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Potential synergistic action of 19 schizophrenia risk genes in the thalamus

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Abstract

A goal of current schizophrenia (SZ) research is to understand how multiple risk genes work together with environmental factors to produce the disease. In schizophrenia, there is elevated delta frequency EEG power in the awake state, an elevation that can be mimicked in rodents by N-methyl-D-aspartate receptor (NMDAR) antagonist action in the thalamus. This thalamic delta can be blocked by dopamine D2 receptor antagonists, agents known to be therapeutic in SZ. Experiments suggest that these oscillations can interfere with brain function and may thus be causal in producing psychosis. Here we evaluate the question of whether well-established schizophrenia risk genes may interact to affect the delta generation process. We identify 19 risk genes that can plausibly work in a synergistic fashion to generate delta oscillations.

Keywords

Schizophrenia; NMDAR hypofunction; dopamine receptor hyperfunction; delta oscillations; nucleus reticularis; relay cells

It is now widely accepted that there is both environmental and genetic causation of schizophrenia (SZ). Risk genes for SZ have been identified by copy number variations (CNVs) (Walsh et al., 2008; Kirov et al., 2012) or single-nucleotide polymorphisms (SNPs) (Ripke et al., 2014). Importantly, the effect size of each gene is small, meaning that the presence of a risk gene in an individual only marginally increases the risk of the disease. It is therefore generally supposed that the disease itself requires the concerted action of many risk genes on some critical brain process. What might that critical process be and what is the nature of the interaction?

One possible answer comes from another line of investigation that has sought to understand a well-established symptom of schizophrenia: the elevation of low-frequency (delta; 1–4Hz

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Conflict of interest

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and theta; 4–7Hz) EEG oscillations in the awake state (here termed simply “delta”) (Clementz et al., 1994). A number of studies have identified increased delta in both medicated and unmedicated SZ patients, primarily in the temporal and parietal areas and generally bilateral (Fehr et al., 2001; Fehr et al., 2003; Weinbruch et al., 2003; review in Seikmeier & Stufflebean, 2011). This increase is not seen in first-degree relatives of SZ patients (Venables et al., 2009). Furthermore, significant correlations have been found between the increase in delta power and both positive (Fehr et al., 2001) and negative symptoms of SZ (Fehr et al., 2003).

Insights into the network basis of the delta abnormality have been gained using the NMDAR hypofunction model of the disease (Coyle, 1996; Javitt and Zukin, 1991), a model justified by the fact that NMDAR antagonists can reproduce many of the positive, negative, and cognitive symptoms of the disease (see (Moghaddam and Krystal, 2012)). Notably, NMDA antagonists can elevate low-frequency oscillations in rodents and man (Buzsaki, 1991; Zhang et al., 2012b).

Importantly, the work in animal models has identified the thalamus as the site where NMDAR antagonists produce delta (Buzsaki, 1991; Zhang et al., 2012b), and much has been learned about the underlying cellular and molecular processes (Lisman et al., 2010; Zhang et al., 2012a; Zhang et al., 2009; Zhang et al., 2012b). Furthermore, optogenetic experiments have established that the induction of abnormal delta oscillations in a particular thalamic nucleus (reuniens) is sufficient to interfere with cognitive function (Duan et al., 2015). Specifically, the results show that optogenetic stimulation at delta frequency interfered with spatial working memory, an established function of the nucleus reuniens and a function known to be affected in schizophrenia. While elevated delta activity is also seen in several other disorders (Knyazev, 2012), it has been proposed (Schulman et al., 2011) that low-frequency oscillations can occur in different parts of the cortex and the associated thalamic nuclei, with the presentation of particular symptoms depending on the functions of the thalamic nuclei affected. Thus different symptoms (positive/negative/cognitive) of schizophrenia could potentially relate to which thalamic nuclei are involved.

