

REVIEW

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Disturbed theta and gamma coupling as a potential mechanism for visuospatial working memory dysfunction in people with schizophrenia

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Abstract

Working memory (WM) deficits have been repeatedly observed in people with schizophrenia (PSZ) and their unaffected biological relatives (REL). Given the apparent association with genetic liability for schizophrenia, WM deficits have been proposed as a potential endophenotype for the disorder. Abnormal neural responses during WM performance have likewise been observed in PSZ and REL and may reflect the expression of genetic liability for schizophrenia in brain function. Relatively recent investigations have examined the role of neural oscillatory activity during visuospatial WM function in healthy people, as well as dysfunction in psychopathology. This research was in part motivated by a neural model of WM proposed by Lisman and Idiart (*Science* 267:1512–1515, 1995) that delineated a mechanism for representing multiple stimuli within WM through systematic interactions between neural oscillations in the theta- and gamma- frequency ranges. Aberrant oscillatory activity in theta and gamma frequency ranges has since been proposed as a potential underlying factor in WM dysfunction in PSZ and REL. The experimental evidence derived from studies of healthy people that pertains to the theta-gamma model of WM is reviewed herein. Although scarce, direct examinations of theta-gamma interactions in PSZ and REL are likewise reviewed in addition to reports of separate deficits in theta and gamma frequencies observed in PSZ during WM. The implications of theta and gamma oscillatory deficits reported in PSZ are discussed in the context of the Lisman and Idiart (*Science* 267:1512–1515, 1995) model, as well as how these deficits may result in aberrant theta-gamma interactions that give rise to visuospatial WM dysfunction. Given evidence supporting the Lisman and Idiart (*Science* 267:1512–1515, 1995) model of theta-gamma interactions in WM and the lack of direct exploration of the model in schizophrenia, there is an imperative to carry out formal testing of theta-gamma interactions in PSZ and REL during WM.

Keywords: Working memory, Schizophrenia, Theta, Gamma, Cross-frequency coupling

Background

Visuospatial working memory (WM), comprised by the coordination of processing, maintaining, manipulating, and retrieving spatial and visual information within the brain [1], has been implicated in a variety of tasks necessary for the navigation of day-to-day life, including wayfinding [2] and visuomotor learning [3, 4]. Prominent WM

deficits have been demonstrated across multiple sensory modalities in people with schizophrenia (PSZ), including in the visuospatial realm ([5 reviewed in 6]). Furthermore, better visuospatial WM function in PSZ has been shown to predict better functional and social outcomes [7, 8]. Spatial WM deficits are likewise observed in unaffected first-degree relatives of PSZ [9–11], suggesting they may represent genetic liability for schizophrenia and thus constitute a potential endophenotype for the disorder [12–15].

Electroencephalography (EEG) has been widely used to investigate the neural underpinnings of WM processes, traditionally in the form of event-related potential (ERP) studies (reviewed in [16]). PSZ have been found to demonstrate deficits in ERPs elicited from WM tasks [17–19] and tasks probing sustained attention [20–24], among others; similar deficits have been observed in first-degree relatives of people with the disorder [22, 25, 26]. More recently, EEG research has examined oscillatory activity in the brain associated with WM. Oscillatory activity in the brain, which arises from the rhythmic activation of large numbers of synapses [27], is crucial to coordinated activity in the normally functioning brain [28]. PSZ demonstrate many abnormalities in oscillatory activity, which interfere with efficient integration of activity within the brain and may contribute to the prominent cognitive and functional deficits observed in the disorder [27–29].

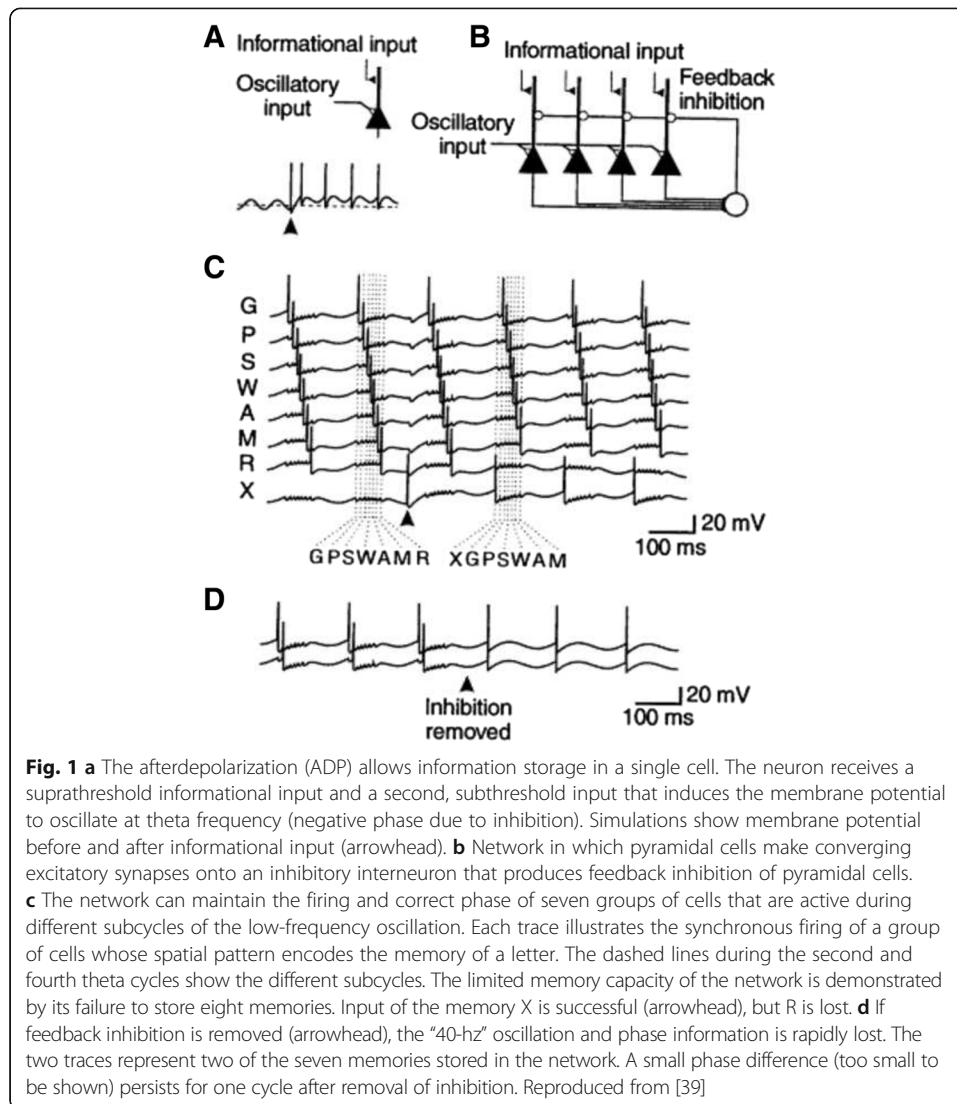
Generally speaking, high frequency oscillations are associated with synchronization in local cortical networks, and lower frequency oscillations with synchronization between brain structures/across greater distances [28]. Oscillations in the gamma-band (25–100 Hz) and the theta-band (4–8 Hz) in particular have been widely implicated in episodic memory and WM alike (reviewed in [30]). Furthermore, the synchronized superimposition of gamma cycles on oscillatory theta activity has been proposed as a mechanism for the representation of multiple items in WM, a mechanism termed the “theta/gamma code” [31]. Multi-item WM has been associated with phase-phase coupling (see Fig. 3) between theta and gamma frequencies in healthy people (e.g., [32]). In addition, theta-gamma phase-amplitude coupling (Fig. 3) has been observed in the hippocampus [33, 34] as well as from scalp EEG [35, 36] in healthy humans and, in both cases, has been predictive of WM performance [33–36]. Given these findings, abnormal theta-gamma coupling has been proposed as a mechanism for impaired WM function in PSZ [37, 38], though this hypothesis has yet to be formally investigated.

Much research has already shown abnormalities in the gamma- and theta- bands in PSZ, suggesting dysfunction in neural integration on local and global scales. The present review examines gamma and theta abnormalities during WM in PSZ in the context of the theta/gamma neural code. Though the theta/gamma code has not been formally investigated in schizophrenia to date, the mechanism and hypothesized utility of the superimposition of gamma cycles on theta cycles in relation to WM in healthy people will be reviewed. Subsequently, this review will recount observed abnormalities in PSZ for activity in the gamma-band, theta-band, and interactions between the two during WM, discussing how such abnormalities may interfere with efficient theta/gamma coding in schizophrenia. Through integration of current findings regarding abnormalities in gamma- and theta-band oscillations in schizophrenia during WM, the present review will attempt to elucidate the potential implications of these abnormalities with respect to the theta/gamma neural code.

