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"Thalamo-Cortical Communication, Glutamatergic Neurotransmission and Neural Oscillations: A Unique Window into the Origins of ScZ?"

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Abstract:

The thalamus has recently received renewed interest in systems-neuroscience and schizophrenia (ScZ) research because of emerging evidence highlighting its important role in coordinating functional interactions in cortical-subcortical circuits. Moreover, higher cognitive functions, such as working memory and attention, have been related to thalamo-cortical interactions, providing a novel perspective for the understanding of the neural substrate of cognition. The current review will support this perspective by summarizing evidence on the crucial role of neural oscillations in facilitating thalamo-cortical (TC) interactions during normal brain functioning and its potential impairment in ScZ. Specifically, we will focus on the relationship between NMDA-R mediated (glutamatergic) neurotransmission in TC-interactions. To this end, we will first review the functional anatomy and neurotransmitters in thalamic circuits, followed by a review of the oscillatory signatures and cognitive processes supported by TC-circuits. In the second part of the paper, data from preclinical research as well as human studies will be summarized that have implicated TC-interactions as a crucial target for NMDA-receptor hypofunctioning. Finally, we will compare these neural signatures with current evidence from ScZ-research, suggesting a potential overlap between alterations in TC-circuits as the result of NMDA-R deficits and stage-specific alterations in large-scale networks in ScZ.

Keywords: Thalamus, Schizophrenia, Neural Oscillations, NMDA-Receptors, Glutamate

1. Introduction

Despite a hundred years of research and rapid advances in the basic neurosciences, the search for the causes of schizophrenia (ScZ) has remained largely elusive. While earlier work had focussed on circumscribed alterations in brain regions and specific cognitive processes, more recent work has highlighted a distributed neural and cognitive impairment that is likely to result from systemic disturbances involving fundamentally a disruption in the dynamics of neural processes in large-scale networks (Lisman et al., 2008; Stephan et al., 2009; Uhlhaas and Singer, 2012). The important question arising from this observation is whether such a systemic disturbance is the result of pathophysiological processes that target diverse circuits in subpopulations of ScZ-patients and, as a result, lead to a mosaic of abnormalities in a multitude of brain regions, transmitter-systems and cognitive functions in large patient cohorts. An alternative perspective is that it could implicate abnormalities in specific, circumscribed neural circuits that are of fundamental importance for large-scale networks and common to the majority of ScZ-patients and whose dysfunctions triggers a cascade of secondary processes in cortical and subcortical circuits. It is obvious from these considerations that the latter may provide a more attractive and testable hypothesis that, if proven correct, could rapidly advance our understanding of the origin of ScZ.

The hypothesis that we would like to advance in this paper is that the thalamus and its interactions with the cortex (TC-interactions) could constitute such a core abnormality in ScZ. Historically the thalamus is considered to act as a ‘gateway’ for relaying inputs from the sensory organs to the cerebral cortex (Figure1A)(Sherman, 2005) (see also Sherman in this issue). However, more recent evidence suggests that the TC-interaction have a much more wider role including facilitating large-scale communication and higher cognitive processes (Saalmann and Kastner, 2011; Schmid et al., 2012; Sherman, 2007). As a result, alterations in TC-interactions may provide a crucial mechanism

for the diverse physiological as well as perceptual and cognitive deficits that have been observed in ScZ. Specifically, we will propose that alterations in glutamatergic neurotransmission mediated by N-Methyl-D-Aspartat Receptors (NMDA-Rs) in TC-interactions may reflect abnormalities in network-interactions and oscillatory signatures observed during the early stage of ScZ.

1.1 Thalamus: Cognition, Connectivity and Neurotransmitters

Our current understanding of thalamic function is thus largely influenced by the notion that the thalamus acts as a gateway for ascending inputs from the environment. More recently, however, several studies have implicated different thalamic nuclei involved in the modulation of cortical-cortical communication and associated with higher cognitive processes, thereby provoking a renewed interest in the operations performed by different thalamic nuclei. **"First order" thalamic nuclei are involved in the processing of sensory information, while "higher order" thalamic nuclei deal less with sensory processing, but rather play a prominent role in cognitive function.** The mediodorsal (MD) thalamus is of particular interest given its status as a higher order thalamic nucleus with reciprocal glutamatergic connections with orbitofrontal and prelimbic cortex. Lesion studies in rodents and non human primates support a role for the MD in a range of cognitive processes, such as working memory (WM), attention and cognitive flexibility (Chudasama et al., 2001; Floresco et al., 1999) (Baxter, 2013) (Hunt and Aggleton, 1998); see (Mitchell, 2015) for review). Evidence from recent Designer Receptors Exclusively Activated by Designer Drugs (DREADD) and optogenetic approaches, providing a more precise spatial and temporal manipulation of brain structures than classical lesion approaches, has shown that MD thalamus-PFC connections play distinct roles in reversal learning and WM processes (Parnaudeau et al., 2013a; Parnaudeau et al., 2015).