Given that abnormal delta in the thalamus might be the critical process affected in schizophrenia, it becomes important to consider whether identified risk genes could act together to produce abnormal delta. In this brief review, we seek to evaluate this possibility. Fig. 1 shows the two cell types of the thalamus most relevant to delta generation, the inhibitory cells of the nucleus reticularis (nRT) and excitatory cells of relay nuclei. Relay cells excite the cells of the nRT, which in turn inhibit the relay cells. Although individual cells can themselves be oscillatory, thalamo-cortical oscillations are ultimately a network process to which both excitatory and inhibitory cells of the thalamus contribute (Crunelli et al., 2014). Delta oscillations, which are accompanied by bursting in a large fraction of cells in the thalamus (Crunelli et al., 2014), may interfere with the function of affected thalamic nuclei by jamming the normal transmission of information through the nuclei (Duan et al., 2015), thereby potentially contributing to the functional disconnection of cortical regions in SZ (Schulman et al., 2011).

The number of genes for which there is some evidence of linkage to SZ is enormous, but the statistical power of the linkage is often weak. Therefore, in our attempt to understand gene interactions, we have focused on a few studies that are particularly strong; we have considered only genes identified by one or more of the three approaches described below.

The most common method to identify risk genes is to do a genome-wide association study (GWAS) of SNPs, comparing patients and normal controls. The regions around each SNP (risk locus) are then evaluated to identify risk genes or regulatory sequences. We have used the list of 108 risk loci identified or confirmed by the Schizophrenia Working Group of the Psychiatric Genetics Consortium in 2014 (Ripke, 2014), the largest such study. The consortium drew from a pool of 36,989 patients with schizophrenia and 113,075 controls.

An independent approach has been to apply multivariate association analysis between EEG and SNPs. A group of risk genes was thereby directly linked to the increased delta frequency power found in patients with schizophrenia (Narayanan et al., 2015).

As a third source of strongly implicated risk genes, we drew from several studies that focused on identifying the genes associated with large (>100kb) duplications or deletions of DNA, CNVs, that were found to confer an increased risk of schizophrenia (Walsh et al. 2008; Kirov et al., 2012; Fromer et al., 2014). Of specific interest is the DiGeorge syndrome deletion at 22q11.2 that carries a 30% risk of schizophrenia. Deletions of this region can be of varying size, but a core deletion (DiGeorge Critical Region) of approximately 1.5 MB containing approximately 30 genes has been identified (Chun et al., 2014; Kobrynski and Sullivan, 2007).

A crucial physiological process that underlies delta generation in the thalamus is the delta frequency Ca spikes generated by T-type Ca channels. Importantly, these channels are themselves regulated by membrane potential. At normal resting potential, these channels are inactivated and delta oscillations are not present. When membrane potential becomes hyperpolarized, the T-type Ca channels become functional (deinactivated) and generate Ca spikes at delta frequency, thereby contributing to delta oscillations in the cortical EEG. Based on this perspective, we consider four mechanisms for elevated delta generation: 1) the mechanism directly involved in delta generation; 2) the mechanism by which excess dopamine action (dopamine hyperfunction) produces hyperpolarization and therefore promotes delta by deinactivating T-type Ca channels; 3) the mechanism by which blocking NMDARs (NMDAR hypofunction) in the thalamus produces hyperpolarization and thereby produces delta by deinactivating T-type Ca channels; and 4) the mechanisms of synaptic signaling that might indirectly affect delta generation.

19 Risk genes that could act synergistically to produce abnormal delta

We now consider how schizophrenia risk genes in these groups might affect the generation of oscillations. Table 1 shows the loci of each gene as well as the studies that identified it.

Group 1: Delta generation mechanism

1. T-type Ca channel (CACNA1i or Cav3.3)

This channel is necessary for generating the low-threshold Ca spikes required for delta generation in the nRT (Astori et al., 2011; David et al., 2013; Zhang et al., 2009). Cav3.3 is the only type of T-type Ca channel in the nRT, and it is notable that this was the particular isoform identified in both (Ripke, 2014) and (Narayanan et al., 2015), where it was the highest-rated candidate gene.