The superimposition of gamma-band oscillations on theta oscillations: the theta/gamma neural code

The theory of a theta/gamma code as first posited by Lisman and Idiart [39] and elaborated elsewhere (e.g., [40]) offered three primary, interrelated proposals: 1) that systematic coupling of oscillatory activity of different frequencies within the brain is meaningful, 2) that this coupling serves to form a temporal code in which distinct pieces of information are associated with simultaneous activity across several cells at particular phases within a cycle of theta, and 3) that the theta/gamma code model can explain central features of WM. In an effort to support their first two hypotheses regarding the importance of cross-frequency coupling as a temporal code, the authors first addressed the plausibility of oscillatory activity as a sustained temporal organizer. The neuromodulators acetylcholine and serotonin have been shown to be released in the brain during periods of oscillatory activity [41, 42]. In the presence of these neuromodulators, firing of neuronal cells induces a period of membrane afterdepolarization (ADP) rather than the typical afterhyperpolarization, leading to a transient increase in cell excitability [43–45]. Building off these findings, the authors used computer simulations to show that the duration of ADP was on the time scale of oscillations in the alpha-theta range (5 to 12 Hz), and that such ADP could be propagated for many cycles. Thus, a single excitatory input could lead to sustained firing on subsequent oscillatory cycles, potentially serving a storage function (Fig. 1a; [39]). Furthermore, the authors noted that in Sternberg's [46] classic work on serial scanning in WM, the addition of each stimulus to the string of stimuli to be recalled resulted in an increase in reaction time of roughly 38 ms—an increase corresponding to the cycle of a neural oscillation in the beta-gamma range. Jensen and Lisman [47] elaborated on this observation, showing that the theta-gamma code model could effectively account for reaction time data and serial position effects reported by Sternberg [46, 48].¹ Roughly seven cycles in the beta-gamma range could be superimposed on a lower frequency cycle in the alpha-theta range—such as those cycles induced by the ADP—which Lisman and Idiart [39] emphasized corresponded to the canonical average capacity of WM determined by Miller [49]. Thus, Lisman and Idiart [39] demonstrated the potential for theta-gamma cross-frequency coupling to serve an ongoing, organizing function.

In their discussion of the temporal properties of theta and gamma oscillations in relation to Sternberg's classic studies [46, 48], Lisman and Idiart [39] transition to their final proposal regarding the role of the theta/gamma code in WM. The authors demonstrated through simulation how differing, non-overlapping stimuli or “memories” ([39], p. 1515) could be stored through systematic variation in the phases of the different high-frequency subcycles, with each stimulus being represented by different groups of cells that maintain the stimulus by firing simultaneously at a particular high-frequency subcycle within the nesting lower frequency cycle (Fig. 1c). Thus, particular stimuli or memories are represented by the particular spatial pattern of a group of cells, or neural ensemble [37], these memories are propagated or maintained through interactions between oscillatory activity in the theta and gamma frequencies, and sequential information regarding these memories are linked to the particular gamma subcycle within the nesting theta cycle a given memory's neural ensemble produces (or perhaps more accurately, the phase offset between the neural ensemble's gamma cycle and the nesting theta cycle; [37, 39]). The theta-gamma neural code as proposed by Lisman and

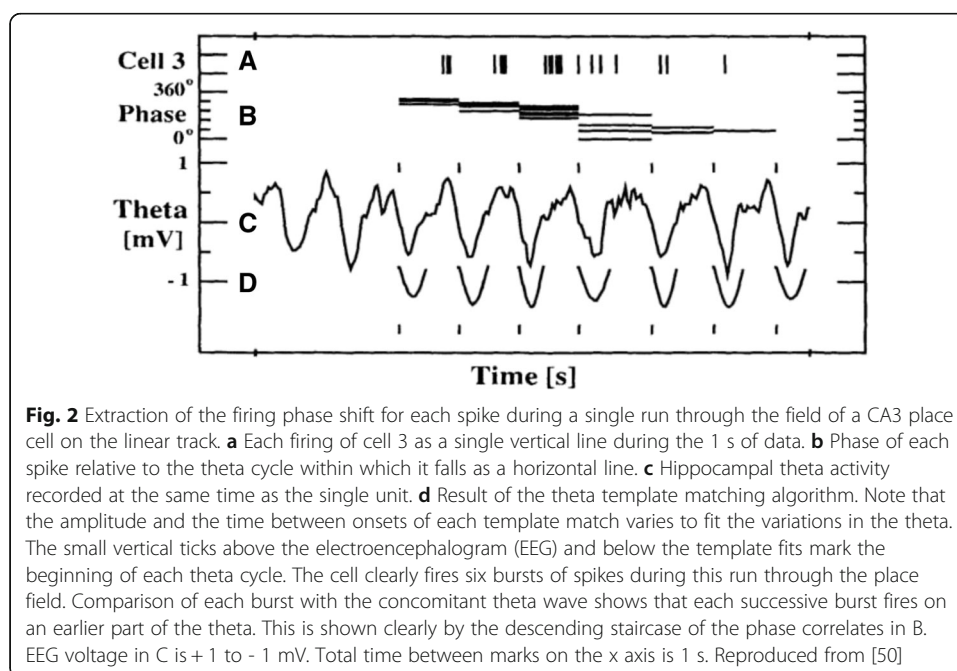


Idiart [39] represents a theoretical framework which, at its inception, integrated a number of experimental findings to provide a plausible model for the storage of multiple items in WM. This framework, which has since been further developed [e.g., 31, 37], has served as the basis for a substantial body of experimentation over the past twenty years, the vast majority of which has produced results supporting the Lisman and Idiart [39] model. A brief review of this sizeable body of literature follows, focused on studies probing WM function.

Empirical support for the theta-gamma neural code

The experimental support for Lisman and Idiart’s [39] model of the theta-gamma neural code is now widespread. In addition to other supporting observations, Lisman and Idiart [39] cited as some of the most significant early support for the theta-gamma neural code model the work of O’Keefe and Recce [50] (later clarified by [51]). These researchers examined pyramidal cells from the hippocampus of rats known as place

cells, which fire bursts of spikes as the animal moves through a particular area in its environment termed the place field of that cell [50]. Concurrent to these bursts, theta band activity also occurs in the hippocampal EEG as a rat relocates itself in its environment. Though phase correlations between theta-band activity and bursts of hippocampal activity had then been well-established [52–55], the nature of the relationship was not well clarified. Using a combination of single unit and EEG recordings from hippocampal CA1 and CA3 place cells, O’Keefe and Recce [50] showed that for a single run through the field of a given place cell on a linear track, the cell fired bursts of spikes at progressively earlier parts of the of the concomitant theta cycle, a phenomenon termed “phase precession” ([51], p. 149; Fig. 2). This finding was taken to indicate that the hippocampus may use a neural code in which theta phase conveys important information [31]—namely, the theta-gamma neural code that Lisman and Idiart [39] proposed. Skaggs and colleagues [51] replicated and elaborated this finding to demonstrate that the phase precession effect was indeed robust throughout the rat hippocampus, and observed as animals moved through two-dimensional in addition to one-dimensional space. More significantly, the researchers emphasize the support their findings lend to the notion that the theta phase-offset at which a place cell fires carries important spatial information [51]. A considerable body of work has shown that this spiking in the hippocampus and entorhinal cortex is time locked to local gamma-activity, such that firing is effectively limited to discrete, gamma-locked time windows (see [56] and [57]). Bieri, Bobbitt, and Colgin [58] similarly observed theta-gamma phase precession in rat CA1 hippocampal cells and suggested differential relationships between coupling between high- and low-gamma signals. Phase precession has likewise been observed in entorhinal grid cells [59], supporting the organization of multi-item WM by way of theta- and gamma- cycles as by Lisman and Idiart’s [39] model and its elaborations. Phase-precession is further reviewed in [56].



Much subsequent experimentation has added to the support for Lisman and Idiart's [39] model, demonstrating systematic relationships between theta- and gamma- oscillatory activity. These relationships are most frequently presented in one of two forms: phase-phase coupling (also called phase-synchrony, or simply phase-coupling), in which a given phase angle of a cycle of ongoing theta-activity tends to occur at a given phase angle of concurrent gamma-activity; and phase-amplitude coupling, in which the amplitude of gamma activity is modulated by the phase of concurrent theta-oscillations (Fig. 3). Though these types of coupling are most frequently reported separately, it has been suggested that they are likely two expressions of a single phenomenon [60, 61].

