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Exploring intermediate phenotypes with EEG: Working memory dysfunction in schizophrenia

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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

1 tasks [9]. The content of WM stores can be derived from sensory (e.g. visual, auditory, tactile
2 etc.) information or internal processes (e.g. retrieving information from long-term memory).
3 Due to its ubiquity WM has been selected as a promising measure to improve quality of life
4 in schizophrenia (Cognitive Neuroscience Treatment Research to Improve Cognition in
5 Schizophrenia, CNTRICS). WM spans a variety of processing levels (perceptual to cognitive)
6 and is comprised of a number of component tasks. First, the information needs to be
7 accurately perceived and encoded, second, the internal representation needs to be precisely
8 maintained and defended against interference, and third it needs accurately to be compared
9 with the relevant information in the probe. Additionally tasks may also involve the
10 manipulation of items in WM (reordering of letters, spatial or object transformations) [e.g.
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21 Deficits in WM task performance can potentially arise from impairments in any of these
22 phases irrespective of sensory modality or information source. In fact, patients with
23 schizophrenia show deficits in fundamental processes during the early stages of sensory
24 processing (e.g., lateral inhibition) up to deficits in higher cognitive processing in prefrontal
25 areas. Nonetheless, many studies of WM impairments in schizophrenia have focussed on the
26 later stages of processing (i.e. memory maintenance and retrieval) and particularly the
27 contribution of prefrontal cortex (PFC) dysfunction. This bias is attributable both to the well
28 documented physiological effects of schizophrenia on PFC function and Goldman-Rakic'
29 [66] highly influential theory regarding the importance of the DLPFC in WM, which suggests
30 that the sustained delay-period activity of neurons in PFC provides a neurophysiological
31 substrate of the storage buffer proposed by the standard WM cognitive model [9]. Although
32 this approach has been extremely fruitful it is becoming increasingly apparent that it cannot
33 account for all empirical findings and that other approaches are needed [164]. Indeed, due to
34 the traditional disciplinary divisions, executive and perceptual dysfunctions in patients with
35 schizophrenia have largely been studied separately. In this review we argue that the study of
36 visual working memory (WM) provides a natural opportunity for bridging the gap between
37 these approaches because it inherently involves basic sensory and higher strategic processes.
38 However, it is important to emphasise that WM deficits in schizophrenia have been reported
39 from a wide variety of tasks that span across modalities some of the mechanisms described
40 within the current review may apply quite generally across domains.
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1 Neurophysiological and functional neuroimaging studies of visual WM in normal participants
2 emphasise its dependence upon an extended network of neural areas including the prefrontal,
3 parietal, primary and higher sensory cortices [133, 242]. For example, Pasternak and
4 Greenlee [159] emphasise the nature of early (visual) areas contributing to WM. Importantly,
5 areas within the WM network may be differentially associated with the various components
6 of WM processing, but there may also be considerable interactions between areas
7 contributing to these component processes. For example, top-down processes may contribute
8 to the fidelity of visual representation during encoding.
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15 In recent years there has been considerable interest in the dynamics of network interactions
16 through analysis of functional connectivity and the time course of network activity. One
17 proposed mechanism is that functional networks are created transiently by the
18 synchronisation of periodic firing of groups of neurons (termed oscillatory activity) within
19 and between cortical areas [194, 195, 225]. Oscillatory activity has been shown to occur at a
20 wide range of temporal frequencies (3 to over 100 Hz) and associated with a variety of
21 cognitive functions [194]. These include a number of processes likely to be critical for WM
22 performance including visual perception, object recognition, attention and memory
23 maintenance [98, 208].
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32 This raises the possibility that abnormalities in synchronous oscillatory activity [121, 218]
33 may provide a parsimonious account for many of the cognitive deficits observed in
34 schizophrenia [163]. This is in line with the observation that the pathological process in
35 schizophrenia does not respect regional (and functional) boundaries. For example, Selemon et
36 al. [188] reported post-mortem changes in regions as widespread and functionally diverse as
37 the primary visual and prefrontal cortices in schizophrenia [188]. As a consequence a number
38 of researcher propose that core aspects of the pathophysiology of the disorder arise from a
39 dysfunction in the integration and coordination of distributed neural activity [4, 57, 163]. This
40 disconnection hypothesis is supported by reports of altered functional connectivity in
41 schizophrenia during WM particularly between prefrontal and parietal areas [104, 144, 212]
42 which indicates that perceptual deficits may in part result from impairments in reciprocal
43 interactions between sensory and higher cortical areas [54]. Our own recent results confirm
44 the important contribution of early visual processes to successful WM performance in healthy
45 subjects and deficits in patients with schizophrenia [76, 77].
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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

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

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18 The earliest stages of WM involve extracting the critical information from a transient sensory
19 input to form a more durable WM representation. This necessitates a variety of processes,
20 collectively described under the term encoding, which if impaired can potentially contribute
21 to impaired WM performance. Since the first evidence of WM impairments in patients with
22 schizophrenia [158], several behavioural studies have shown impairments associated with
23 WM encoding performance [60, 95, 120, 123], but the underlying causes remain to be fully
24 understood.
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32 A WM encoding deficit may be attributable to documented disturbances in basic visual
33 processing in schizophrenia. In a number of studies Butler et al. [25, 27, 94 for review] have
34 provided evidence for a specific impairment in the magnocellular pathway. This is a visual
35 pathway which specialises in the processing of luminance information, while chromatic
36 information is subserved by parvo- and koniocellular pathways [112]. Interestingly, the rapid
37 and transient signal transmission in the magnocellular pathway makes it ideal for quick links
38 between early visual and higher cognitive areas. In fact, recent models of visual perception
39 posit that the efficiency and speed of everyday vision largely rely on early bottom-up/top-
40 down interactions between occipital and prefrontal areas of the cortex which are driven by
41 magnocellular projections from early visual areas [12, 114]. As a consequence magnocellular
42 pathway deficits might contribute to encoding problems by causing basic difficulties in
43 perceptual discriminability or top-down enhancement of earlier representations. Further
44 fundamental perceptual difficulties that might affect WM have been reported by Dakin et al
45 [34]. They showed that individuals with schizophrenia are less prone to the visual ‘contrast–
46 contrast’ illusion (Fig. 2), which suggests that they have weaker visual contextual suppression
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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

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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

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

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

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

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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,