2–3. L-type Ca channel

Two Ca channel subunits are candidate risk genes (CACNA1C or CaV1.2, CACNB2). While expressed throughout the brain, CACNA1C expression is high in the thalamus, especially within relay nuclei (Lein et al., 2007; Allen Mouse Brain Atlas). These subunits assemble into L-type Ca channels. These may contribute to the Ca spikes that generate delta (e.g., the high-threshold Ca spikes seen in a subset of LGN relay cells (Hughes and Crunelli, 2007)).

4. Serca2 (ATP2A2)

This Ca pump is heavily expressed throughout the thalamus (Lein et al., 2007; Allen Mouse Brain Atlas) and serves an important role in delta generation (Cueni et al., 2008). Furthermore, the 22q11.2 copy number variant affects SERCA2 expression through a change in a microRNA that controls SERCA2 levels (Earls et al., 2012).

5. HCN1

This isoform of HCN is found in relay cells, but not in the nRT (Notomi and Shigemoto 2004; Lein et al., 2007; Allen Mouse Brain Atlas). During the hyperpolarization phase of thalamic relay cell firing, the opening of HCN channels initiates the membrane depolarization that leads to the next cycle of delta oscillatory activity (Jahnsen and Llinas, 1984).

6. GRM3

Within the thalamus, this metabotropic glutamate receptor is strongly localized to the nRT (Lourenco Neto et al., 2000). Activation of GRM3 leads to cell hyperpolarization and may thereby deactivate T-type Ca channels and thereby promote delta oscillations (Carter et al., 2004).

Group 2: Dopaminergic regulation of delta oscillations

7. DRD2

The clinical effectiveness of antipsychotic drugs used in the treatment of SZ correlates with their affinity for dopamine receptors (Creese et al., 1976; Seeman and Lee, 1975). Within the thalamus, DRD2 is predominantly expressed in relay nuclei but is also expressed in the nRT to a lesser extent (Lein et al., 2007; Allen Mouse Brain Atlas). D2 activation was shown to hyperpolarize thalamic cells by activating K channels (Lavin and Grace, 1998), a hyperpolarization that enhances delta (Zhang et al., 2009).

8. DGCR8

This gene is located at 22q11.2, and the protein product of this gene, pasha, is a miRNA processing enzyme. In animals haploinsufficient for DGCR8, D2 receptor expression is increased in the thalamus (Chun et al., 2014) and may therefore produce hyperpolarization and delta oscillations.

9. COMT

This gene is also localized to the 22q11.2 and codes for an enzyme that degrades catecholamines such as dopamine and norepinephrine (Grossman et al., 1992). As such, a decrease in COMT activity would increase dopamine concentration and therefore increase delta (see (Zhang et al., 2009)).

Group 3: NMDAR hypofunction

GluN2C is the particular NMDAR isoform that is predominant in the thalamus (Zhang et al., 2012a). Blockage of this channel hyperpolarizes the resting potential, deinactivating T-type Ca channels, which then generate delta oscillations (Zhang et al., 2009). NR2C has not yet been identified as a risk gene for SZ; however, as has been previously noted, multiple SZ risk genes are linked to the function of all NMDAR isoforms (Balu and Coyle, 2015). These genes could thus contribute to delta generation by producing NMDA hypofunction.

10. SRR

The product of the gene, serine racemase, is a glial enzyme responsible for the conversion of L-serine to D-serine, an NMDAR co-agonist (Wolosker et al., 1999). Lack of D-serine could reduce NMDAR activity and hyperpolarize thalamic cells, inducing delta.

11–12. GSTT2/MSRA

These are widely expressed genes that affect cellular redox potential and thereby affect biochemical processes implicated in schizophrenia (Behrens and Sejnowski, 2009). MSRA, which is a highly ranked risk gene (Narayanan et al., 2015), protects cells from oxidative damage. Such damage has been found to be significantly increased in patients with early onset first psychotic episodes (Micó et al., 2011). Given that NMDARs are strongly inhibited by oxidation, disruption of these genes can produce NMDAR hypofunction (Bodhinathan et al., 2010; Guidi et al., 2015) and thereby increase delta.

