibition generates gamma oscillations. Bottom: In individuals with schizophrenia, decreased NMDA receptor signalling alters the monitoring function of the inhibitory neuron, which down regulates its output, disinhibiting the excitatory neuron. This process is compounded by reductions in GABA-related proteins. Altered GABA neurotransmission by PV-containing neurons is indicated by PV reductions,

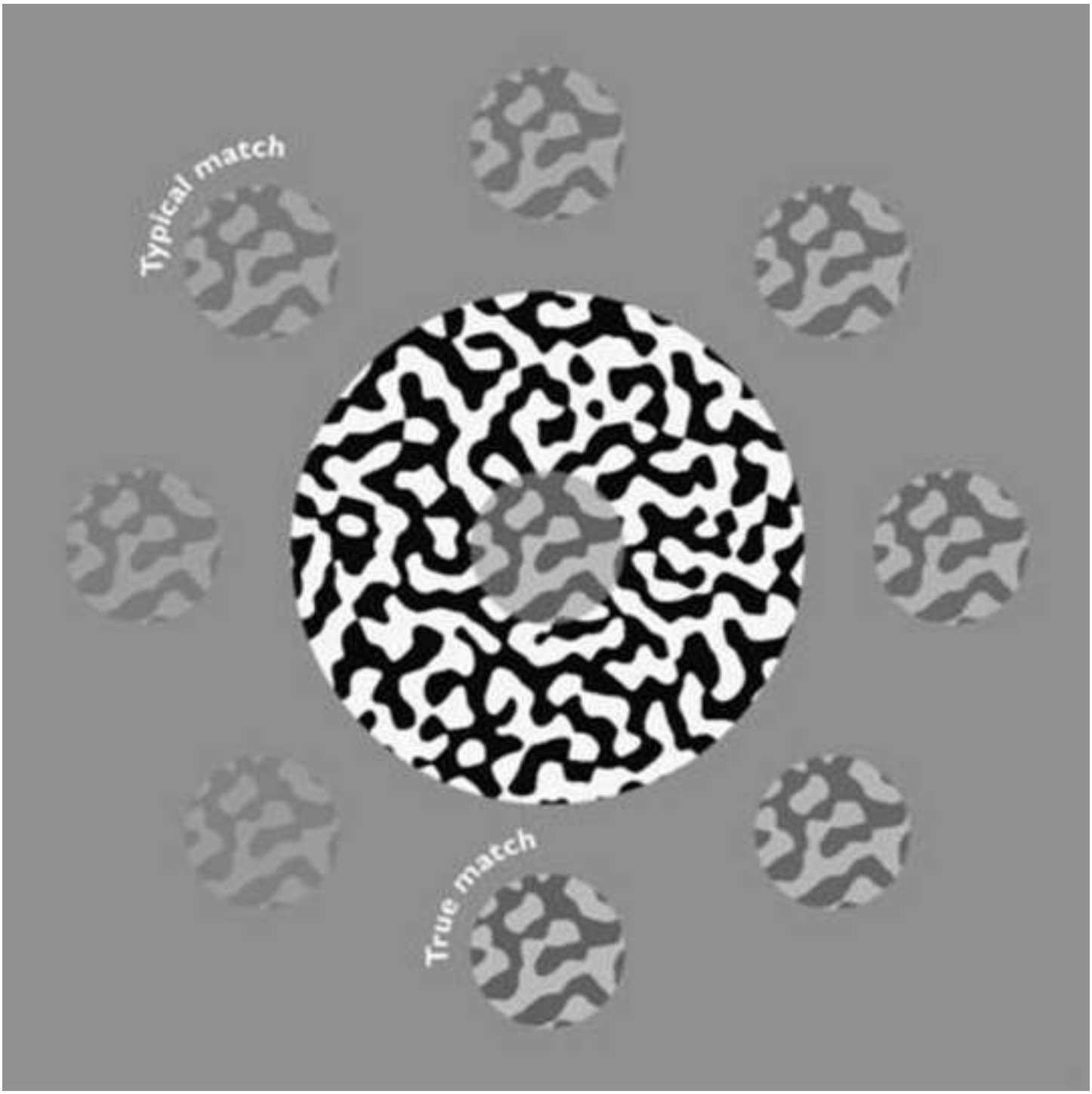
reduced GAD 67 (GABA synthesis), a decrease in GAT1 (GABA membrane transporter) expression and an upregulation of $GABA_A$ receptor α2-subunit at the pyramidal neurons (enlarged circle). [Modified from 69, 128, 134].