1 stimulus-driven encoding processes, which is commonly measured by averaging the response
2 across all trials and then examining power in a specific frequency band. It can also be
3 measured by examining the variability in the phase of a stimulus elicited response at a
4 specific electrode across individual trials (termed inter-trial phase locking or inter-trial
5 coherence (ITC)).
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9 Although induced activity is also elicited in direct response to the appearance of the stimulus
10 its timing reflects internal network processes and is therefore less tightly linked to stimulus
11 onset, which is commonly measured by examining the power in each frequency band for
12 individual trials and then averaging this power across trials¹. Finally, long-range synchrony
13 measures phase coupling between electrodes, which reflects the degree to which activity at
14 those sites form part of a common functional network of activity. In general long-rang
15 synchrony is considered to depend upon coordination in the lower frequency ranges (theta,
16 alpha, beta) [185, 226] because synchronization at lower frequencies tolerates longer
17 conduction delays [108] necessary for forming temporal synchronised networks over large
18 distances. All these forms of synchronised oscillatory activity provide mechanisms to
19 integrate neural activities that instantiate the stable, salient and coherent representations
20 required for WM even when information is no longer available in the environment [98].
21 Additionally, they provide mechanisms for understanding the fundamental basis of WM
22 processes.
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34 The relationship between synchronised oscillations at different frequencies has been
35 proposed to explain WM capacity limitations. More specifically, Lisman and Idiart [135]
36 used computer simulations to demonstrate that working memory capacity can in principle be
37 explained by the number of gamma cycles (where each cycle represents an individual
38 memory item) per theta cycle. Subsequent physiological studies provided evidence to support
39 such a relationship between memory capacity and activity in the gamma and theta frequency
40 range [5, 182]. Axmacher et al [5] showed that cross-frequency coupling between the phase
41 of the theta activity and gamma band amplitude in the human hippocampus accompanies
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51 ¹ Following the recent report of Yuval-Greenberg et al ([243] S. Yuval-Greenberg, O. Tomer, A. Keren, I. Nelken, L. Deouell,
52 Transient induced gamma-band response in EEG as a manifestation of miniature saccades., *Neuron* 58 (2008) 429-441. see also
53 [142] L. Melloni, C. Schwiedrzik, M. Wibral, E. Rodriguez, W. Singer, Response to: Yuval-Greenberg et al., "Transient
54 Induced Gamma-Band Response in EEG as a Manifestation of Miniature Saccades." *Neuron* 58, 429-441., *Neuron* 62 (2009) 8-10;
55 author reply 10-12.), the possibility of a relationship between induced gamma band activity and microsaccades should also be
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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

1 schizophrenia have a specific deficit in the magnocellular pathway [e.g. 26, 183, but see
2 Skottun BC, Skoyles J. for an alternative view], which is associated with high temporal
3 frequency visual responses. Furthermore, Butler et al. [25, 28] demonstrated a correlation
4 between impaired SSVEP generation and reduced integrity of the optic radiation in patients
5 with schizophrenia.
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9 There is also evidence for reduced evoked oscillatory activity in response to stable
10 non-flickering visual stimuli [200, 201, 219]. Spencer et al. [200] examined responses to
11 illusory Kanizsa triangles, which evoked gamma frequency oscillations and a high-degree of
12 inter-trial phase locking at electrodes associated with visual processing in healthy
13 participants, but these responses were considerably attenuated in patients. Finally, patients
14 show reduced evoked [239] and induced [73] gamma band oscillations in response to
15 backward visual masking. In comparison to controls patients showed a specific deficit in
16 evoked gamma-band activity for masked targets but not unmasked targets.
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23 Steady-state evoked potentials can also be elicited by periodic auditory stimulation.
24 Light et al. [132] showed impairments at 30 and 40 Hz for the auditory steady state response
25 and demonstrated an association with reduced working memory performance (measured
26 with the Letter-Number Sequencing test). This suggests that deficits at early sensory-
27 perceptual stages of processing may contribute to WM encoding difficulties across sensory
28 modalities. A more global deficit in thalamocortical projections, perhaps mediated through
29 dysfunction in one of the key neurotransmitter systems (glutamatergic, GABAergic,
30 cholinergic) may thus underlie these impairments in stimulus-driven oscillations. However,
31 reduced gamma oscillations in schizophrenia are not confined to situations where the
32 oscillations are driven by external stimuli (and reduced power could thus be an effect of
33 impaired sensory input channels), but also occurred with direct transcranial cortical
34 stimulation [50].
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45 In a recent series of studies we have directly examined the effects of WM encoding
46 deficits in schizophrenia, which are assumed to arise in large part due to the visual processing
47 difficulties described above. We first measured neural activity with event-related potentials
48 (ERPs) during WM encoding of up to three abstract test shapes that were presented
49 sequentially and followed by a probe shape, which was either drawn from the test shapes
50 (50%) or was a non match (a visual delayed discrimination task). For control participants, but
51 not patients, a prominent early P100 (related to stimulus encoding) increased with WM load
52 and predicted performance (Fig. 3A). Furthermore, the P100 reduction in patients was
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1 mirrored by reduced activation of visual areas in fMRI [77]. A reduced P100 during WM
2 encoding has recently also been reported in participants with high schizotypy compared to
3 low schizotypy [109]. Together with the P100 reduction observed in relatives of patients
4 with schizophrenia these results point to a role of such neurophysiological changes as trait
5 markers of schizophrenia, or indeed of a psychosis spectrum [32], considering that similar
6 effects have also been reported in bipolar disorder [240].
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22 One possible explanation for this P100 deficit is an increase in neuronal response
23 variability (“cortical noise”) in patients. This would lead to a higher trial to trial variation of
24 the P100 response and thus the average would be reduced compared to controls. In a
25 subsequent paper we examined these deficits in patients with schizophrenia in greater detail
26 by looking at the effects of oscillatory activity in a broad frequency range. We demonstrated
27 that patients show reduced evoked theta, alpha, and beta oscillatory activity during WM
28 encoding [76] (Fig.3B). Importantly, in contrast to ERPs and evoked oscillatory activity,
29 induced oscillatory activity can be used to assess directly the processes occurring during the
30 maintenance period. In our study, induced gamma activity increased monotonically across all
31 tested loads in controls, but reached an asymptote at load 2 in patients, reflecting a greater
32 impact of task difficulty in patients.
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43 Although most neurophysiological studies of cognitive tasks in patient groups focus
44 on the mechanisms of cognitive deficit, it is of equal interest to investigate the mechanisms
45 that support the cognitive abilities that are preserved or provide some compensation. One
46 possibility is that patients use selective attention to enhance the salience of items to be
47 encoded into WM, because this function is largely unaffected in patients with schizophrenia
48 [64, 65]. Consistent with this proposal we recently demonstrated that alpha phase-locking
49 during encoding correlates with working memory performance in patients (but not controls)
50 [78]; activity in this frequency band has been linked to selective visual attention [214, 234].
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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