Findings of both types of coupling are summarized in Tables 1 and 2. Review of the animal studies in Table 1 reveals well-documented increases of theta-gamma coupling using intracranial recordings from the entorhinal-hippocampal system of rodents during performance of memory-focused tasks (e.g., Table 1, references i-xi). Theta-gamma coupling is likewise observed using intracranial recordings from the entorhinal cortex and hippocampus during free exploration, sleep and anesthetization (e.g., xii-xxvi) as well as from *in vitro* isolated samples (e.g., xxvii-xxix) in rats and mice. Primate studies have also revealed theta-gamma coupling in auditory cortex (xxx) during a passive listening task as well as from anterior cingulate cortex during an attention task (xxxi). Thus, WM processes are associated with increased theta-gamma coupling in the animal literature, though coupling observed in less-memory-dependent paradigms indicates that theta-gamma coupling may represent a more widespread means of communication in the brains of rodents and primates.

Table 2 reports findings of theta-gamma coupling in humans. Here, we see intracranial recordings utilized to demonstrate phase-phase coupling (e.g., Table 2, references i, vii) as well as phase-amplitude coupling (e.g., ii-vi) between theta- and gamma- activity in hippocampal areas as well as throughout the cortex. Furthermore, scalp-level recordings have shown phase-phase theta-gamma coupling in humans over primarily frontal, parietal and occipital areas (e.g., viii-xi, xv), as well as phase-amplitude coupling over much of the scalp, including prefrontal, occipital and parietal sites (e.g. xi, xiii, xiv). Notably, one recent experiment temporarily increased individuals' short-term memory capacities by using transcranial alternating current stimulation to slow their theta

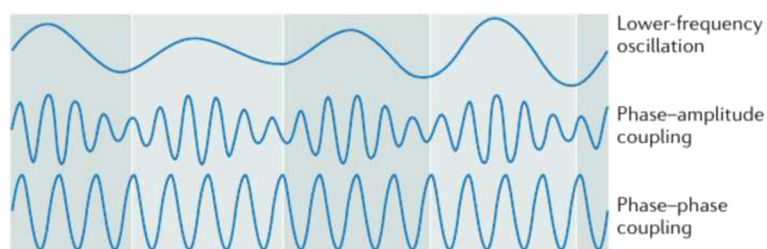


Fig. 3 Schematic overview of two cases in which oscillatory activity of a higher-frequency oscillation may be related to the phase of a lower-frequency oscillation. Dark and light boxes separate consecutive cycles of the lower-frequency oscillation. The lower-frequency oscillation of fluctuating amplitude (*top*) shows phase-amplitude coupling with a higher-frequency oscillation of fluctuating amplitude (*middle*). In this example, amplitudes of the higher-frequency oscillation are maximal during the up-phase of the lower-frequency oscillation. A higher-frequency oscillation of stable amplitude (*bottom*), shows phase-phase coupling with the low-frequency oscillation. Here, peaks of the higher-frequency oscillation always coincide with the same phase values of the lower-frequency oscillations. Reproduced from [79]

Table 1 Animal findings regarding theta-gamma coupling (TGC)

Authors & Year of publication	Subjects	Measure	Region of brain examined	Task performed / behavior during measurement	Relevant findings	Conclusions
Studies featuring memory-related tasks						
i. Tort et al. (2008) [80]	6 male Sprague–Dawley rats	iEEG	Striatum, hippocampus	T-maze	<ul style="list-style-type: none"> - Theta phase modulated high frequency (80-120Hz) but not low frequency (30-60Hz) gamma in striatum - TGC between low and high gamma power and theta phase in hippocampus - TGC strongest during decision making portions of task - Striatal theta phase modulated hippocampal high gamma power 	<ul style="list-style-type: none"> - Low and high frequency gamma may represent distinct physiological processes - TGC phase-amplitude coupling likely related to engagement of cognitive processes across varying time scales
ii. Tort, Komorowski, Manns, Kopell, & Eichenbaum (2009) [81]	6 male Long-Evans rats	iEEG	Hippocampus (CA3)	<ul style="list-style-type: none"> - Freely behaving - Item-context learning task 	<ul style="list-style-type: none"> - Theta phase modulated low gamma power in CA3 during free behavior - TGC in CA3 increased during learning and remained high during overtraining sessions - Strength of TGC predicted mean performance accuracy 	TGC important to memory processing
iii. Shirvalkar, Rapp, & Shapiro (2010) [82]	6 male Long-Evans rats	iEEG	Hippocampus	Matching-to-place task (six-arm radial water maze)	<ul style="list-style-type: none"> - Power-power TGC increased during retrieval as compared to exploration (encoding) - Power-power TGC higher for successful versus unsuccessful recall - Strength of TGC predicted memory performance, while indices of theta or gamma power alone did not 	Power-power TGC in hippocampus is important to memory-dependent behavior
iv. Belluscio, Mizuseki, Schmidt, Kempster, & Buzsáki (2012) [60]	6 male Long-Evans rats	iEEG	Hippocampus (CA1 pyramidal cells)	<ul style="list-style-type: none"> - Maze exploration - REM sleep 	<ul style="list-style-type: none"> - Phase-phase and phase-amplitude TGC 	TGC aids in coordinating neuronal spiking across multiple time scales, potentially helpful in transfer of information and plasticity dependent upon spike timing

Table 1 Animal findings regarding theta-gamma coupling (TGC) (*Continued*)

v. Cabral et al. (2014) [83]	8 NR1-KO mice ("knockouts" lacking NR1 NMDAR subunit in principal CA1 neurons), 7 littermate controls	iEEG	Hippocampus (dorsal CA1)	Five-armed "starmaze"	<ul style="list-style-type: none"> - Control mice showed increased TGC between theta phase and high-gamma amplitude for place-strategy/allocentric trials and increased TGC between theta phase and low-gamma amplitude during sequence-strategy/egocentric trials - Excess high and low gamma observed in knockout mice 	<ul style="list-style-type: none"> - Preferred frequency of gamma in TGC associated with spatial WM dependent on strategy used - Dynamic strategy switching is disrupted by NMDAR disruption
vi. Igarashi, Lu, Colgin, Moser, & Moser (2014) [84]	17 male Long-Evans rats	iEEG	Entorhinal cortex (medial and lateral, layer III), hippocampus (CA1)	Odor-place association task	<ul style="list-style-type: none"> - Odor-place learning was accompanied by increased phase-amplitude TGC in CA1 during odor-sampling (retrieval) - Phase-amplitude TGC was observed in lateral EC from beginning of task - Gamma (20-40Hz) power in both regions was unaltered 	<ul style="list-style-type: none"> - TGC in hippocampus important to retrieval of learned memories - Learning associated with more extensive coupling of already-existing gamma rhythms
vii. Nishida, Takahashi, & Lauwereyns (2014) [85]	4 male Wistar/ST rats	iEEG	Hippocampus (CA1)	Memory-guided spatial alternation task	Modulation of gamma-activity by theta phase strengthened overall from beginning to end of session	Increase in TGC may reflect plasticity of CA1-CA3/C A1-EC network, suggestive of optimized communication between these areas
xiii. Schomburg et al. (2014) [57]	9 male Long-Evans, 3 male Sprague-Dawley rats	iEEG	Hippocampus, entorhinal cortex	<ul style="list-style-type: none"> - Linear track - T-maze - Open field - REM Sleep 	<ul style="list-style-type: none"> - Strong TGC between theta phase and gamma power in hippocampus during memory recall - Gamma amplitude also modulated by theta phase in EC - Preferred theta phase dependent upon from where input is being received 	Temporal coordination of activity in entorhinal-hippocampus complex primarily supported by theta- and low-frequency gamma activity

Table 1 Animal findings regarding theta-gamma coupling (TGC) (Continued)

ix. Takahashi, Nishida, Redish, & Lauwereyns (2014) [86]	4 male Wistar/ST rats	iEEG	Hippocampus (CA1)	Memory-guided spatial alternation task	Gamma-amplitudes in CA1 were phase-locked to theta during a "fixation" period prior to task performance - Preferred theta-phase differed between high- (60–90 Hz) and low- (30–45 Hz) gamma - low-gamma activity increased with a concurrent decrease in high-gamma activity towards the end of the fixation period	High-gamma activity associated with externally cued information processing, low-gamma with internally generated information processing
x. Trimper, Stefanescu, & Manns (2014) [87]	6 male Long-Evans rats	iEEG	Entorhinal cortex	Novel object recognition memory task	- Increased theta-high-gamma phase-amplitude coupling in the hippocampi of rats exploring novel objects - Gamma-gamma phase synchrony between CA3 and CA1 LFPs that varied with relative theta- phase and was greatest for objects subsequently remembered	TGC associated with memory processing, but differentially dependent on frequency of gamma activity
xi. Siegle & Wilson (2014) [88]	Male parvalbumin-Cre (PV-Cre) heterozygote mice	iEEG	Hippocampus	T-maze	- High-gamma modulated by theta-phase during T-maze performance - Optogenetic stimulation of inhibitory interneurons at trough of theta improved task performance during retrieval, while stimulation at theta peaks improved performance during encoding	- Encoding and retrieval processes occur at different preferential theta phases - Phase-specific inhibition may reduce the response to task-irrelevant inputs
Studies featuring free exploration, sleep or anesthetization						
xii. Buzsáki, Leung, & Vanderwolf (1983) [53]	43 male Long Evans rats	iEEG	Hippocampus	- Activity wheel - Immobility	- Fast EEG (gamma: 25-70Hz) as well as interneuron spiking superimposed upon and modulated by theta phase - More prominent in activity than immobility	Slow activity (theta) may be generated through feed-forward inhibition from septum and direct excitation from entorhinal cortex