The thalamic reticular nucleus (TRN), a thin strip of cells surrounding the lateral and ventral aspects of

the remainder of the thalamus (Mitrofanis and Guillery, 1993), is proposed to be a key functional communication hub between thalamic nuclei and the cortex (for review see (Pratt and Morris, 2015)). Lesions of the TRN produce deficits in attentional orienting tasks in rodents (Weese et al., 1999) and recordings of the TRN in monkeys showed that TRN activity is modulated by shifts of attention (McAlonan et al., 2006). Optogenetic approaches combined with multielectrode recordings support the idea that distinct subgroups of TRN neurons can facilitate the switching of attention from external stimuli (e.g. visual) to an internal one (Halassa et al., 2014).

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One reason for the extended involvement of the thalamus in higher cognitive processes is its dense connectivity with cortical regions, in particular the prefrontal cortex (PFC). The PFC receives an especially dense innervation from the thalamus relative to other regions of the cerebral cortex, (Zikopoulos and Barbas, 2006). This glutamatergic pathway derives from the MD, and a corresponding set of glutamatergic fibres descends in the reverse direction from PFC pyramidal neurones (primarily in layers V and VI) to complete the loop by terminating in the MD. Equivalent glutamatergic loops link temporal cortex and the thalamic pulvinar and geniculate nuclei, and the hippocampal formation with the nucleus reuniens of the thalamus (Jones, 2007). In every case, both thalamocortical and corticothalamic fibres in the circuit synapse in the TRN *en route* to their final destination (Mitrofanis and Guillery, 1993). The GABAergic neurons of the TRN innervate the entire rest of the thalamus, exerting a strong inhibitory action, due to their relatively high resting firing rates (McAlonan and Brown, 2002; McAlonan et al., 2006), thereby imposing rhythmic oscillatory activity on thalamocortical networks, facilitated by electrical coupling between TRN neurons (Long et al., 2004; Steriade et al.,

1985). Apart from high levels of GABA synthesizing enzymes such as GAD67, TRN neurons also contain high levels of the calcium-binding protein parvalbumin, along with various neuropeptides including NPY (Covenas et al., 1991; Morris, 1989).

As might be expected, thalamic and cortical regions express the full range of GABAergic and glutamatergic receptors. Of note, however, is the particularly high expression of $GABA_A$ receptor $\alpha 4$ and $\beta 2$ subunits in the thalamus (excluding the TRN) (Wisden et al., 1992). Also prominent is the particularly high expression of the GluA4 AMPA receptor subunit and the GluN2C and GluN2D NMDA-R subunits in the TRN (Jones et al., 1998; Lin et al., 1996), suggesting a particularly important role for these receptor types in regulating thalamocortical networks via the TRN.

The importance of NMDA receptors is exemplified by studies showing that blockage of NMDA receptors on the TRN GABAergic cells leads to reduced TRN firing and reduced TRN-cortical coherence (Troyano-Rodriguez et al., 2014)**.** The GluN2C NMDA receptor subtype is proposed to play a prominent mechanistic role in the TRN as this subtype lacks Mg2+ block and thus endogenous glutamate can partially activate GluN2C at the resting membrane potential. Blockage of the GluN2C NMDA receptor subtype produces hyperpolarization which results in bursting of T type Ca channels and delta frequency burst firing. This burst firing then leads to altered firing in thalamocortical networks (Zhang et al., 2009b) (Figure 2)**.**

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1.2. Thalamus and Network Oscillations

Given the prominent expression of both glutamatergic/NMDA-Rs and GABAergic receptors in the

thalamus, it is not surprising that oscillations at different frequencies have been observed that could facilitate interactions between different nuclei as well as to their cortical target regions (Jones, 2009).[1] Pinault and Deschenes (1992) showed robust 40 Hz activity of neurons in TRN, suggesting a pacemaker function in the generation of 40 Hz-oscillations. In addition, 30-100 Hz spontaneous activity has been recorded in other regions of the thalamus, including in the ventro-lateral, the intralaminar centrolateral nuclei and LGN (Timofeev and Steriade, 1997). Ghose and Freeman (1992) observed that a large percentage of LGN cells showed gamma-band oscillations ~ 50 Hz that were actually stronger than responses in cortical cells.