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

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4 In addition to these studies, which focused on impairments in measures of power,
5 there is also EEG and some MEG evidence for impairments in functional connectivity during
6 WM tasks. Measures of functional connectivity in neural networks can be obtained through
7 correlation analysis [160] or graph theory [15, 36, 145, 155]. Networks with “small-world
8 properties” are characterised by a combination of local clustering of activity and a short
9 characteristic path length as an index of global integration and cost efficiency. Patients with
10 schizophrenia exhibited dysfunctional organization of neuronal networks during WM. Bassett
11 et al [15] used small-world properties to demonstrate that working memory performance in
12 the N-back task was associated with greater cost efficiency in the beta frequency band in
13 controls than in patients with schizophrenia, indicating cortical inefficiency within these
14 networks. In addition to reduced efficiency, De Vico Fallani et al. [36] also reported an
15 increase in cortical synchronization in the high alpha (11-13 Hz) frequency range in a group
16 of high functioning patients with schizophrenia who were able to perform the N-back task as
17 well as controls, which was interpreted as a compensatory mechanism (see also Haenschel et
18 al., 2010 for findings of relationship between alpha phase locking and performance in
19 patients with schizophrenia).
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32 In summary, the reviewed studies suggest a relationship between impairments in
33 synchronized oscillatory activity and perceptual and higher-level cognitive processing
34 contributing to WM deficits in schizophrenia. Additionally, correlations in synchronized
35 activity and performance may also indicate the use of compensatory mechanisms to perform
36 the task, e.g. increased alpha phase locking as an indicator of increased attention. In the next
37 section we review the evidence for a link between impairments in oscillatory activity and
38 neurotransmitter dysfunctions.
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47 **Neuropharmacological mechanisms underlying WM and oscillatory activity**

48 Contemporary models understand WM dysfunctions as a result of cortical circuit
49 abnormalities. One way of gaining insights into the neural circuits in which the WM
50 dysfunction is embedded it to investigate the actions and interaction of neurotransmitters
51 involved in the disorder [16, 134]. The relationship between the dopaminergic, GABAergic,
52 glutamatergic and cholinergic systems and WM has long been established. Both animal and
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1 human studies [170] also point to effects on WM-related brain activation. However, we only
2 start to understand the relationship between these neurotransmitters and impaired oscillatory
3 activity contributing to WM deficits.
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7 Dopamine

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9 First evidence for a relationship between neuromodulators and WM came from a study
10 showing that dopamine depletion in the monkey DLPFC markedly impaired WM [22].
11 Sawaguchi & Goldman-Rakic [179] reported selective impairment of working memory
12 (delayed saccades) after local infusion of D1, but not D2 antagonists; further studies showed
13 that response-related but not mnemonic activation is D2 receptor-dependent [228], which
14 provides insight into the specific pharmacology of WM subprocesses. [179, 180]. Because
15 administration of dopaminergic drugs in humans has not consistently resulted in memory
16 improvement, it is likely that any WM-enhancing effects of dopamine will depend on the
17 specific receptor and postsynaptic signaling cascade and/or the homeostatic state of
18 dopamine. Regarding the latter, it has been proposed that dopamine promotes cognitive
19 function during hypodopaminergic states but can disrupt it during hyperdopaminergic states.
20 Functional polymorphisms of genes related to the dopamine system may provide a non-
21 invasive way of measuring these states. For example, the Val(108/158)Met polymorphism on
22 the gene for catechol-O-methyltransferase (COMT), a dopamine-degrading enzyme,
23 influences dopamine concentration. Val-carriers, who have reduced prefrontal dopamine
24 levels, show slightly reduced performance on the n-back WM task [211] and higher noise
25 levels in prefrontal activity, measured by ERPs [232]. These effects may interact with genetic
26 variants that influence the concentration of postsynaptic dopamine receptors [203]. Such
27 interactions may explain why low intrinsic dopamine levels alone are not sufficient for
28 dopaminergic medication to enhance working memory. A recent study on emotional face
29 working memory in Parkinson's disease found changing emotion biases (from sad to angry)
30 after dopaminergic medication, but no overall improvement [206in revision]. Furthermore,
31 recent evidence for epistatic effects between variants on the genes for the dopamine D2
32 receptor and the alpha-4 subunit of the nicotinic acetylcholine receptor on WM capacity at
33 higher WM loads suggests an interplay of multiple neuromodulatory systems [139].
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56 It has further been suggested that dopamine/D1 signaling modulates the cortical signal-to-
57 noise ratio by enhancing selective inputs to both pyramidal cells and inhibitory interneurons
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1 [67] and it has been shown that reduced D1-receptor signaling on prefrontal pyramidal cells
2 attenuates GABA_A and NMDA- receptor induced currents [45, 186, 187]. Dopamine may
3 thus modulate frequency-dependent signal transmission and thereby adjust oscillations in
4 cortical networks [91]. Recent evidence for the importance of dopaminergic modulation of
5 parietal in addition to prefrontal areas [141] suggests that similar mechanisms may also apply
6 to other parts of the cortical WM. Dopaminergic input can have inhibitory or excitatory
7 effects on pyramidal neurons, depending on which group of dopamine receptors (D2, D3, D4
8 or D1, D5) are activated, and thus may reduce or enhance oscillatory activity. A study of the
9 effects of functional polymorphisms in the dopamine transporter and D4 receptor genes has
10 provided first EEG evidence for such divergence [40], but further receptor-specific studies
11 are needed to determine the direction of the effects of dopamine on gamma oscillations.
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20 Dopamine modulates glutamatergic and GABAergic transmission, and is also under
21 the influence of the same synaptic proteins. Dystrobrevin-binding protein-1 (dysbindin-1)
22 regulates both dopamine and glutamate release and trafficking. Genetic variability in
23 dysbindin-1 contributed to interindividual differences in spatial working memory in
24 schizophrenia patients [42] and in working memory for emotional faces in healthy controls
25 [233]. The neurophysiological effects of dysbindin-1 variants have been investigated with
26 both early/ perceptual ERPs (P100) [43] and indices of (prefrontal) cognitive control [48].
27 These findings underline the importance of looking beyond the classical neurotransmitter
28 pathways of synthesis, release, receptor binding, transport and degradation and assess
29 functional differences in the synaptic apparatus, which is likely to be crucial for the
30 maintenance of oscillatory activity as well.
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41 GABA