Table 1 Animal findings regarding theta-gamma coupling (TGC) (*Continued*)

xiii. Soltesz & Deschenes (1993) [89]	Male and female Sprague Dawley rats	iEEG	Hippocampus (CA1, CA3)	Ketamine-xylazine anesthesia	- Injection of Cl ⁻ ions into pyramidal cells brought on high frequency (25-50Hz) oscillation modulated at theta-frequency	- Fast oscillations generated by Cl ⁻ dependent GABA _A receptors - Theta modulation of fast oscillation in hippocampus likely arises through interaction between cholinergic and GABAergic neurotransmitter systems
xiv. Bragin et al. (1995) [90]	45 male and female Sprague–Dawley rats	iEEG	Hippocampus (dentate hilus)	- Freely behaving - Immobility - REM Sleep	- Prominent theta-phase to gamma-amplitude coupling, particularly in dentate hilus region, during activity and REM sleep	- TGC due to reciprocal connections between interneurons, hilar mossy cells and CA3 pyramidal cells
xv. Chrobak & Buzsáki (1998) [91]	19 Sprague Dawley rats	iEEG	Entorhinal cortex (layers II & III), Hippocampus	Freely behaving	- Nesting of gamma oscillations within theta oscillations in the entorhinal cortex and hippocampus - Neuronal spiking in entorhinal cortex in phase with the local, nested gamma oscillations - Synchronization between theta-gamma rhythms in entorhinal cortex and dentate hilar region of hippocampus	Systematic phase-locking of gamma oscillations to nesting theta oscillations is necessary for communication within perforant pathway
xvi. Buzsáki et al. (2003) [92]	13 hybrid (C57B6/J & 129S6/SvEvTac) and 3 inbred (C57B6/J) mice	iEEG	Hippocampus (CA1 pyramidal layer, dentate gyrus)	- Freely behaving - Immobile awake - Sleeping	Gamma, interneurons and pyramidal cells all phase-locked to concurrent theta rhythm during free behavior	- Mouse brain is similar to rat brain - Interneurons critical to gamma generation
xvii. Csicsvari, Jamieson, Wise, & Buzsáki (2003) [93]	12 male Sprague–Dawley rats	iEEG	Hippocampus (CA1, CA3, granule cell layers)	- Freely behaving - Immobility - Slow wave sleep - REM sleep	- Gamma power varied with theta phase when theta present but irregularly otherwise - Gamma field power greater in CA1 during theta-associated behaviors - Gamma CSD power greater in granule cell layer during theta-associated behaviors	Concurrent theta is not necessary for gamma oscillation, but theta enhances and modulates gamma when present

Table 1 Animal findings regarding theta-gamma coupling (TGC) (*Continued*)

xviii. Hentschke, Perkins, Pearce, & Banks (2007) [94]	B6129SF2/J wild-type mice	iEEG	Hippocampus (CA1, all laminae)	- Freely behaving - Immobile awake	- Phase-amplitude TGC during exploration and immobility, highest around hippocampal fissure - Significantly decreased by injection of atropine, a muscarinic antagonist	Phase-amplitude TGC in CA1 influenced by neurons with muscarinic receptors
xix. Sirota et al. (2008) [95]	28 rats, 11 mice	iEEG	Hippocampus, neocortex	- Active ($n = 28$ rats, 11 mice) - Anesthetized ($n = 27$ rats)	- Phase-phase coupling between hippocampal theta rhythms and gamma oscillations in multiple regions of neocortex, including prefrontal cortex and primary sensory areas	TGC between hippocampus and neocortex means for transfer of information from neocortex to hippocampus
xx. Wulff et al. (2009) [96]	PV- $\Delta\gamma 2$ mice (mice with GABA _A receptor $\gamma 2$ subunit ablated from parvalbumin-positive interneurons in hippocampus); normal litter-mates as controls	iEEG	Hippocampus	Freely behaving	- Phase-amplitude TGC nearly three times as weak in PV- $\Delta\gamma 2$ as control mice	PV+ neurons involved in coupling of theta to gamma activity
xxi. Quilichini, Sirota, & Buzsáki (2010) [97]	39 male Sprague–Dawley rats	iEEG	Entorhinal cortex (layers II, III, V)	- Anesthetized	- Gamma (including high frequency) power modulated by theta phase in all layers - Different theta phase preferences from layer to layer	Gamma activity can be generated locally in individual EC layers and relate to phase of hippocampal theta activity
xxii. De Almeida, Idiart, Villavicencio, & Lisman (2012) [59]	Rats	iEEG	Entorhinal cortex (grid cells)	- Open field exploration - Traversal of linear track	- Phase precession observed in grid cells with two varying “modes”: inbound (firing occurs as rat approaches center of place field) and outbound (firing occurs as rat leaves center)	Grid cells have different modes which account for upcoming locations versus those recently passed, serving both storage and predictive functions of hippocampus
xxiii. Caixeta, Cornélio, Scheffer-Teixeira, Ribeiro, & Tort (2013) [65]	8 male Wistar rats	iEEG	Left hippocampus	- Open field exploration - Saline injection - Ketamine injection	- Ketamine increased motor activity and gamma power - Prominent phase-amplitude coupling between theta- and high-gamma (60–100Hz) as well as high frequency	Some symptoms of schizophrenia may be explained by aberrant TGC and/or theta-HFO coupling

Table 1 Animal findings regarding theta-gamma coupling (TGC) (*Continued*)

					oscillations (HFO; 110–160Hz) pre-ketamine injection		
					- Theta-HFO coupling increased with ketamine, while theta-gamma coupling increased at the lowest dosage but markedly disturbed at the highest dosage		
xxiv. Newman, Gillet, Climer, & Hasselmo (2013) [98]	6 male Long-Evans rats	iEEG	Entorhinal cortex (medial)	- Lap-running on circular track - With and without scopolamine injection	- Robust phase-power TGC for both low- (20-40Hz) and high- (60–120Hz) gamma - Scopolamine selectively reduced high gamma power at peak of theta	- Encoding and retrieval may occur at peak and through of theta, respectively - Acetylcholine influences balance between encoding and retrieval processes	
xxv. Pernia-Andrade & Jonas (2014) [99]	Wistar rats	Whole cell recording	Hippocampal (dentate gyrus) granule cells	- Anesthetized - Free exploration	- EPSCs coherent with LFP theta oscillations; IPSCs coherent with LFP gamma oscillations - Action potentials phase locked to theta-gamma oscillations in LFP	- TGC in dentate gyrus may reflect inhibitory gamma currents phase locked to theta currents and initiated by excitation from the entorhinal cortex - Compound signal may serve as temporal reference signal for encoding in granule cells	
xxvi. Yamamoto, Suh, Takeuchi, & Tonegawa (2014) [100]	MECIII-TetX MT Mice (allow for reversible silencing of synaptic transmission of MEC layer III pyramidal cells), control litter-mates	iEEG	Hippocampus (CA1), entorhinal cortex (medial, layer III)	Open field exploration	- High-frequency and low-frequency gamma modulate to different phases of theta	High-frequency gamma contributes uniquely to WM function	
In vitro or isolate studies							
xxvii. Cunningham, Davies, Buhl, Kopell, & Whittington (2003) [101]	Male Sprague–Dawley rats	iEEG	Hippocampus, entorhinal cortex	In vitro	- Amplitude of field gamma activity modulated at theta frequency in presence of kainate receptor activation	EC can generate intrinsic theta activity	