Along these lines, these oscillatory signatures could be a candidate mechanism to regulate the efficacy of information transmission in TC circuits. Saalmann and colleagues (Saalmann et al., 2012) demonstrated that synchronous alpha oscillations are involved in relaying pulvinar inputs between two functionally coupled areas in the visual pathway (V4 and TEO). This effect was modulated by spatial attention, thereby supporting the hypothesis that trans-thalamic routes are involved in cortico-cortical communication during cognitive processing (Saalmann, 2014; Sherman, 2007). Another important observation from the study by Saalmann et al. (2014) was that the envelope of cortical gamma power in V4 and TEO was coupled to the phase of cortical alpha oscillations. This suggests that synchronous TC alpha oscillations generated in higher-order nuclei could support the emergence of coherent gamma oscillations in cortico-cortical networks (Schmid et al., 2012).

A recent MEG-study from our group showed that the phase of thalamic oscillations modulated the power of 30-80 Hz power at rest (Roux et al., 2013), highlighting the role of phasic inhibition in the coordination of cortical activity. This is furthermore supported by recent electrophysiological recordings

[1] In this paper, we will focus in particular on the contribution of oscillations at higher (alpha (8-12 Hz), beta (13-30 Hz) and gamma (30-200 Hz) frequencies. The contribution of delta (1–4 Hz), theta (4–8 Hz) oscillations and its role in TC-communication as well as in ScZ will be discussed by Lisman et al., this issue)

and computational models of LGN activity that show that during strong phasic inhibition the spiking of geniculate neurons and pyramidal cells will be phase-coupled with the trough of the alpha cycle, whereas during weaker inhibition spiking activity will be coupled to the peak of the alpha cycle (Lorincz et al., 2009; Vijayan and Kopell, 2012). As a result, alpha based synchronization of geniculate and cortical responses may lead to a temporal framing of neuronal responses that could modulate the transmission of information from the LGN to cortex (Lorincz et al., 2009).

Further evidence for the role of rhythmic activity in TC-interactions has been obtained through optogenetic inhibition of MD that suppresses task-dependent modulation of MD-PFC synchrony (Parnaudeau et al., 2013b). Morever, TRN lesions induce disturbance of cortical delta and gamma oscillations and loss of sleep spindles (Marini et al., 2000; Steriade et al., 1985). Conversely, optogenetic activation of TRN rapidly leads to increased power of cortical delta oscillations (Lewis et al., 2015) and induction of cortical spindle-like discharges (Halassa et al., 2014; Halassa et al., 2011).

2. NMDA-R Hypofunctioning and TC-Interactions: A window into the pathophysiology of Schizophrenia?

Given the importance of TC-interactions in assuring higher cognitive functions (Saalmann and Kastner, 2011) and the involvement of NMDA-Rs in this process (Gil and Amitai, 1996; Santana et al., 2011a), recent studies from our group have examined the consequences of aberrant glutamatergic transmission on the architecture of large-scale networks and their oscillatory signatures. The underlying hypothesis is that changes in NMDA-R functions may crucially impact on TC-interactions which in turn could provide crucial insights into the pathophysiology of ScZ. NMDA-receptor numbers and functionality have been critically implicated in the pathophysiology of ScZ (Kirov et al., 2012; Moghaddam and Javitt, 2012) and abnormalities in glutamatergic transmission are a candidate

mechanism for disturbed high-frequency oscillations in the disorder (Carlen et al., 2011; Korotkova et al., 2010). Furthermore, there is increasing evidence that TC-interactions are disturbed in ScZ and could provide a core pathophysiological mechanism for cognitive deficits and certain symptoms of the disorder (Anticevic et al., 2013b; Ferrarelli et al., 2012; Lisman, 2012; Pinault, 2011).