13. DISC1

This gene is robustly expressed in the thalamus (specifically in the nucleus reuniens and the nucleus reticularis); expression decreases with age (Austin et al., 2004). DISC1 downregulates D-serine production by promoting degradation of serine racemase (Ma et al., 2013). A decrease in D-serine levels due to serine racemase degradation would lead to NMDA hypofunction, thus promoting delta generation. Another line of work has investigated the activity-dependent formation of a complex between DISC1 and D2R, a complex that has downstream effects on β -arrestin. The DISC1-D2R complex has been shown to favor the formation of the β -arrestin-PP2A-Akt complex over the β -arrestin-

clathrin-AP2 complex; this leads to higher levels of GSK-3 phosphorylation and inhibition of D2R internalization (Su et al., 2014). Elevated levels of the complex, which have been found in postmortem tissue from patients with schizophrenia (Su et al., 2014), may thus increase D2 activity and result in hyperpolarization of the resting membrane potential and thereby promote delta generation. A parallel line of work has found an effect of DISC1 misassembly on dopamine homeostasis and D2R activity. Specifically, overexpression of the full-length DISC1 transgene leads to a shift from low-affinity to high-affinity D2 receptors (with an 80% increase in high-affinity D2 receptors in the dorsal striatum) and consequent amphetamine supersensitivity, which is also seen in SZ patients (Trossbach et al., 2016).

Group 4: General Synaptic function

The genes listed below are important in synaptic function. These genes could therefore affect delta oscillations but, unlike the other three groups, may be more indirectly involved.

14. ARC

Within the thalamus, this gene is almost exclusively expressed in the nRT. Altered expression of this protein has multiple effects on glutamatergic synaptic function and plasticity (Korb and Finkbeiner, 2011).

15–18. GluA1 (GRIA1)/ErbB4/DLG1(SAP-97)/DLG2(PSD-93)

GluA1 is an AMPA channel important for relay cell function (Kielland et al., 2009). ErbB4 activation in the nRT has been reported to decrease cortical drive onto the nRT (Ahrens et al., 2015). The MAGUKs SAP-97 and PSD-93 have multiple roles in PSD structure and in the function of glutamatergic synapses (Zhu et al., 2016).

19. CHRNA3

CHRNA3 is a subunit of nicotinic cholinergic receptor expressed in the relay nuclei of the thalamus (Lein et al., 2007; Allen Mouse Brain Atlas). Cholinergic input from mesopontine nuclei (the peribrachial (PB) area of the pedunculo pontine tegmental nucleus and the laterodorsal tegmental (LDT) nucleus) has been shown to depolarize thalamic relay nuclei and transform their firing from bursting into tonic mode (Curro and Steriade, 1991), a process essential to reach the awake state. The decreased activity of the channel would therefore decrease depolarizing input and thus hyperpolarize the cells, promoting delta generation. Disruption of these processes could affect the transition between sleep and wake states and could explain the abnormalities seen in thalamically generated sleep spindles, as seen in the EEG of SZ patients (Ferrarelli and Tononi, 2016).

Discussion

Although there has been enormous effort to identify risk genes for SZ, with increasing success, relatively little effort has been made to understand how these genes could work together to produce the disease. Previous work has pointed out the possible interaction of eight risk genes in producing NMDA hypofunction (Balu & Coyle, 2014), thus supporting the NMDA hypofunction model of the disease. Here we carry the analysis a step forward by

incorporating the NMDA hypofunction into a larger framework that potentially provides a mechanism for understanding the delta oscillation abnormality in SZ.

The focus of this larger framework is processes within the thalamus that are critical in delta generation. All of the risk genes we have considered could plausibly increase delta and could there affect cognitive processes (Duan et al., 2015). Some risk genes work by directly producing NMDAR hypofunction, and others produce dopamine hyperfunction, while yet others directly affect the generation of Ca spikes. All of these processes affect delta generation, thereby producing the potential for interaction among SZ risk genes. Even though many of the risk genes here are widely expressed throughout the brain, their co-localization in the thalamus with other genes that promote delta oscillations may be critical for the gene interactions that underlie the disease.