Figure(s)
Click here to download high resolution image



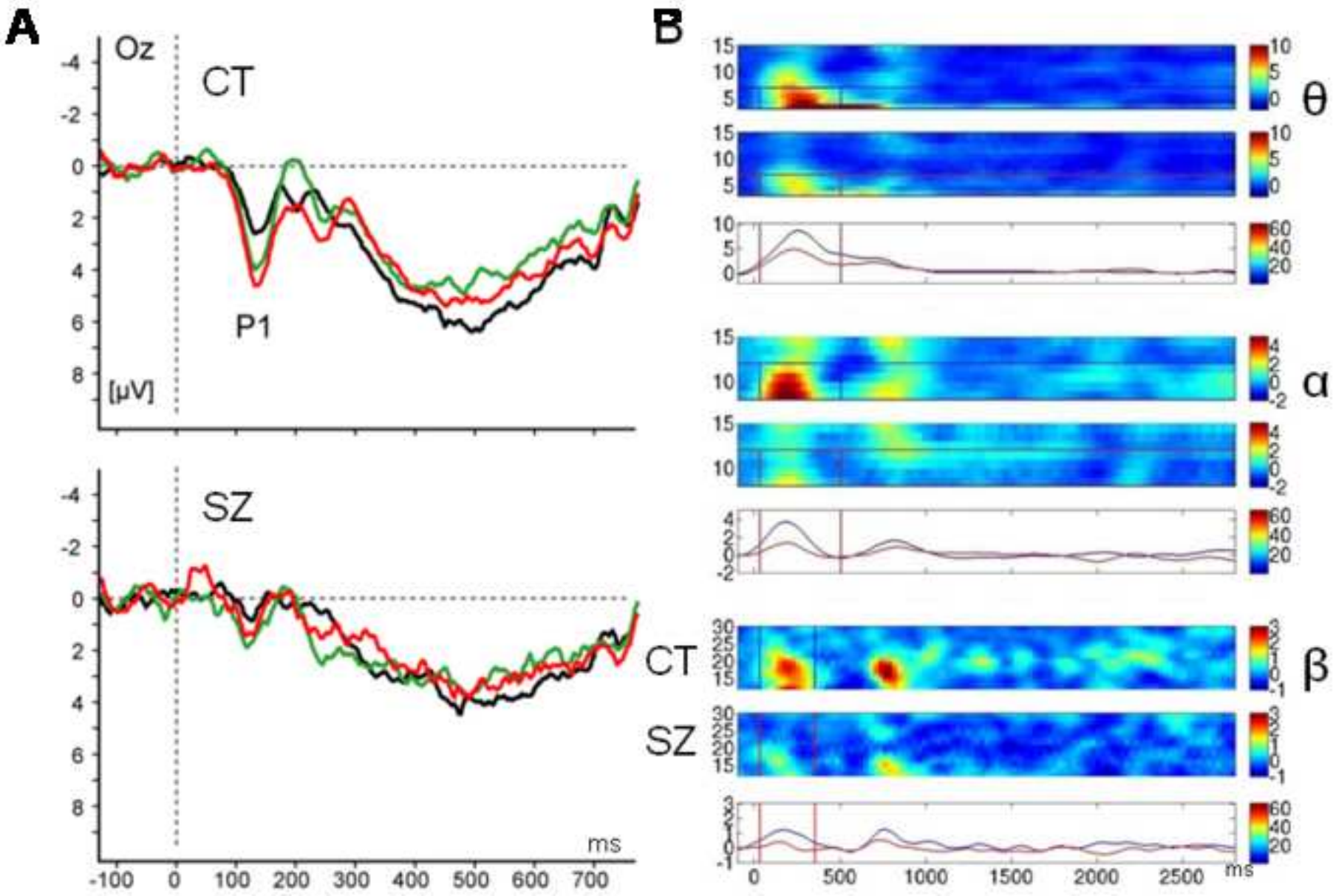
Figure(s)

Click here to download high resolution image



Figure(s)

Click here to download high resolution image



Figure(s)
Click here to download high resolution image