2.1 Preclinical data

Evidence from preclinical studies in rodents strongly supports the hypothesis that dysfunctional TC-networks may play an important role in the neurobiological dysfunctions that underlie ScZ. As noted above, lesions of MD or TRN in rodents produce cognitive impairments that seem similar to those observed in patient populations. Moreover, data from preclinical studies in rodents have provided strong support for the hypothesis that NMDA-Rs critically impact on TC-interactions (Morris et al., 2005). NMDA-R blockage in vitro inhibits spindle-like oscillations in slices of rodent thalamus (Jacobsen et al., 2001a). Systemic NMDA-R antagonists disrupt the firing of rodent MD neurons (Santana et al., 2011b), and increase hippocampal delta oscillatory activity via a site of action within the thalamus (Zhang et al., 2012b). NMDA-R antagonists also decrease rodent PFC-TRN coherence (Troyano-Rodriguez et al., 2014) via an action in the TRN.

An important anatomical site of action for schizophrenia-related effects of NMDA-R antagonists has been assumed to be the PFC, at NMDA-Rs on fast-spiking parvalbumin-containing GABAergic interneurons, post-synaptic to pyramidal neurone collaterals (Homayoun and Moghaddam, 2007). However, various lines of evidence suggest a primary site of action for NMDA-R antagonists that is outwith the PFC (Lopez-Gil et al., 2007; Lorrain et al., 2003; Rotaru et al., 2011). In particular, as noted above, TRN GABAergic neurons express NMDA-Rs that can be activated at resting membrane potentials due to the presence of GluN2C/2D subunits (Gentet and Ulrich, 2003; Jacobsen et al.,

2001a; Jacobsen et al., 2001b; Zhang et al., 2012a; Zhang et al., 2009a). Indeed, many ScZ-related neurobiological changes in the PFC can be induced secondary to TRN dysfunction (Pratt and Morris, 2015). Using the NMDA-R antagonist phencyclidine, (PCP) in a chronic, intermittent, low-dose treatment protocol, we showed that treated rats developed metabolic hypofrontality and PFC GABA interneuron deficits that parallel impairments in ScZ-patients (Cochran et al., 2003). Interestingly, this chronic PCP treatment also reduced metabolic activity and parvalbumin expression in the TRN (Cochran et al., 2003), with the TRN changes actually preceding those in the PFC (Cochran et al., 2002).

To further explore the effects of NMDA-R hypofunctioning on TC-interactions, we examined the consequences of both acute and chronic ketamine/PCP administration upon functional brain connectivity and brain network properties in rodents. The acute administration of subanaesthetic ketamine reduced thalamo-prefrontal functional connectivity, with the exception of the TRN which showed increased functional connectivity with the PFC (Dawson et al., 2013) (Figure 3). The increased connectivity between the TRN and PFC under ketamine treatment suggests that the influence of the TRN on PFC activity becomes greater in ketamine treated animals, and that the influence of other thalamic nuclei (e.g. mediodorsal thalamus) on PFC activity is lost. This effect is likely to be mediated, in part, through the direct inhibitory effects of ketamine on NMDARs on TRN neurons (Gentet and Ulrich, 2003), and is consistent with ketamine's ability to reduce TRN metabolism (Dawson et al., 2013), resulting in the disinhibition of other thalamo-cortical projections from thalamic nuclei under inhibitory control from the TRN. This disinhibition would contribute to the PFC hypermetabolism seen under ketamine treatment, and the observation that the PFC becomes abnormally hyperconnected in brain networks when rodents (Dawson et al., 2013; 2014) and humans (Anticevic et al., 2015) are treated with subanaesthetic doses of ketamine. Importantly,

hyperconnectivity is also observed in early stages of ScZ (Antivevic et al 2015). Subanaesthetic ketamine treatment also induces thalamic hypometabolism with a contrasting PFC hypermetabolism (Dawson et al., 2015; Dawson et al., 2014) which parallels observations when ketamine is administered to humans (Langsjo et al., 2004).