Table 1 Animal findings regarding theta-gamma coupling (TGC) (*Continued*)

xxviii. Goutagny et al. (2013) [102]	TgCRND8 mice (develop at 3 months of age amyloid-beta plaques typical of Alzheimer's disease and accompanied by similar cognitive decline)	iEEG	Hippocampus	N/A (hippocampal isolate)	- Some TgCRND8 showed alterations in phase-amplitude TGC prior to accumulation of amyloid-beta plaques or cognitive decline - Exclusive to theta coupling with fast gamma, not slow gamma	Declines in TGC are early electrophysiological indicators of hippocampal network dysfunction
xxix. Pastoll, Solanka, van Rossum, & Nolan (2013) [103]	Adult Thy1-ChR2-YFP line 18 mice	iEEG	Entorhinal cortex (medial)	N/A (isolated brain slices, though with simulated movement)	- Optogenetic stimulation of medial entorhinal cortex at theta frequency sufficient to produce nested gamma activity with both phase and amplitude coupled to theta phase - Nested gamma is mediated by feedback inhibition	Local medial entorhinal cortex circuit produces TGC with "clock-like" (p. 153) consistency; coupled signals may serve as temporal references for other neuronal computations
Primate studies						
xxx. Lakatos et al. (2005) [104]	4 male macaque monkeys	iEEG	Primary auditory cortex	Passive listening task	Spontaneous gamma-activity found to fluctuate at theta-frequency, and theta-activity found to subsequently fluctuate at delta frequency	Oscillatory activity is organized in a hierarchical manner, not exclusively limited to gamma and theta activity
xxxi. Voloh, Valiante, Everling, & Womelsdorf (2015) [105]	2 macaque monkeys	iEEG	Medial and lateral PFC (anterior cingulate cortex)	Attention task	- Theta-phase to gamma-amplitude TGC between various sites in ACC and PFC during task performance, but not before errors	TGC essential to integration of varied and distributed activities, including attention, in neural networks

WM working memory, *TGC* theta-gamma coupling, *iEEG* intracranial EEG, *LFP* local field potential, *CSD* current source density, *EC* entorhinal cortex, *HFO* high-frequency oscillation, *ACC* anterior cingulate cortex, *PFC* prefrontal cortex

Table 2 Human findings regarding theta-gamma coupling (TGC)

Authors & Year of Publication	Subjects	Measure	Region of Brain/Scalp Examined	Task Performed/Behavior during Measurement	WM Subprocess(es) Analyzed	Relevant Findings	Conclusions
Studies utilizing intracranial EEG (iEEG)							
i. Fell et al. (2003) [106]	9 patients with pharmacoresistant temporal lobe epilepsy	iEEG	Hippocampus, entorhinal cortex	Single-trial word list learning paradigm	Encoding	<ul style="list-style-type: none"> - Phase-phase TGC across the rhinal cortex and hippocampus during WM encoding - Coupling greater for words successfully recalled 	TGC crucial to actual memory formation rather than general state of WM encoding
ii. Mormann et al. (2005) [76]	12 patients with pharmacoresistant temporal lobe epilepsy (5 women, aged 40.3 ± 10.1 years)	iEEG	Hippocampus, rhinal cortex	Continuous visual word recognition paradigm	Continuous recognition (Combination of encoding and retrieval)	<ul style="list-style-type: none"> - Modulation of gamma-amplitude by theta- phase in both rhinal cortex hippocampus - Rhinal modulation greatest for correct rejections, hippocampal modulation greatest for hits 	Phase-amplitude TGC may underlie encoding processes in rhinal cortex and retrieval processes in hippocampus
iii. Axmacher et al. (2010) [33]	14 participants with pharmacoresistant temporal lobe epilepsy (3 female, aged 38.3 ± 11.8 years)	iEEG	Hippocampus	Visual analogue of Sternberg task	Maintenance	<ul style="list-style-type: none"> - Theta phase to gamma power TGC increased during maintenance compared to baseline - More precise coupling associated with faster reaction times - Increased WM load related to less modulation of gamma 	<ul style="list-style-type: none"> - Medial temporal lobe involved in WM when multiple stimuli are to be maintained - TGC functionally relevant to WM processes
iv. Canolty et al. (2006) [61]	5 females (aged 24 to 45 years)	iEEG	Frontal, temporal, parietal lobes	<ul style="list-style-type: none"> - Passive listening - Active listening/target detection - Picture naming - Verb generation - Finger tapping - Mouth movement & articulation - Auditory/vibrotactile stimulus presentation 	Unclear	<ul style="list-style-type: none"> - Strong modulation of gamma throughout examined areas by theta phase across all tasks; highest modulation in high gamma (80–150Hz) - Largest gamma amplitudes occur at trough of theta 	TGC coordinates various cortical regions for purposeful activity

Table 2 Human findings regarding theta-gamma coupling (TGC) (Continued)

				with unimodal target detection - Auditory N-back task - Visual search task - Visual silent reading task - Facial emotion recognition task - Motor, auditory and tactile imagery			
v. van der Meij, Kahana, & Maris (2012) [107]	27 patients (12 female) with pharmacoresistant epilepsy	iEEG	Frontal, temporal, parietal, occipital, limbic	Sternberg task	Encoding, maintenance	Widespread phase-amplitude coupling between multiple frequency bands across distances greater than 10 cm between sensors spread throughout cortex and other measured areas	<ul style="list-style-type: none"> - Phase-amplitude coupling is pervasive, has a wide spatial distribution, and varies greatly in terms of frequencies involved and phases preferred - As such, phase-amplitude coupling likely involved in various forms of selective communication between brain areas
vi. Maris, van Vugt, & Kahana (2011) [108]	26 patients with implanted electrodes for purpose of presurgical diagnosis	iEEG	Varied from patient-to-patient, but included frontal, temporal and parietal sites	Sternberg task	Encoding, maintenance	<ul style="list-style-type: none"> - Phase to amplitude coupling widely distributed across frequency as well as location; included frontal, temporal and parietal sites - TGC most prominent in within-electrode analyses - Phase-amplitude coupling increased in some areas during WM and decreased in others - In most coupling patterns, high-frequency bursts are synchronized across locations 	<ul style="list-style-type: none"> - WM processes affect coupling heterogeneously, depending on location and frequencies involved - Phase-amplitude coupling important to coordination of neural activity spatiotemporally

Table 2 Human findings regarding theta-gamma coupling (TGC) (*Continued*)

vii. Chaieb et al. (2015) [34]	14 patients with pharmacoresistant temporal lobe epilepsy	iEEG	Hippocampus	Modified Sternberg paradigm featuring facial stimuli	Maintenance	<ul style="list-style-type: none"> - Increases in phase-phase TGC observed for multi-item but not single-item trials for coupling factor of 6 (e.g., 6 gamma cycles to 1 theta cycle) - Changes in coupling measures across WM loads predicted WM capacities 	TGC particularly important to multi-item WM
Studies utilizing scalp-level recordings							
viii. Schack, Vath, Petsche, Geissler, & Möller (2002) [70]	10 right-handed female adults (aged 25 to 35 years)	Scalp EEG	Frontal, prefrontal, frontopolar regions	Sternberg tasks featuring number words and random figures	Encoding, maintenance and retrieval	<ul style="list-style-type: none"> - Phase-coupling between theta activity over frontal areas and gamma activity over frontopolar areas during maintenance of number words 	TGC is prominent during human maintenance of information in WM, supporting Lisman & Idiart's [1] model
ix. Baerbel Schack & Weiss (2005) [109]	23 females (aged 23.7 ± 2.7 years)	Scalp EEG	Scalp-wide	Single-trial word list learning paradigm	Encoding	<ul style="list-style-type: none"> - Increased frontocentral phase-phase TGC for words later recalled vs. those not - Phase-phase TGC also observed <i>between</i> Fz and Cz 	Gabor expansion is a useful means of assessing phase-phase TGC from scalp EEG
x. Sauseng, Klimesch, Gruber, & Birbaumer (2008) [69]	22 analyzed patients (19 females, average age of 23.6 years)	Scalp EEG	Scalp-wide	Cued visual attention task	Target presentation	<ul style="list-style-type: none"> - Phase-phase TGC over posterior areas enhanced by attention shift to cued visual field - Stronger TGC over areas contralateral to cued visual field 	Phase-phase TGC over posterior areas reflects matching of stored information to incoming visual input
xi. Sauseng et al. (2009) [32]	21 right-handed participants (15 females, aged 23.9 ± 4.4 years)	Scalp EEG	Scalp-wide	Visuospatial delayed match-to-sample task	Maintenance	<ul style="list-style-type: none"> - Phase-amplitude TGC over bilateral parietal and occipital sites - Phase-phase TGC modulated by WM load over right posterior sites, exclusive to relevant information - Degree of phase-phase TGC modulation by WM load predictive of WM capacity 	<ul style="list-style-type: none"> - TGC, and particularly phase-phase relationships, are central to visual WM function - Independent mechanisms for maintenance of relevant vs. suppression of irrelevant info