42 The work on the link between dopamine and WM was later complemented by studies
43 showing that in monkeys' activity of gamma-aminobutyric acid (GABA) neurons in DLPFC
44 are essential for normal WM function [169, 181]. Interestingly, this work was based on
45 previous results showing that GABA_A mediated inhibition plays an important role in the
46 generation of spatial selectivity in the primary sensory areas of cortex. For instance, in the
47 primary visual cortex both broadening of orientation tuning [47, 178, 191] and reduction of
48 directional selectivity [151] have been observed with the application of bicuculline
49 methiodide, a GABA_A receptor antagonist. Rao et al. [169] showed that GABA_A mediated
50 inhibition plays an important role at the cellular level in the processes underlying spatial
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1 working memory in the dPFC as well, improving spatial selectivity and possibly playing
2 critical roles in the attentional control mechanisms of central executive function.
3 Interestingly, Yoon et al. [241] showed a reduced GABA concentration in visual cortex in
4 patients with schizophrenia. They found a correlation with GABA concentration and
5 orientation-specific surround suppression as further evidence for impaired lateral inhibition
6 [34] and thus a deficit in early visual processing.
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10 GABAergic inhibition has also been functionally linked to the generation of cortical
11 oscillations within different frequency bands [130, 134, 217, 231]. For instance, gamma band
12 oscillations can be produced and propagated intracortically by network interactions among
13 large groups of inhibitory and excitatory neurons. These networks consist of interconnected
14 inhibitory interneurons that are coupled to each other and shaped into a rhythmic pattern
15 through their mutual connections. When this network of inhibitory neurons is tonically
16 excited by excitatory pyramidal neurons, the interneurons entrain each other and impose a
17 synchronised inhibition across the population. When the synchronised inhibition decays, the
18 neurons will enable and determine when a pyramidal cell to which they project will fire
19 [231]. In summary the inhibitory network receives a steady tonic drive, which makes the
20 network oscillate. It is thus providing a clock, which determines when pyramidal cells can
21 fire, if they receive suprathreshold, excitatory afferent inputs (Jefferys, Traub & Whittington,
22 1996) and thus generates oscillation in different frequency bands.
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34 Inhibition from subclasses of GABA neurons has been shown to be important for
35 synchronised oscillatory activity. For instance, whereas selective activation of the
36 interneurons containing the Ca²⁺-binding protein parvalbumin (PV) is sufficient to generate
37 gamma oscillations in mice in vivo [197], the multipolar GABA neurons that express both
38 PV and calbindin may give rise to theta frequency (4–7 Hz) oscillations [19].
39 Muthukumaraswamy et al. [152] provided further support for a relationship between GABA
40 concentration and gamma band frequency. The authors showed a correlation between the
41 individual gamma frequency and the GABA concentration measured in visual cortex with
42 MR-spectroscopy [46, 152].
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51 PV neurons are characterized by a fast-spiking pattern and control the excitability of
52 pyramidal neurons [58]. The release of GABA from PV neurons is controlled by the growth
53 factor neuregulin 1 (NRG1) through its ErbB4 receptor. Selective ablation of these receptors
54 in mice resulted in a phenotype with schizophrenia-like features, including impaired working
55 memory, reduced pre-pulse inhibition and hyperactivity. Some of these features normalized
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1 after treatment with diazepam, a positive allosteric modulator of the GABA_A receptor. Thus,
2 reduced GABAergic activity can lead to schizophrenia-like phenotypes in experimental
3 animals. It is interesting that both the NRG1 and the ErbB4 gene have been suggested to be
4 susceptibility genes for schizophrenia [13, 229].
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7 In ErbB4 knockout mice both the number of PV-interneurons and induced gamma
8 oscillations have been shown to be reduced [51]. Furthermore, blocking GABA_A receptors
9 alters the dynamic profile of gamma oscillatory activity to changes in the network drive [216,
10 231]. Genetically modified mice, in which GABA_A receptor-mediated synaptic inhibition
11 onto PV-interneurons was removed exclusively, exhibited altered theta oscillations and
12 altered coupling between theta and gamma oscillations [235]. In contrast, gamma oscillations
13 were not changed, indicating that mutual inhibition between PV interneurons is not necessary
14 for the generation of oscillations in this frequency range [68 for review, 235].
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22 However, a direct link between alterations in glutamatergic (using ketamine) onto
23 GABAergic neurotransmission and gamma oscillatory activity has been found in animal
24 models of schizophrenia [33, 174], demonstrating a deficit in rhythmogenesis. It has therefore
25 been suggested that the abnormalities of GABAergic networks in schizophrenic patients may
26 lead to reduced oscillatory activity and thus to WM deficits.
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31 Thus it is not surprising that alterations in the GABA system have been suggested to
32 underlie WM deficits. Several studies have suggested alterations of the GABA system in the
33 brains of patients with schizophrenia [17, 126, 130] providing evidence of a dysfunction of
34 inhibitory interneurons in schizophrenia (Fig. 4). Postmortem studies have shown that the 67-
35 kiloDalton isoform of glutamic acid decarboxylase (GAD67) responsible for the synthesis of
36 GABA is reduced in patients with schizophrenia [224]. In general, the GABAergic system is
37 vulnerable to changes and can be modified by a variety of factors [246]. For instance, there is
38 some evidence that GAD67 can be reduced by sensory deprivation [31, 84].
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46 Using network simulation Vierling-Classsen et al. [222] showed that increasing the
47 time the decay time at the GABA_A synapse from interneuron to pyramidal neuron can model
48 the gamma band deficits found in schizophrenia. Increasing the decay time of the extended
49 inhibitory postsynaptic current (IPSCs) resulted in longer inhibition and a reduced probability
50 of pyramidal cell spiking for a longer duration. As expected from these simulations, patients
51 showed pronounced 20 Hz (beta band), but reduced 40 Hz activity in an auditory steady state
52 paradigm. Interestingly, these authors noted that the fidelity of the networks is not only
53 dependent on the GABAergic interneurons, but also on the strength of the drive of the input
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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 $\alpha 2$ 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 neurotransmission [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