Enter Figure 3 about here

The pattern of functional connectivity and brain network properties following repeated (chronic) NMDA receptor blockage in rodents shows some differences compared to acute effects. Chronic intermittent PCP treatment reduced thalamic functional connectivity when functional brain networks were characterised on a global scale (Dawson et al., 2014) and also induced reduced thalamo-prefrontal connectivity when regional connectivity was characterised (Dawson et al., 2012). A primary role for NMDAR-induced TRN disconnectivity is supported in this model, as chronic intermittent PCP treatment both reduces TRN functional connectivity to the PFC (Dawson et al., 2012) and cause the TRN to lose its status as a highly connected functional "hub" in the brain network of PCP-treated animals (Dawson et al., 2014). Intriguingly, the reduced thalamo-cortical connectivity seen in chronic PCP-treated animals parallels that observed in the brains of patients with chronic schizophrenia (Anticevic et al., 2013b; Anticevic et al., 2015a; Woodward et al., 2012).

2.2. Consequences of NMDA-R Antagonists on TC-Interactions in Human EEG/MEG/fMRI-Data

Despite the extensive evidence for disruptions of TC-pathways as a result of dysfunctioning of NMDA-Rs in preclinical research, the systematic investigation into the effects of NMDA-antagonists on large-

scale networks in human participants has only begun recently. This issue is potentially important because such data could allow comparisons with neural signatures in ScZ-patients to test the hypothesis if the pattern of brain abnormalities is consistent with the NMDA-R model of ScZ.

To examine the possibility that TC-networks are critically involved in the dysregulation of neural oscillations following NMDA-R hypofunctioning, we investigated the impact of ketamine on resting-state activity in MEG-recordings in healthy volunteers (Rivolta et al., 2015). Our data showed a pronounced upregulation of gamma-band activity at both sensor and source-level which occurred in subcortical and cortical areas (Figure 4 and 5). The largest increases of gamma-band activity were observed in the right hippocampus and right/left thalami, followed by parietal, temporal and frontal structures (Figure 5). Decreases in beta-band activity were localized to brain regions that were distinct from gamma-band generators.

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Overall, these data are consistent with preclinical research indicating that acute blockage of NMDA-Rs is associated with elevated levels of high-frequency activity. In-vivo and in-vitro electrophysiological studies using NMDA-R antagonists have revealed an increase of spontaneous power at both low (30-60 Hz) and high (60-130 Hz) gamma-band ranges as well as at ripple frequencies (130-200 Hz) (Hunt and Kasicki, 2013)(see also (Hong et al., 2010; Muthukumaraswamy et al., 2015) for similar findings in EEG/MEG-data). Specifically, our findings of enhanced gamma-band activity in the hippocampus and thalamus is consistent with data by Zhang et al. (2012) who reported gamma-activity increase after ketamine injection by 308% in the hippocampus and 258% in the thalamus.

Until recently, the possibility of applying source reconstruction towards MEG-activity in deeper

brain structures has remained challenging because magnetic fields decay rapidly with increasing distance. However, contributions from deeper sources should be detectable in MEG data, given that their fields are strong enough to propagate to the sensor array of MEG-SQUIDs. This hypothesis is supported by several studies that have localized MEG signals in subcortical regions (Attal et al., 2007; Kaplan et al., 2014; Roux et al., 2013).

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To further explore the contribution of alterations in TC-interactions on aberrant high-frequency activity, we performed a connectivity analysis between sources that were modulated by ketamine at beta/gamma-band frequencies. Analysis of directed interactions through a transfer entropy (TE) (Wibral et al., 2013) approach revealed that ketamine impacted in particular on TC-pathways. Specifically, ketamine administration caused an increase in the average TE-values (see Figure 6A for uncorrected effects) which particularly involved connections between the thalamus and temporal and visual regions, suggesting a central role of aberrant TC-interactions in the dysregulation of neural oscillations following ketamine-application in humans.

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The finding of elevated TC-interactions at beta/gamma-band frequencies is consistent with preclinical data (Dawson et al., 2013), highlighting that acute Ketamine administration affects prominently thalamo-cortical interactions (but see (Muthukumaraswamy et al., 2015) for a recent MEG-study reporting a different finding on connectivity patterns). Moreover, several resting-state fMRI studies

reported increased functional connectivity between thalamus and cortical regions (Anticevic et al., 2013a; Hoflich et al., 2015; Klingner et al., 2014; Woodward et al., 2012), albeit some report mixed findings (Woodward et al., 2012). **Interestingly, there are some indications for differential alterations in the connectivity of first order versus higher order thalamic nuclei in patients with schizophrenia (Woodward et al., 2012; Anticevic et al., 2014).**

3. NMDA-Rs, TC-Interactions, Neural Oscillations and ScZ

An important question concerns the similarities between the pattern of TC-interactions following NMDA-R hypofunction and the evidence on abnormal large-scale network-activity in ScZ-patients. A central finding from our work that combines both pre-clinical and human MEG-data is that acute ketamine-administration is associated with a disinhibition of TC-circuits resulting in elevated gamma-band oscillations and connectivity. However, it should be noted that, while connectivty changes in our MEG-data were generally increased (Rivolta et al., 2015), alterations in the pattern of TC-interactions in our preclincal data were increased only for TRN-PFC interactions (Dawson et al., 2013).