Table 2 Human findings regarding theta-gamma coupling (TGC) (*Continued*)

xii. (Holz, Glennon, Prendergast, & Sauseng (2010) [68]	18 participants (13 female, aged 23.67 ± 2.99 years)	Scalp EEG	Scalp-wide	Visuospatial delayed match-to-sample task	Retrieval	<ul style="list-style-type: none"> - Increased phase-phase TGC over parieto-occipital brain regions soon after probe presentation - Matching increased TGC in right hemisphere; non-matching increased TGC in left hemisphere 	Comparison of stored information to visual inputs leads to phase-phase TGC over parieto-occipital regions
xiii. Park, Lee, & Lee (2011) [36]	31 older participants (19 females, aged 66.45 ± 5.75 years)	Scalp EEG	Scalp-wide	Spatial delayed match-to-sample task	Maintenance	<ul style="list-style-type: none"> - TGC between theta phase and gamma power across scalp, enhanced in left centro-parietal regions - Strength of TGC at FP1 predicted task performance - Strength of TGC at P8 predicted delayed figure recall performance 	TGC is important to visual memory function (e.g., parietal correlation) but may also reflect attentional processes (e.g., prefrontal correlation)
xiv. Park, Jhung, Lee, & An (2013) [35]	13 right-handed participants (5 females, aged 20.8 ± 3.1 years)	Scalp EEG	Scalp-wide	Visuospatial 2-back task, vigilance task	Maintenance	TGC between theta phase and gamma power most prominent over prefrontal areas in WM task but not vigilance task	TGC recorded from scalp represents WM processes rather than attentional processes
xv. Lee & Yang (2014) [110]	9 right-handed males (aged 21.22 ± 0.97 years)	Scalp EEG	Scalp-wide	Visuospatial delayed match-to-sample task	Maintenance	Strength of phase-phase TGC at P8 predicted task performance	Phase-phase TGC can be used as a measure of WM ability
xvi. Vosskuhl, Huster, & Herrmann (2015) [111]	33 right-handed participants (14 females, aged 25.74 ± 2.69 years)	Scalp EEG	F3, Fz, F4, C3, Cz, C4	Transcranial alternating current stimulation; digit span task; 3-back task	Encoding during stimulation	<ul style="list-style-type: none"> - Short-term memory capacity as assessed using forward digit span was increased during stimulation - Theta amplitude increased after stimulation 	Supports theory that the length of theta cycle (e.g., theta frequency) limits how many gamma cycles can be superimposed upon it

Table 2 Human findings regarding theta-gamma coupling (TGC) (*Continued*)

xvii. Heusser, Poeppel, Ezzyat, & Davachi (2016) [77]	20 right-handed males (aged 21–25; mean age 28)	MEG	Scalp-wide; left lateral and posterior clusters of sensors used for analyses	Visual temporal order memory paradigm	Encoding	<ul style="list-style-type: none"> - Peak of gamma power shifted progressively later with memory stimuli progressively later in presented sequence - Relative gamma peaks reflected the order of stimulus presentation in sequence 	Strongly supports notion that the sequential order of stimuli is encoded using a theta-gamma code
xviii. Alekseichuk, Turi, de Lara, Antal, & Paulus (2016) [112]	47 healthy people (25 females, aged 19–28)	Scalp EEG	Scalp-wide	Transcranial alternating current stimulation; 2-back visuospatial memory test	Encoding/retrieval during stimulation	<ul style="list-style-type: none"> - Transcranial alternating current stimulation improved task performance and increased phase connectivity across scalp - 80Hz to 100Hz stimulation during theta peak produced optimal effects 	<ul style="list-style-type: none"> - Transcranial current in gamma frequency range improved WM performance - High gamma may be particularly important to WM-related coupling

WM working memory, TGC theta-gamma coupling, iEEG intracranial EEG, LFP local field potential, CSD current source density, EC entorhinal cortex, HFO high-frequency oscillation, ACC anterior cingulate cortex, PFC prefrontal cortex

cycles (xvi), while another used MEG to show progressively later peaks in gamma activity relative to concurrent theta activity for progressively later memory items in an encoding sequence (xvii). In addition, measures of theta-gamma coupling have similarly been related to WM performance in experimentation with humans (e.g., vii, xi, xiii, xv). Thus, theta-gamma coupling has been repeatedly associated with WM processes in both the animal and human literature.

The role of abnormal theta-/gamma- oscillations in schizophrenia

Given the well-documented importance of theta-gamma modulations to memory processes in animal and human studies alike, abnormal interactions between theta- and gamma-oscillations have been proposed to explain the prominent WM deficits observed in PSZ [37, 38]. In particular, predictive relationships demonstrated between indices of theta-gamma coupling and WM capacity [32, 34] as well as performance on WM tasks [36, 107] in healthy people suggest that impaired WM performance observed in PSZ may be attributed to deficient theta-gamma coupling. Formal investigation of this proposal has been scarce to date. As such, in addition to the few direct examinations of theta-gamma coupling in PSZ, demonstrated abnormalities in theta- and gamma- oscillations independently are likewise reported, and their potential relevance to interactions between the two frequency bands is discussed.

Theta-gamma coupling in people with schizophrenia

Few studies have directly examined interactions between theta- and gamma- activity in PSZ. Allen and colleagues [62] examined phase-amplitude coupling between low- and high-frequencies using independent component analysis (ICA) of EEG recorded from PSZ during performance of an auditory oddball task. In this ICA, data for comodulation between various frequencies were decomposed into separate components based on spectral and spatial composition. One such component showing widespread coupling between lower-frequency phases and higher-frequency amplitudes across the entire scalp was less prominent in PSZ data compared to that of healthy controls, and another component depicting modulation of high frequency amplitude by low frequency phase at frontotemporal sites was more prominent for PSZ than controls. Another component revealed strong theta-gamma coupling over occipital-parietal areas, but the loading parameters for said component did not differ between groups (e.g., the component was equivalently strong in PSZ and healthy controls). First-degree relatives of people with the disorder were included in this study and showed coupling intermediate to that of PSZ and healthy controls, though their data were not tested statistically due to power limitations. The authors interpret their results to indicate that abnormal cross-frequency coupling may represent an endophenotype for schizophrenia, particularly in light of genetic associations they report for genotypes for certain genes and loading parameters for various independent components in PSZ. However, though patterns of cross-frequency coupling were altered in PSZ, theta-gamma coupling is still prominent, especially over posterior sites. As such, theta-gamma coupling may not be significantly altered in the disorder, at least in the context of novelty detection. No correlations between measures of cross-frequency coupling and performance were observed [62]. Thus, this study provides evidence for preserved theta-gamma phase-amplitude coupling in PSZ; however, given the minimal role WM plays in the oddball paradigm, the theta-gamma interactions examined in this study may be distinct from those related to WM.

The only other published work examining theta-gamma cross-frequency interactions in PSZ comes from Kirihara and colleagues [63]. Using scalp EEG recorded during presentation of 40-hz steady state auditory stimuli, the authors found reduced intertrial phase coherence, increased theta amplitude, and undisturbed theta-gamma phase-amplitude coupling in PSZ relative to healthy controls. The authors interpret these findings to indicate a preserved hierarchical organization of theta and gamma activity in PSZ despite abnormalities in theta- and gamma- activity independently [63]. Notably, the simple auditory processing task used in this study does not tap memory processes, for which theta-gamma interactions have been shown to be essential and greatly impaired in PSZ; thus, the reported intact theta-gamma coupling should not be interpreted as indicative of preserved coupling at large.

Two additional studies investigated theta-gamma coupling under influence of ketamine, an NMDAR antagonist which is used as a pharmacological model of schizophrenia in both animals and humans. Neymotin and colleagues [64] used a computer model of hippocampal CA3 to investigate the effect of the application of simulated ketamine. Ketamine administration disrupted theta-gamma coupling in the simulation, apparently due to its antagonistic effect on NMDA receptors on oriens-lacunosum moleculare cells (OLM); normal coupling was restored via injection of a continuous, depolarizing current into these OLM cells, suggesting a potential intervention for treating deficits in WM and other cognitive processes in PSZ. Similarly, Caixeta and colleagues [65] found that ketamine altered theta-gamma coupling in the hippocampus of rats, again suggesting the importance of theta-gamma interactions to cognitive deficits in PSZ. Still, theta-gamma coupling in the context of memory function in PSZ has not yet been directly examined.