1 positive and negative symptoms of schizophrenia [96]. The NMDA receptor has consistently
2 been related to the cognitive symptoms of schizophrenia. Several studies investigated the
3 effects of acute ketamine on different aspects of working memory tasks [147]. NMDA
4 receptor antagonists have been shown to disrupt encoding processes [30] and to have an
5 effect on manipulation but not on maintenance in frontal-parietal regions measured with
6 fMRI [88]. Furthermore, in an N-back study ketamine was associated with decreased scores
7 on the one-back and two-back, but not the zero-back condition [2, 148], indicating stronger
8 effects with higher WM loads.
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14 NMDA receptors play a crucial role in neuronal communication. Blocking NMDA
15 does not only interfere with excitatory transmission and synaptic plasticity, but it also reduces
16 the drive to inhibitory interneurons [230] (see Figure 3). Several recent studies demonstrate
17 that altered GABA neurotransmission may be secondary to abnormalities in NMDA receptor
18 functioning [87, 246]. This is based on the finding that ketamine reduces the activity of
19 GABA interneurons and thus disinhibits pyramidal neurons [75]. In addition to the effect of
20 acute intake, chronic ketamine intake has been shown to result in a reduction in the number
21 of parvalbumin-containing axoaxonic cartridges (see Fig 4). These are synaptic terminals of
22 inhibitory chandelier cells [149]. The reduced input on parvalbumin- containing interneurons
23 (indicating low pyramidal activity) have been suggested to not only reduce parvalbumin, but
24 to also downregulate GAD67, the principal synthesizing enzyme for GABA [149, 246]. This
25 can be seen as an maladaptive attempt to restore pyramidal cell activity to the correct levels
26 [134]. Taken together, these abnormalities may interfere with the generation of oscillatory
27 activity and may lead to the observed changes in schizophrenia.
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53 There is evidence both from in vivo recordings from mouse hippocampus [119] and
54 from human EEG [89] using the auditory paired-click gating paradigm that ketamine
55 increases gamma oscillatory activity and reduces slow frequency activity. Interestingly, Hong
56 et al. [89] showed that the increase in gamma and decrease in delta frequency predicted
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1 withdrawal–retardation symptoms measured using the Brief Psychiatric Rating Scale (BPRS)
2 directly following the EEG recording.

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4 There is however in-vitro evidence for reduced oscillatory high-frequency activity in
5 response to ketamine as well, which fits better with the cellular models of interneuron
6 inhibition discussed above [33, 41, 174]. Roopun et al. [174] showed that ketamine can have
7 region-specific effects with an increase in gamma in one region and reduced or no effect in a
8 different region. They argued that reduced power in one region may lead to phase delays
9 between oscillating networks across the cortex and as a consequence changes in long-range
10 synchrony may occur. In addition, this would explain a reduction in lower frequencies, but
11 also an increase in phase variability. Any of these changes may result or contribute to WM
12 deficits in schizophrenia. These results emphasize the importance of understanding the time
13 course of differential contributions of areas comprising the WM-network.
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17 Alternatively, differential effects of acute or chronic ketamine have to be taken into
18 account when using this as a model for schizophrenia [see 89, 166]. Whereas acute ketamine
19 augments glutamate concentration measured with MR-spectroscopy in humans [175], it is the
20 chronic use of ketamine that results in NMDA receptor hypofunction. Indeed, glutamate
21 concentration has been shown to be higher in patients with recent onset of schizophrenia [24]
22 but reduced in chronic schizophrenia [215].
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26 Chrobak et al [30] tested the effects of ketamine on the encoding, retrieval and
27 retention of memory in a delayed-match-to-place radial water maze task and showed
28 impairment in encoding of new location information because of an increase of proactive
29 interference. The authors suggested that the strength of the encoded representation is
30 weakened with ketamine administration, which is in line with previous results of
31 hippocampal place cells [103]. They also suggest that ketamine produces changes in theta and
32 gamma power and coherence and that it decouples the phase relationship between the two
33 frequencies, which may contribute to reduced WM capacity found in individuals with
34 schizophrenia.
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38 In addition to the abnormalities of excitatory NMDA-receptor transmission on
39 shaping the inhibitory GABAergic transmission, these functional impairments may also
40 interact with structural abnormalities [21], such as reductions in amount of cortical neuropil,
41 axon terminals and dendritic spines density on cortical pyramidal neurons in schizophrenia
42 [62, 126]. Dendritic spines are the principal targets of excitatory synapses to pyramidal
43 neurons. These abnormalities have mainly been found in deep layer 3 pyramidal neurons in
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1 DLPFC and other areas as well [126], which suggests an involvement in primarily
2 intracortical circuits, and thus recurrent excitation [199]. This is in line with the
3 dysconnection theory, according to which reduced synaptic connectivity results in abnormal
4 functional integration of neural systems [57, see 204 for a recent review]. Furthermore,
5 Friston (1999) suggested that this would be compatible with deficient backward modulatory
6 connections given that backward (top-down) connections are slow, modulatory (voltage-
7 sensitive NMDA receptor dependent) and divergent (less topographically specific) [10, see
8 review in 56]. Reductions in spine density reflecting reduced network connectivity would
9 provide an explanation for the impairments in long-range synchrony and could contribute to
10 deficits in WM network functioning.
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20 Cholinergic system 21

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23 Finally, there is some suggestion that abnormalities in the cholinergic system may also
24 contribute to the WM deficits [92, 113]. The involvement of the cholinergic system in
25 schizophrenia has been suggested by the extremely high prevalence of smoking in patients
26 with schizophrenia and by the clinical observation that patients use smoking as self-
27 medication for symptom relief. Nicotine transiently improves ERP indices (the repetition
28 positivity, [see 80] of stimulus encoding and sensory memory trace formation in a auditory
29 roving oddball paradigm [11], performance and related fMRI activity in a rapid visual
30 information processing task [118] and performance in the N-back task [113] in healthy
31 smokers and nonsmokers. Furthermore, in patients with schizophrenia nicotine normalizes
32 the auditory sensory gating (P50) deficit [3] that has been specifically related to alterations in
33 the $\alpha 7$ nicotinic receptor, improves deficits in spatial WM [124], sustained attention [125]
34 and performance in the N-back task [92]. Jacobsen et al. [92] also demonstrated that in line
35 with performance improvement, nicotine also enhanced activity of and functional
36 connectivity between brain regions involved in WM using fMRI in schizophrenia.
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49 Evidence is starting to emerge that can explain these network functions. The $\alpha 7$
50 nicotinic receptors are concentrated on interneurons [110] and, by enhancing the excitation of
51 the GABAergic interneurons, they may enhance their inhibitory output [134, 227]. Indeed,
52 nicotine increases the gamma oscillations that are dependent on interneuron function in rat
53 hippocampal slices [198]. Furthermore, cholinergic modulation (mainly via muscarinic
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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 $\alpha 7$ and the $\alpha 4/\beta 2$ 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