Traditionally, connectivity changes in ScZ have emphasized reductions in functional interactions between brain regions as the underlying cause for cognitive deficits and certain symptoms of the disorder (disconnectivity) (Bleuler, 1911). However, more recent work has highlighted a more complex pattern of network abnormalities that involve both the reduction as well enhanced interactions that is captured by the concept of „dysconnectivty“ (Stephan et al., 2009). Indeed, evidence is emerging for elevated connectivity mediated by TC-interactions in ScZ from several studies that have examined functional connectivity in early-stage ScZ with resting-state fMRI (Anticevic et al., 2015a; Cetin et al., 2014) and Diffusion Tensor Imaging (DTI) (Cho et al., 2015) **(but see Woodword et al.**

(2012) for a different finding).

In a recent study, Anticevic et al. (2015b) further examined TC-interactions in fMRI-resting state data in 243 individuals at ultra-high-risk (UHR) for psychosis to test the hypothesis that aberrant TC-interactions characterize the at-risk state and could potentially constitute a biomarker for early detection and diagnosis. UHR-participants showed widespread hypoconnectivity between the thalamus and prefrontal and cerebellar areas, which was more prominent in those who converted to psychosis. Conversely, there was marked thalamic hyperconnectivity with sensory motor areas, again most pronounced in those who converted to full-blown illness.

Further evidence for potentially stage-specific changes in neural oscillations in ScZ have been also obtained from EEG-data in First-Episode-Psychosis (FEP)-patients which could potentially mirror in part the oscillatory signatures observed in healthy volunteers during ketamine administration. Andreou et al. (2015) examined resting-state gamma-band connectivity in 22 patients with FEP and 22 healthy controls. FEP-ScZ patients displayed increased mean gamma-band connectivity in a network consisting of frontal, temporal and parietal areas. In addition, Kikuchi et al. (2011) obtained resting-state EEG data in medication-naive, FEP-ScZ, patients and found significantly elevated gamma-band power over frontal electrodes in those patients.

However, it should be noted that this pattern, which is consistent with the effects of NMDA-R hypofunctioning in healthy volunteers (Rivolta et al., 2015), has not been replicated in some other studies that investigated EEG-data in at-risk cohorts for spectral signatures during resting-state EEG-activity (Ramyead et al., 2015). Moreover, ketamine administration in healthy volunteers is also associated with elevated high-frequency activity during perceptual and motor-paradigms (Hong et al., 2010; Muthukumaraswamy et al., 2015), a finding that is commonly not observed in either FEP or chronic ScZ-patients (Grutzner et al., 2013; Sun et al., 2013).

Support for the possibility that NMDA-R mediated disinhibition is present in ScZ at illness-onset is provided by our recent data in unmedicated first-episode-ScZ patients, suggesting an excessive spreading of neural activity indexed by event-related fields during sensory processing in MEG data (Rivolta et al., 2014). Together with the role of TC-interactions for the selection of relevant sensory inputs, these data highlight the possibility that dysfunctional TC-interactions may contribute towards the characteristic changes in self-experiences at the onset of psychosis, such as the reduced ability to differentiate between relevant and irrelevant information, a symptom commonly observed in the early stages of ScZ (McGhie and Chapman, 1961; Uhlhaas and Mishara, 2007). Moreover, an additional manifestation of aberrant TC-interactions are the changes in sleep-patterns that predate the onset of psychosis (Zanini et al., 2015) as well as the reductions in sleep-spindels observed in EEG-recordings in FEP-patients (Manoach et al., 2014) (see also Ferrarelli and Tononi in this issue). Specifically, Ferrarelli and Tononi (2011) proposed that the GABAergic nucleus of the TRN could be crucially involved in attentional dysfunctions as well as sleep spindles abnormalities in the disorder.