Theta- and gamma- band abnormalities in people with schizophrenia

Though research on theta-gamma coupling in schizophrenia is sparse, findings from the individual bands support the notion of WM impairments in PSZ stemming from aberrant theta-gamma interactions. Abnormalities in theta- and gamma-activity during WM reported in PSZ are summarized in Table 3. These abnormalities include deficits in theta-synchrony (e.g., Table 3, reference iv) and aberrations in overall theta-amplitudes (e.g., i-iv) as well as modulations in response to task demands (e.g., i, iv), though results are variable regarding whether PSZ show enhanced or reduced amplitudes/modulation as compared with controls. Despite this variability, all studies show a failure of PSZ to modulate theta amplitudes with changes in task demands compared to controls, suggesting an inefficient allocation of cognitive resources (suggested by i, iii, iv) and/or deficiencies in neural responses associated with sequential presentation of stimuli (suggested by ii). Amplitudes of gamma-activity during WM have similarly been found to be abnormal in PSZ (e.g., v-ix), though findings are again mixed as to whether these abnormalities are enhancements or reductions compared to controls; as with theta, however, PSZ frequently fail to modulate (e.g., vi, viii-ix) or abnormally modulate (vii) gamma responses with changes in task demands. Again, these findings suggest that PSZ either lack or misallocate cognitive resources as compared to healthy controls. Discrepancies in whether oscillatory responses are increased or decreased in PSZ relative to controls have many potential sources, including heterogeneity in symptomatology, differences in stage of illness (e.g., early onset

Table 3 Theta and gamma abnormalities in people with schizophrenia (PSZ) during working memory processes

Authors & Year of Publication	Subjects	Measure	Region of Brain/Scalp Examined	Task Performed/ Behavior during Measurement	WM Subprocess(es) Analyzed	Relevant Findings	Conclusions
Theta abnormalities							
i. Schmiedt, Brand, Hildebrandt, & Başar-Eroğlu (2005) [113]	- 10 inpatient PSZ (aged 34 ± 6 years) - 10 healthy controls (aged 24 ± 4 years)	Scalp EEG	Fz, Cz, Pz, Oz, F3, F4, T5, T6	Visual variable N-back with action monitoring/ rule-switching	Maintenance, encoding	- Widespread reduced theta-amplitude in PSZ during maintenance compared to controls - Enhanced amplitude in PSZ at left temporal locations in first 250 ms post-stimulus - PSZ failed to modulate frontal theta amplitude with task changes, whereas controls' amplitudes increased with task difficulty	- Increased temporal theta indicates pathological processes in frontal and temporal regions in PSZ - Failure to modulate theta suggests deficits in executive processes related to WM
ii. Haenschel et al. (2009) [29]	- 14 patients with early onset schizophrenia (onset prior to age 18; 5 females, aged 17.76 ± 1.44 years) - 14 controls (aged 17.37 ± 1.41 years)	Scalp EEG	Scalp-wide	Delayed visual discrimination task	Encoding, maintenance and retrieval	- PSZ showed reduced theta-amplitudes during encoding and retrieval as compared to controls - Evoked posterior theta decreased with increasing WM load during encoding in controls but not PSZ - Evoked anterior theta during encoding predictive of performance in controls but not PSZ	- Reduced evoked theta during encoding may reflect impaired phase resetting to stimuli; reductions during retrieval may reflect a failure in PSZ to recognize previously encountered stimuli - Lack of decrease in theta amplitude in PSZ may reflect deficient responses to initial stimuli as well as habituation processes
iii. Missonnier et al. (2012) [114]	- 15 patients with first-episode psychosis (3 females, aged 21.9 ± 2.6 years, 6 diagnosed schizophreniform, 9 schizophrenia) - 18 controls (9 females, aged 24.4 ± 1.5 years)	Scalp EEG	Scalp-wide	- Visual oddball task - Visual N-back task - Simple detection task	Maintenance, encoding	- PSZ showed increased sustained theta amplitudes in frontal areas for the retention period of detection and 1-back tasks, as well as delayed maximums of phasic event-related theta synchronization, compared to controls	PSZ fail to appropriately modulate brain activation to address increasing demands on WM

Table 3 Theta and gamma abnormalities in people with schizophrenia (PSZ) during working memory processes (*Continued*)

iv. Griesmayr et al. (2014) [115]	- 21 PSZ (5 females, aged 22 to 46.02 years, mean age = 31.96 years) - 21 healthy controls (5 females, aged 20.05 to 47.02 years, mean age = 31.55)	Scalp EEG	Scalp-wide	Visuospatial delayed match-to-sample task with manipulation	Maintenance/manipulation	- Reduced phase-synchrony in PSZ: primarily reductions between frontal and posterior regions, but reductions within posterior areas also observed during high WM-load - PSZ showed increased theta amplitude for manipulation versus maintenance processes; controls showed no such difference - Controls demonstrated increase in posterior theta amplitude with increasing load; PSZ did not	- Deficits in theta phase-synchrony represent binding difficulties in PSZ - Modulation of theta amplitude in PSZ may suggest inefficient allocation of cognitive resources rather than pure WM processes
Gamma abnormalities							
v. Kissler, Müller, Fehr, Rockstroh, & Elbert (2000) [116]	- 15 PSZ (4 females, aged 30.2 ± 6.5 years) - 15 healthy controls (4 females, aged 35.8 ± 9.4 years)	MEG	Whole-head	Mental arithmetic task	Manipulation	Controls showed increases in frontotemporal gamma activity during arithmetic; PSZ did not, but instead showed reduced gamma-amplitudes at temporal and occipital areas	- Gamma-activity can be generated without external stimuli - Schizophrenia may be associated with abnormalities in thalamocortical loop
vi. Başar-Eroğlu et al. (2007) [117]	- 10 PSZ (aged 34 ± 6 years) - 10 healthy controls (aged 24 ± 4 years)	Scalp EEG	Fz, Cz, Pz, Oz, F3, F4, T5, T6	Visual variable N-back with action monitoring/rule-switching	Maintenance, encoding/retrieval	- Trend towards increased gamma-power across scalp in PSZ relative to controls - Controls showed gradual increase in gamma during maintenance, while PSZ showed increased gamma amplitudes pre- and post-stimuli - Controls' gamma responses increased with WM load, while PSZs' did not	PSZ may need to inefficiently initiate cognitive control on simple tasks that controls may complete via automated processes

Table 3 Theta and gamma abnormalities in people with schizophrenia (PSZ) during working memory processes (*Continued*)

vii. Haenschel et al. (2009) [29]	<ul style="list-style-type: none"> - 14 patients with early onset schizophrenia (onset prior to age 18; 5 females, aged 17.76 ± 1.44 years) - 14 controls (aged 17.37 ± 1.41 years) 	Scalp EEG	Scalp-wide	Delayed visual discrimination task	Encoding, maintenance and retrieval	<ul style="list-style-type: none"> - PSZ showed reductions in induced gamma-power during retrieval over both anterior and posterior sites as compared to controls - Controls showed an increase in induced gamma amplitudes during late maintenance from load 1 to 2 and a subsequent decrease from 2 to 3; PSZ showed the opposite pattern 	<ul style="list-style-type: none"> - PSZ may have difficulties effectively retrieving stimulus representations - Differing patterns of gamma modulation during maintenance may reflect a lower storage capacity limit in PSZ as compared to controls
viii. Barr et al. (2010) [118]	<ul style="list-style-type: none"> - 24 participants with schizophrenia ($n = 19$) or schizoaffective disorder ($n = 5$); 10 females, aged 37.09 ± 11.04 years) - 24 healthy controls (11 females, aged 37.71 ± 10.12 years) 	Scalp EEG	Scalp-wide; only frontal electrodes used for evoked gamma analyses	Visual N-back task	Maintenance	Increased evoked gamma-power over frontal sites as well as failure to modulate gamma-power with increasing WM load in PSZ as compared to healthy controls	PSZ may allocate attentional resources inefficiently
ix. Chen et al. (2014) [119]	<ul style="list-style-type: none"> - 12 PSZ (3 females, aged 31 ± 10.79 years) - 12 controls (6 females, aged 33.08 ± 8.23 years) 	Scalp EEG	Scalp-wide; only frontal electrodes used for gamma-analyses	Modified Sternberg paradigm	Encoding, maintenance, retrieval	<ul style="list-style-type: none"> - PSZ showed reduced frontal (F3) gamma amplitudes during all three WM stages as compared to controls - Gamma amplitudes correlated with duration of illness in PSZ - PSZ failed to modulate gamma amplitudes across all WM stages as compared to controls (Supplementary materials) 	<ul style="list-style-type: none"> - PSZ demonstrate impaired inter-regional connections involving the frontal lobe - PSZ both lack and misallocate cognitive resources as compared to controls

WM working memory, PSZ people with schizophrenia, MEG magnetoencephalography

and/or first-episode patients), electrode site selection (e.g., single channel versus pooled sites) or means of collection (e.g., MEG vs. EEG). The literature nonetheless demonstrates consistent reports of abnormalities in theta- and gamma-band activity for PSZ as compared to healthy controls during WM processes, particularly in response to changes in task conditions related to WM function.

Though the present review focuses on the relation of theta- and gamma-oscillations to WM dysfunction in PSZ, the role of oscillatory activity in other frequencies and in relation to other cognitive functions has been reviewed elsewhere [28, 38, 66, 67]. Thus, abnormalities in oscillatory activity in PSZ do not appear to be limited to theta- and gamma-band activity, and may contribute to a wide variety of symptomatology observed in the disorder.