1 has focused upon visual WM as an exemplar system, and we have emphasized the
2 importance of early perceptual and encoding processes. We gave two main reasons for this: 1.
3 the ability to encode stimuli into WM inherently acts as a limiting factor upon WM and, thus,
4 impairments in this process will affect performance. 2. Understanding the links between
5 impairments in neurochemical and system level processes in sensory areas is likely to
6 contribute to understanding abnormalities at higher levels. Current models suggest that a
7 distinctive pattern of molecular changes in neurotransmitter systems creates abnormalities in
8 cortical network that underlie the core perceptual and cognitive deficits contributing to WM
9 dysfunctions [for instance 134].
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17 The review has focused upon the role of synchronized oscillatory activity as a bridge
18 between basic neurochemical impairments and consequent performance deficits. The current
19 evidence indicates that dysfunctional coordination of distributed neural activity associated
20 with a variety of perceptual and cognitive functions leads to WM deficits in schizophrenia.
21 These dysfunctions arise from impairments in a wide range of frequencies and associated
22 processes. Importantly, correlations between WM performance and synchronous oscillatory
23 activity can also identify the operation of compensatory mechanisms recruited by patients to
24 perform tasks, e.g. the correlation between alpha phase locking and patients' performance
25 indicating increased use of attention relative to controls. Recent methodological
26 developments will help to further clarify the dynamic interactions of perceptual and executive
27 processing areas contributing to working memory. For instance dynamic causal modeling
28 (DCM) can be used to measure the strength and direction of connectivity between neural
29 ensembles [55, 161], which will reveal the time-course of these interacting processes.
30 Furthermore, combining measures of oscillatory activity and functional and structural fMRI
31 [244, 245] will further elucidate the relationship between reductions in grey and white matter
32 and impairments in oscillatory activity.
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47 As noted earlier, synchronous oscillatory activity provides not only a window into
48 working memory dysfunctions in schizophrenia but also a method by which in vivo, in vitro
49 and computer simulation studies can be usefully combined. Measures of neuronal synchrony
50 have been defined for both human and animal electrophysiology and can be studied at various
51 levels of spatial analysis, from microscopic (e.g., single-unit recordings) to macroscopic (e.g.,
52 EEG) measurements [195, 220]. As a consequence they are uniquely suited for the testing of
53 models of schizophrenia from molecular through to behavioural levels. Additionally,
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1 oscillatory activity provides a powerful tool for examining the effects of translational
2 research into the treatment of cognitive dysfunction in schizophrenia by illuminating the
3 effects on the underlying neural mechanisms a basis for the development of biologically
4 motivated animal models.
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8 Understanding the relationship between neurochemical processes and oscillatory
9 activity has resulted in the development of new pharmacological models developed in vitro.
10 For instance, there is now some evidence that improving signaling through GABA_A receptors
11 containing an $\alpha 2$ subunit ameliorates working memory impairments and enhances gamma
12 band oscillations associated with the specific cognitive task employed [127]. Furthermore,
13 the link between oscillations and neurochemistry provides an important area for extending
14 existing models. For example, the work by Javitt and colleagues demonstrating that deficits
15 induced by NMDA antagonists can be reversed by compounds such as d-serine or glycine
16 transport inhibitors that stimulate NMDA function [93, 102] is likely to be reflected in
17 changes in oscillatory activity.
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27 Recent methodological advances offer the opportunity to understand the relationship
28 between neurochemical and neurophysiological processes in vivo. Specifically, measures of
29 neurotransmitter concentration using magnetic resonance spectroscopy (MRS)² can be
30 combined with EEG/MEG recordings of oscillatory activity. For instance, the specific
31 frequency of oscillatory activity (measured using MEG) has been linked to the magnitude of
32 GABA concentration in the visual cortex [46, 152]. Furthermore, the GABA concentration in
33 visual cortex has now also been shown to be reduced in individuals with schizophrenia [241].
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41 The links between neurochemical and system level processing, outlined in the studies above,
42 offer an important potential future line of research for understanding very recent advances in
43 the development of targeted behavioural therapies for cognitive deficits. Several studies have
44 shown that WM can be improved by extensive adaptive training [106]. Training may target
45 strategic processes, which the participant consciously adapts, or automatically induce plastic
46 changes in the WM-network through repetitive activation. Furthermore, WM-training has
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55 ² MRS relies on detecting resonance properties of the hydrogen atoms in the molecule of
56 interest (GABA, but also glutamate (Glu), glutamine) exposed to magnetic fields in a specific
57 area measured in an MRI-scanner.
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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.

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Legend

1
2 Figure 1. This figure illustrates the hierarchical relationship between different processing
3 levels in the brain from genes to behaviour. Considerable insight into working memory and
4 its dysfunction in disorders like schizophrenia can result from combining understanding
5 gained at different levels in the processing hierarchy. The systems approach provides a bridge
6 between behaviour and molecular mechanisms.
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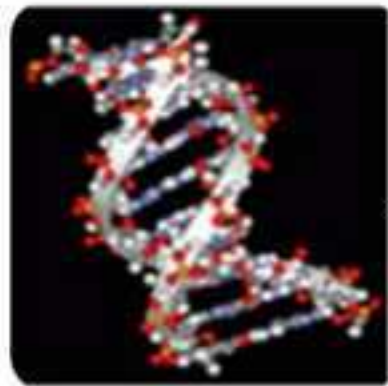
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11 Figure 2. The medium-contrast disk in the centre of the figure is physically identical to the
12 outer-disk at the bottom (labelled “True match”), but most normal participants are unable to
13 ignore the high-contrast surround and match to a much lower contrast (e.g. the disk labelled
14 “Typical match”). Dakin et al [34] showed in this experiment that patients with schizophrenia
15 are generally much more accurate (i.e. immune to the illusion). Patients are more likely to
16 match it to the “true match”. With permission taken from
17 <http://www.ucl.ac.uk/~smgxscd/ClinicalResearch.html>.
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25 Figure 3. Fig. 3A depicts the P100 (P1) ERP component at the central occipital electrode
26 (Oz) for each memory load for controls (CT, top) and patients with early-onset schizophrenia
27 (SZ, bottom). The different WM loads are denoted by the line colour (black for load 1, green
28 for load 2 and red for load 3). Fig. 3B shows the power of evoked oscillatory activity at theta
29 (θ , top), alpha (α , middle), and beta (β , bottom) frequencies during working memory (WM)
30 encoding for both groups at WM load 1. For each frequency the figure depicts the power for
31 each group over time (up to 3s) and a line graph comparing the controls (blue) and patients
32 (red). Modified from [76, 77].
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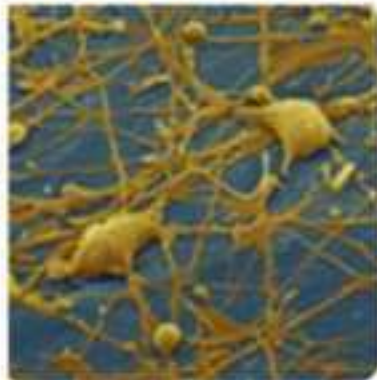
41 Figure 4: Top: Parvalbumin (PV)-containing inhibitory interneurons modulate levels of
42 excitatory activity via release of GABA to pyramidal neurons (excitatory neuron). The PV-
43 containing neurons (for example chandelier cells) are themselves regulated by glutamatergic
44 input, for example through NMDA receptors. In controls, the inhibitory neuron maintains
45 sufficient GABA release and the excitatory neuron sufficient glutamate release to balance
46 inhibition with excitation. The feedback inhibition generates gamma oscillations. Bottom: In
47 individuals with schizophrenia, decreased NMDA receptor signalling alters the monitoring
48 function of the inhibitory neuron, which down regulates its output, disinhibiting the
49 excitatory neuron. This process is compounded by reductions in GABA-related proteins.
50 Altered GABA neurotransmission by PV-containing neurons is indicated by PV reductions,
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reduced GAD 67 (GABA synthesis), a decrease in GAT1 (GABA membrane transporter) expression and an upregulation of GABA_A receptor α 2-subunit at the pyramidal neurons (enlarged circle). [Modified from 69, 128, 134].