Further data indicating illness-stage specific changes in E/I-balance parameters has been obtained from recent meta-analysis of MRS-measured glutamate-levels. At early illness stages, elevated levels of glutamate are present in ScZ-patients and progressively decrease over the course of the illness. (Marsman et al., 2013). The contribution of thalamic glutamate levels towards global E/I-balance changes in ScZ currently is unclear, however. In chronic ScZ-patients, elevated glutamate levels have been observed (Theberge et al., 2002) while in participants meeting UHR-criteria reduced levels were reported ((Egerton et al., 2014).

4. TC-Interactions, Glutamate Transmission and Neural Oscillations in ScZ: Summary

The latest genetic findings point to synaptic NMDA-R hypofunction as a major factor disease aetiology (Morris and Pratt, 2014; Pocklington et al., 2014). The current data from pre-clinical research and human neuroimaging point to the crucial impact of NMDA-R hypofunctioning on TC-interactions which may have relevance for understanding the origin of dysfunctions in large-scale networks in ScZ. Until recently, such an integrative perspective was not available due to the absence of tools and approaches that permitted the examination of TC-interactions in-vivo. However, recent advances in systems neuroscience and human brain imaging have provided novel evidence that the thalamus has a much more profound role in the coordination of large-scale brain networks than previously assumed and that disinhibition in TC-circuits has profound effects on cognition and behavior.

Importantly, the signatures of chronic and acute NMDA-R hypofunctioning on TC-interactions may also hold crucial clues for the pathophysiology of ScZ. It may be that the remarkable ability of NMDA-R antagonist administration to mimic aspects of ScZ reflects an ability to influence thalamocortical networks with some selectivity, potentially via a primary site of action in the TRN. Currently, there is significant evidence to suggest that disinibition of TC-interactions may characterize large-scale network-dysfunctions in the early stages of the disorder. While reduced TC-connnectivity may characterize later illness stages, the converging experimental and clinical data suggest increased excitability of neural circuits at illness onset may lead to increased interactions between thalamus and its nuclei to cortical target regions.

To further test this hypothesis, we believe that a number of questions need to be addressed to support the central contribution of this mechanism towards the manifestation and progression of ScZ. These include the mechanisms underlying the transition from TC-disinhibition at early illness stages towards the “defect-state” in more advanced stages of the disorder characterized by reduced large-scale

connectivity. Longitudinal studies in UHR- and FEP-cohorts with a multi-modal approach that permit the tracking of glutamate levels as well as the assessment of in-vivo TC-interactions with MEG and fMRI will be crucial for this objective. These should be ideally accompanied by pre-clinical models that allow the manipulation of distinct thalamic nuclei to identify the distinct contribution of different TC-interactions towards large-scale disinhibition and the associated cognitive and behavioural manifestations.

If successful, the thalamus could indeed become the Rosetta Stone for ScZ reseach that could allow a deciphering of the diverse neurobiological and behavioural phenomena associated with the disorder from a circumscribed pathophysiological process with very important consequences for the understanding, treatment and eventually prevention of the disorder.

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Figure Legends

Figure 1. Anatomy of the thalamus. (**A**). Nuclei of the dorsal thalamus. (**B**) Schematic representation of trans-thalamic pathways. Higher-order (HO) nuclei such as the pulvinar receive efferent inputs from layer V of one cortical area (area "A") and send afferent inputs to the upper layers of another cortical area (area "B"), thereby forming a trans-thalamic route that could modulate cortico-cortical communication. The thalamic nuclei include the sensory-related first order nuclei (lateral and medial geniculate and the higher order nuclei (pulvinar and mediodorsal) that are linked to higher cognitive processes. Visual and auditory-related information from the periphery is transmitted via the lateral and medial geniculate nuclei respectively to the cortex (layer IV). By contrast, the higher order pulvinar and mediodorsal thalamic nuclei receive their driving inputs from cortical layer V and transmit this to layer 1 of other cortical regions (Ref 1). This non-reciprocal communication pattern has been proposed as an indirect trans-thalamic pathway for cortico-cortical communication (Fig1B).