Although our results suggest potential gene interactions leading to SZ, further work will be required to determine whether and how these alterations in normal genes actually affect function. Importantly, some of the SNPs and CNVs are not located in the coding region of the genes and may not directly affect mRNA levels and protein expression. Generally, it is unclear how the identified risk genes actually affect protein function. Thus, investigations into the functional consequences of genetic alteration for the 19 genes of interest we have identified would be an important next step in evaluating the hypothesis that we have put forward.

Although all 19 genes discussed above are present in the thalamus, their distribution within thalamic nuclei is not the same. This could be important given that each patient might contain a different subset of risk genes that produce dysfunction in different thalamic nuclei. The diversity of gene expression within the thalamus (Nagalski et al., 2016) could lead to the heterogeneity of the symptom set seen among patients. One of the most heterogeneous properties of the thalamus is the density of dopaminergic innervation (Garcia-Cabezas et al., 2009); thus, the synergistic action of genes affecting dopamine hyperfunction may be concentrated in a subset of thalamic nuclei. Similarly, HCN1 has been found to be most expressed in the anterodorsal nucleus of thalamus (Santoro et al., 2000), an area that has strong projections to the cingulate cortex and retrosplenial cortex. A better knowledge of the localization of SZ risk genes within the thalamus and a better understanding of the function of specific thalamic nuclei could provide greater insight into the pathogenesis of schizophrenia.

An important question about the interaction of SZ risk genes is whether this interaction is linear (symptoms directly proportional to the number of risk genes) or whether the interaction is synergistic (supralinear). Synergism interaction produces symptoms greater than the sum of the symptoms produced by each gene alone. Based on our mechanistic model of thalamic delta generation, we suspect that synergism occurs. For instance, given a threshold that hyperpolarization is necessary to deinactivate T-type Ca channels, it is possible that individual risk genes produce a hyperpolarization insufficient to cause any T-channel spikes, whereas multiple genes, acting together to produce sufficient hyperpolarization to deinactivate T-type Ca channels, would allow these channels to produce delta frequency spikes.

A mechanistic theory of SZ should specify how environmental factors interact with risk genes to produce the disease. The following scenario is one possibility (Lisman et al., 2010). Dopamine elevation can be caused by stress, which has been documented as a precipitating factor for psychosis (Anstrom et al., 2009; Corcoran et al., 2003). Dopamine enhances thalamic delta oscillations (Zhang et al., 2009), which then elevates activity in the hippocampus (Zhang et al., 2012b). This, in turn, excites the dopamine neurons of the VTA (Lodge and Grace, 2007; Zimmerman and Grace 2016). Given that dopamine release in the thalamus could then further enhance thalamic delta oscillations, these processes create the potential for positive feedback in the thalamic-hippocampal-VTA loop. In individuals with multiple risk genes, this loop may be closer than normal to the threshold for positive feedback (Lisman et al., 2010); stress may then push the system past that threshold, thereby enhancing and stabilizing delta oscillations. These elevated thalamic oscillations may then interfere with working memory (Duan et al., 2015) and other brain functions affected in schizophrenia (see list in Fig. 1).