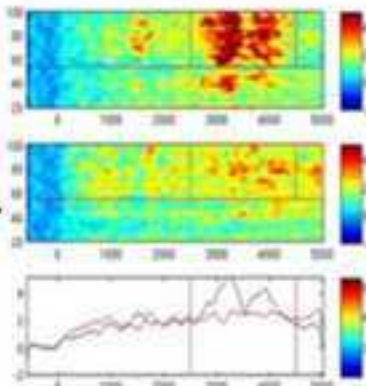
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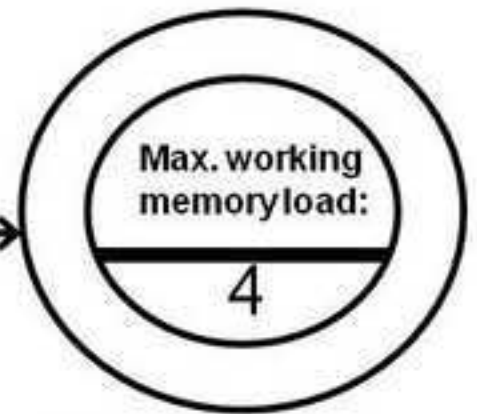
Genome/Transcriptome: i.e. COMT, Dysbindin & GAD1



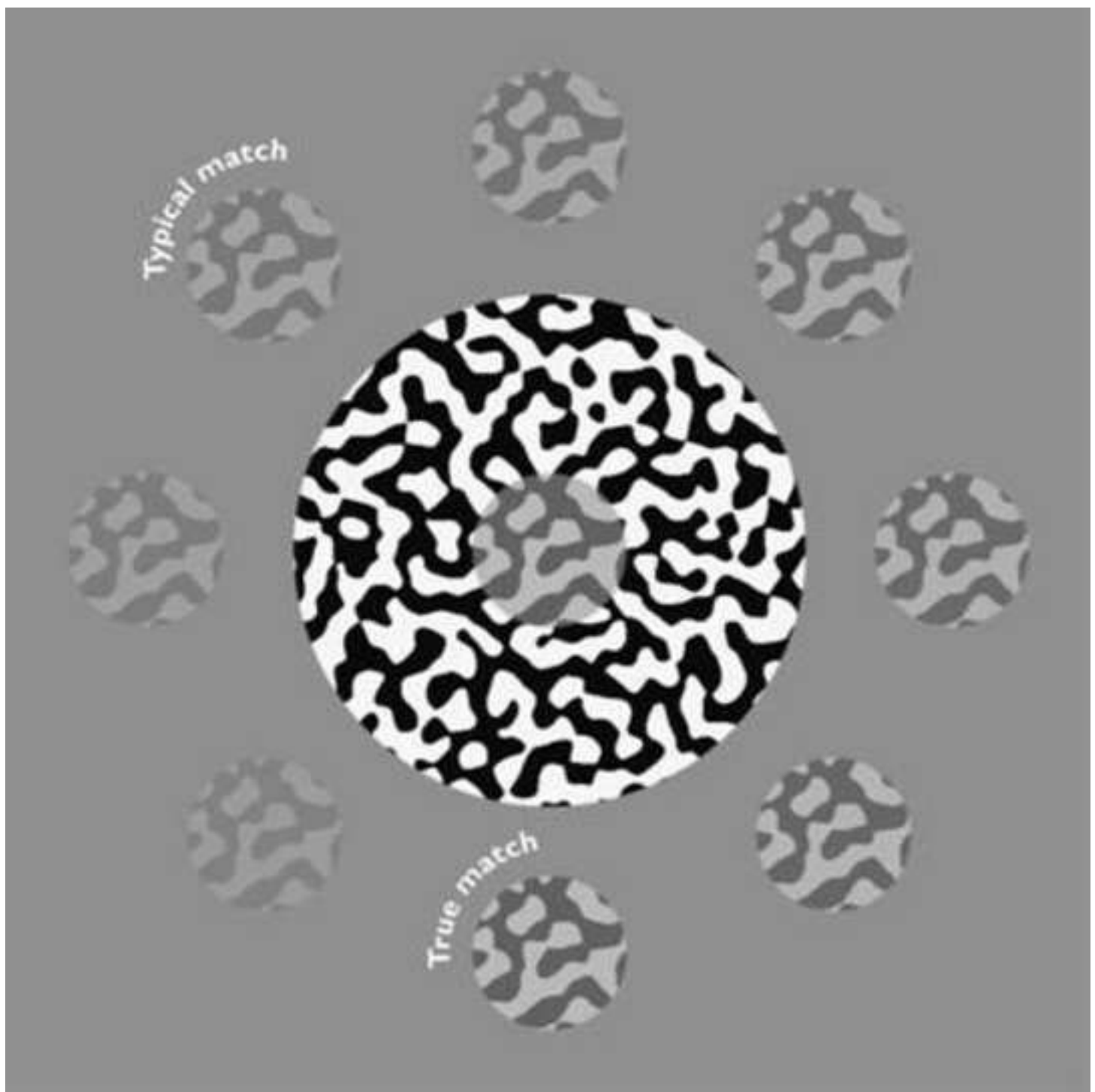
Neurons/Transmitters: i.e. GABA, Glutamate