Figure 2: Simplified schematic diagram showing the influence of the TRN on thalamocortical networks, and the strategic sites of expression of NMDA-Rs containing GluN2C/2D subunits**. While GluN2C/D-containing NMDA-Rs respond to both corticothalamic and thalamocortical innervation (Gentet & Ullrich, 2003), GluA4-containig AMPA-Rs are preferentially sited to respond to corticothalamic activation (Mineff and Weinberg, 2000; Paz et al., 2011)**

Figure 3. Summary diagram of ketamine-induced alterations in thalamo-prefrontal functional connectivity when the medial prelimbic cortex (mPrL) is considered as the PFC seed region for analysis. Red denotes a significant increase in regional functional connectivity to the mPrL whereas

blue denotes a significant decrease in regional functional connectivity. Subanaesthetic ketamine treatment increase functional connectivity between the thalamic reticular nucleus (TRN) and the PFC. By contrast the functional connectivity of other thalamic nuclei including the mediodorsal (MD), anteromedial (AM), centrolateral (CL) and centromedial (CM) to the PFC is significantly decreased by subanaesthetic ketamine treatment. The functional connectivity of the mPrL to a number of other PFC subfields, including the lateral orbital (LO), medial orbital (MO), ventral orbital and anterior prelimbic (aPrL) subfields is increased by subanaesthetic ketamine treatment. **Note that functional connectivity measures indicate the influence of one region upon another and do not necessarily reflect direct anatomical connections. Hence, although there is no anatomical evidence that TRN neurons are directly connected to the cortex, the TRN may affect PFC activity indirectly for example through disinhibition of thalamo-cortical projections from thalamic nuclei under inhibitory control from the TRN.** Adapted from Dawson et al., 2013.

Figure 4. Sensor-level analysis. (**A**) Topoplots representing the average power spectra (fT) of gamma (top) and beta (bottom) frequency ranges in the placebo (left) and ketamine (right) conditions. (**B**) Results of the non-parametric cluster-based statistic highlighting sensors showing a statistically significant effect for gamma (top) and beta (bottom) frequencies. Red colors indicate a statistically significant difference in favor of the ketamine condition, whereas blue colors indicate a difference in favor of the placebo condition (* = $p < .001$).

Figure 5. Source-level analysis. Cluster-based nonparametric statistic highlights statistically significant differences between the placebo and ketamine condition across the gamma (left) and beta (right) frequency bands (red: ketamine > placebo; blue: placebo > ketamine). Gamma-band (30–90 Hz): (1) R-hippocampus [10 −10 −20], (2) R-thalamus [10 −10 10], (3) L-thalamus [−10 −20 10], (4) L-fusiform

gyrus [−40 −10 −30], (5) R-medial frontal cortex [0 40 −20], (6) L-frontal pole [−20 40 −10], (7) L-superior frontal gyrus [−20 40 40], (8) L-superior temporal gyrus [−70 −20 0], and (9) L-middle temporal gyrus [−60 0 −30]. Beta-band (13–30 Hz): (1) cerebellum [0 −40 −20], (2) L-precuneus [−20 −50 20], (3) R-precuneus [30 −50 10], (4) R-middle temporal gyrus [60 −30 −10], (5) L-anterior cingulate [0 20 −10], (6) R-inferior temporal gyrus [50 −60 −20], and (7) R-visual cortex [30 −90 −10].

Figure 6. Transfer entropy (TE) analysis. TE differences between ketamine and placebo conditions. Green diamonds indicate MEG sources reactive to ketamine in the gamma band, blue circles indicate sources reactive in the beta band (see Figure 3). Arrow colors indicate strength of the difference. (**A**) Uncorrected differences in TE. (**B**) Statistically significant differences (Bonferroni corrected: $p < 2.08*10\text{-}4$ the TE differences at a significance threshold of $p < 0.0005$ uncorrected, for the transfer entropy between (**C**) sources reactive in the beta frequency band, (**D**) in the gamma frequency band, and (**E**) between beta- and gamma-sources. Legend: FrontalPole-L = left frontal pole, MFC = medial frontal cortex, SFG-L = left superior frontal gyrus, ACC = anterior cingulate cortex, MTG-L = left middle temporal gyrus, FuG-L = left fusiform gyrus, Th-L= left thalamus, Cb = cerebellum, Prec-L = left precuneus, HI-R = right hippocampus, Th-R = right thalamus, MTG-R = right medial temporal gyrus,Prec-R = right precuneus, ITG-R = right inferior temporal gyrus, VisualCortex-R = right visual cortex.