Relevance of abnormalities in theta- and gamma- activity in people with schizophrenia

PSZ demonstrate abnormalities in theta- and gamma- band activity during WM paradigms. Though no studies of WM in PSZ have examined coupling between theta- and gamma- activities, the ramifications of deficiencies within each of these bands independently on their interaction are easily ascertained. Inconsistencies in phase, as indexed by abnormal phase synchrony measures, would significantly interfere with any meaningful coordination between signals of differing frequencies. Similarly, amplitude deficiencies suggest abnormal generation of neural oscillations, be it through activation of fewer cells or impaired coordination of cellular assemblies that would function more cohesively in the healthy brain. Regardless, less reliable generators of oscillatory activity will limit the unitary functioning of cell assemblies that is necessary for coordination of signals that compose the theta-gamma neural code. Although coupling between theta- and gamma- activity in PSZ has been investigated, the few examinations of interactions between these bands in PSZ have not involved WM directly. Though theta-gamma coupling has been observed during processes other than WM in healthy people, the bulk of the literature ties it to memory processes; thus, further investigation is needed to clarify whether theta-gamma interactions are indeed abnormal during WM processes in PSZ, and whether those abnormalities explain behavioral performance deficits associated with the disorder.

Conclusions: the theta-gamma neural code and visuospatial WM in schizophrenia

Lisman and Idiart's [39] model positing a theta/gamma neural code as a means for representing multiple items in WM has generated a significant body of literature, and has been implicated in an even greater collection of research. A considerable amount of evidence has been accumulated and overwhelmingly supports the notions advanced by the model, namely that the interaction between theta- and gamma- oscillations communicate meaningful information within the brain in terms of memory and potentially other cognitive processes. Recent experimentation with humans has supported the model more directly: gamma activity associated with particular sequentially presented stimuli has been found to peak at different phases of concurrent theta activity in accordance with stimulus position within the sequence, and electrical stimulation in the gamma frequency range has shown to improve WM performance when administered at particular phases of theta. Regardless of how generalized the

theta/gamma code is within the brain, it is difficult to dispute the notion that theta-gamma interactions are central features of WM processes in humans and animals. Furthermore, measures of the strength of coupling between the two bands have repeatedly shown to predict WM performance, supporting the notion that theta-/gamma- interaction and memory are causally linked.

Despite this sizeable body of evidence supporting the importance of theta-gamma coupling to WM processes in humans and animals, few studies have examined interactions between the bands in PSZ [62, 63], and none in the context of WM. As such, much additional experimentation is required to determine whether deficient theta-gamma coupling may explain WM deficits in PSZ. Notably, though several studies have demonstrated predictive relationships between measures of coupling and WM ability in healthy people, few have compared the predictive ability of theta-gamma coupling to other indices of oscillatory activity, including measures of power and/or phase synchrony within theta-, gamma-, and other frequency bands. One notable exception is [32], who found an index of alpha-band power predicted WM capacity better than indices of theta-gamma coupling; the researchers interpreted this alpha measure as an index of the suppression of irrelevant information, a mechanism arguably distinct from that being presently examined. Regardless, the logical question is thus whether deficient theta-gamma coupling truly *explains* WM deficiencies, or if it is merely an important correlate of some other primary cause. Addressing such a question is an important next step in further asserting the causal role of theta-gamma coupling in WM processes as well as the veracity of Lisman and Idiart's [39] theta/gamma neural code.²

Despite the unanswered questions that remain, considerable evidence has been found to support the theory of a theta/gamma code. Much of this evidence is derived from examinations of spatial WM processes in both rodents and humans. Given the well documented deficits in visuospatial WM in PSZ [6] and their relatives [9–11], a clear and testable hypothesis is that abnormal interactions between theta- and gamma-activity explains these deficits in visuospatial WM and WM at large. The hypothesis is supported by the considerable body of literature demonstrating abnormalities in theta- and gamma-bands individually within PSZ, including in connection with WM. Examination of theta-gamma coupling during WM in PSZ may yield a better understanding of mechanisms underlying the prominent WM deficits observed in people with the disorder. Lisman and Idiart's [39] theta-gamma neural code provides a framework for testing a specific source of WM dysfunction in PSZ. Using the Lisman and Idiart [39] model as a guide, we might expect to find generally reduced phase-phase coupling between theta- and gamma-activity during performance of tasks probing WM in PSZ. Theta-gamma coupling in healthy people has been observed prominently over prefrontal and posterior regions in scalp level recordings [32, 35, 36, 68–70]. Thus, deficits in synchrony between the two bands observed over anterior and posterior regions in scalp recordings, as well as in theta-gamma synchrony between the two areas, would particularly support the notion that deficits in the temporal alignment of theta- and gamma- activities are inextricably linked to WM function in the disorder. Furthermore, such synchrony deficits would mirror reports of inefficiencies in prefrontal areas [71] as well as deficient functional connectivity between prefrontal and posterior areas associated with WM processes observed in PSZ using functional MRI [72, 73], and may represent the same dysfunction. Theta-gamma interactions may

likewise be disrupted in the hippocampus in PSZ, given the predominance of reported theta-gamma coupling during WM processes in animals and healthy people (e.g., Table 1) and observations that structural abnormalities in the hippocampus are prominent in schizophrenia [74] and observed even in cases of early-onset [75]. As activity from the hippocampus is difficult to observe using scalp level recordings (see [76]), intracranial EEG would be necessary to investigate hippocampal theta-gamma coupling deficits in PSZ; however, were such studies conducted, the Lisman and Idiart [39] model in combination with previous findings suggest abnormalities in theta-gamma coupling would be likely.

Furthermore, investigations of theta-gamma abnormalities during spatial WM processing in PSZ would be more informative if they included a task with a sequential presentation of stimuli. The Lisman and Idiart [39] model predicts different theta-phase preferences for different stimuli, represented by individual gamma cycles superimposed upon a theta cycle, in a memory sequence. The discussed phenomenon of phase-precession observed in rodents [50, 51, 56, 58, 59] represents one of the primary pieces of evidence supporting the theory and contributing to its continued consideration, and recent work has shown progressive shifts in gamma activity based on stimulus sequence [77]. However, paradigms that would allow for investigation of differential phase-preferences for individual stimuli in a spatial memory sequence are decidedly absent from human study. Thus, utilization of a paradigm featuring a sequential presentation of visuospatial stimuli would allow for a direct examination of whether phase-preferences are present in humans, and/or disrupted in PSZ.

In light of the dearth of literature testing the role of theta-gamma coupling in WM deficits in PSZ and their relatives, further study into these interactions between theta- and gamma-activity associated with WM in people genetically liable for schizophrenia is strongly warranted. Lisman and Idiart's [39] model provides a concrete framework for the design of an ideal investigation of these processes in PSZ, and suggests that deficits in theta-gamma interactions are likely to be observed in such experimentation. Better understanding of how neural oscillations factor into visuospatial WM deficits in the disorder could help inform interventions for improving memory performance, particularly in light of continually developing techniques of neuromodulation that have been shown to improve cognitive function using oscillatory stimulation (e.g., [78]).

Endnotes

¹Sternberg himself recently reviewed the compatibility of Lisman and Idiart's [39] model with high-speed scanning research; see [120].

²Much of this paragraph is derived from insightful commentary from one of the paper's reviewers, which is greatly appreciated.

Abbreviations

PSZ: People with schizophrenia; REL: Unaffected first-degree biological relatives of people with schizophrenia; EEG: Electroencephalography; ERP: Event-related potential; ADP: Afterdepolarization; ICA: Independent component analysis; MRI: Magnetic resonance imaging; TGC: Theta-gamma coupling; iEEG: Intracranial EEG; LFP: Local field potential; CSD: Current source density; EC: Entorhinal cortex; HFO: High-frequency oscillation; ACC: Anterior cingulate cortex; PFC: Prefrontal cortex; MEG: Magnetoencephalography; WM: Working memory

Acknowledgements

We are grateful for the commentary of this paper's reviewers, whose recommendations greatly improved upon the original manuscript.

Funding

This work was supported by grants to Scott Sponheim from the National Institute of Mental Health (R03MH106831) and from the Veterans Health Administration Clinical Science Research and Development Program (ICX000227A).

Availability of data and materials

Data not shared: not applicable (review of existing literature).

Authors' contributions

PAL wrote the submitted manuscript; SRS advised writing of the manuscript and carried out editing of the submission. Both authors read and approved the final manuscript.

Competing interests

Both authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Received: 12 May 2016 Accepted: 26 October 2016

Published online: 15 November 2016

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