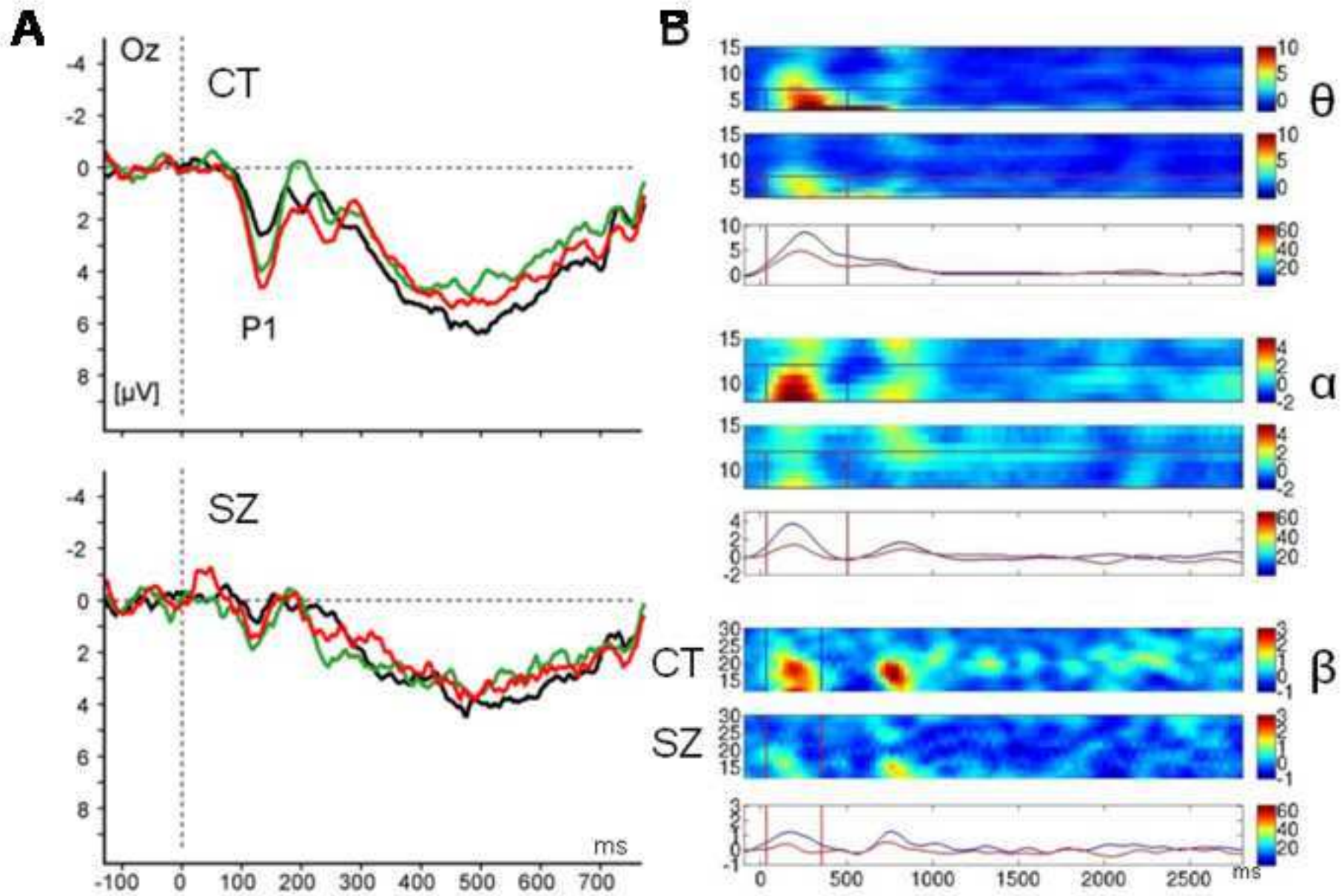
Systems: i.e. Synchronous Oscillatory Activity



Behaviour: i.e. Working Memory



Figure(s)
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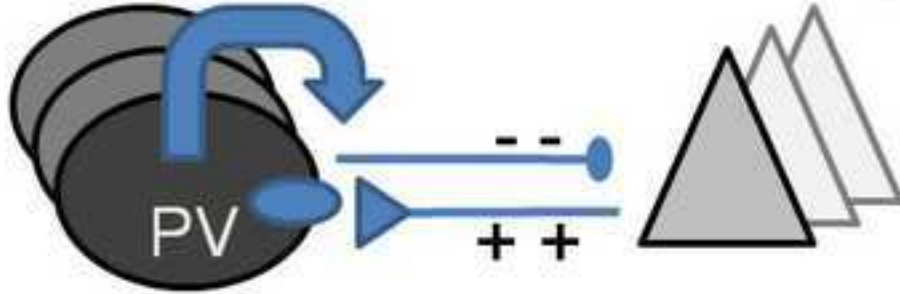
Figure(s)

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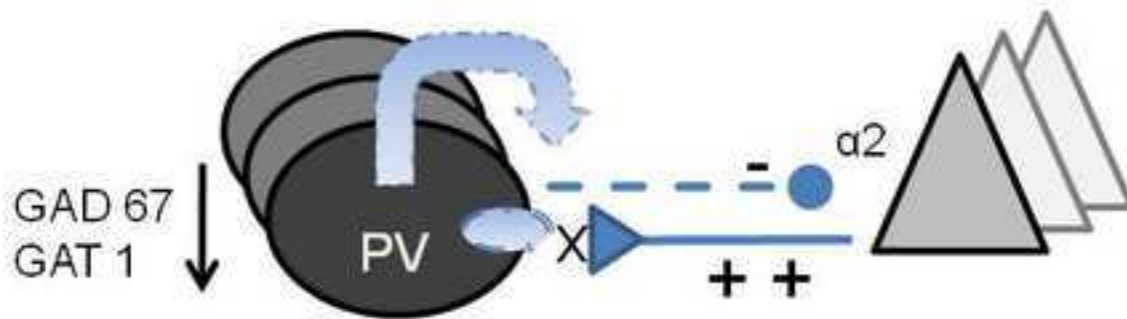


Inhibitory Neuron

Excitatory Neuron



Control



Schizophrenia