Because the onset of schizophrenia is usually around adolescence and early adulthood, some age-dependent factors must be at work as well. One theory posits that the effects of risk genes leading to NMDAR hypofunction may not become significant until near the end of developmental pruning in adolescence, when synaptic connectivity falls below some critical threshold (Frolich and van Horn., 2014). However, it is also possible that there are age-dependent changes in the propensity for delta generation. Several of the risk genes listed above have been shown to have age-dependent expression. HCN1 in thalamic relay cells has been shown to be developmentally regulated with a 6-fold increase in the hyperpolarization activated current (I_h) seen between P3 and P106. Delta oscillations during sleep are not seen prior to P12 in EEG recordings, suggesting that sufficient HCN1 expression is necessary for delta generation (Kanyshkova et al., 2009). Age-dependent effects are also seen with the deletion of 22q11, which has been seen to enhance LTP in the hippocampus of mature (16–20 weeks) but not young (8–10 weeks) mice. A further study found that this effect could be replicated by the micro-deletion of DGCR8, within 22q11, which leads to an overexpression of SERCA2, a Ca pump whose presence in the thalamus contributes to delta generation, in mature mice (Earls et al., 2012). These developmental changes in risk gene expression could potentially be important in explaining the adolescent onset of SZ.

We have suggested how synergistic action of SZ risk genes could lead to the generation of abnormal low-frequency oscillations. While the idea of thalamic low-frequency oscillations being causal in SZ is itself a working hypothesis that requires further validation, the fact that we have been able to identify 19 genes that could plausibly contribute to the observed EEG abnormality in SZ is itself supportive of our model. Our physiological model of thalamic function provides a starting point for the “science of synergism”: the emergence of a nonlinear effect from many minor effects that all contribute to disease. We emphasize that, while synergistic action is an emergent feature of our model, the question of whether risk genes actually interact synergistically (supralinearly) is an experimental question that needs to be investigated. Additionally, it will be important to understand how the environment interacts with various risk genes. As more is learned about how abnormalities in risk genes affect protein function, it will become possible to develop more precise and testable models of how risk genes and environmental factors interact to produce the disease.

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References

- Agim ZS, Esendal M, Briollais L, Uyan O, Meschian M, Martinez LAM, Ding Y, Basak AN, Ozcelik H. Discovery, validation and characterization of Erbb4 and Nrg1 Haplotypes using data from Three genome-wide association studies of schizophrenia. *PLoS ONE*. 2013; 8(1):e53042.doi: 10.1371/journal.pone.0053042 [PubMed: 23301017]
- Ahrens S. ErbB4 regulation of a thalamic reticular nucleus circuit for sensory selection. *Nature Neuroscience*. 2014; 18(1):104–111. DOI: 10.1038/nn.3897 [PubMed: 25501036]
- Allen Institute for Brain Science. [Accessed: 17 August 2016] Allen Mouse Brain Atlas. 2015. Available at: <http://mouse.brain-map.org>
- Anstrom K, Miczek K, Budygin E. Increased phasic dopamine signaling in the mesolimbic pathway during social defeat in rats. *Neuroscience*. 2009; 161(1):3–12. [PubMed: 19298844]
- Astori S, Wimmer R, Prosser H, Corti C, Corsi M, Liaudet N, Volterra A, Franken P, Adelman J, Lüthi A. The $Ca_v3.3$ calcium channel is the major sleep spindle pacemaker in thalamus. *Proceedings of the National Academy of Sciences of the United States of America*. 2011; 108(33):13823–8. [PubMed: 21808016]
- Austin CP, Ky B, Ma L, Morris JA, Shughrue PJ. Expression of Disrupted-In-Schizophrenia-1, a schizophrenia-associated gene, is prominent in the mouse hippocampus throughout brain development. *Neuroscience*. 2004; 124(1):3–10. [PubMed: 14960334]
- Balu DT, Coyle JT. The NMDA receptor “glycine modulatory site” in schizophrenia: -serine, glycine, and beyond. *Current Opinion in Pharmacology*. 2015; 20:109–115. DOI: 10.1016/j.coph.2014.12.004 [PubMed: 25540902]
- Behrendt R. Hallucinations: Synchronisation of thalamocortical gamma oscillations underconstrained by sensory input. *Consciousness and cognition*. 2003; 12(3):413–51. [PubMed: 12941286]
- Behrens M, Sejnowski T. Does schizophrenia arise from oxidative dysregulation of parvalbumin-interneurons in the developing cortex? *Neuropharmacology*. 2009; 57(3):193–200. [PubMed: 19523965]
- Bodhinathan K, Kumar A, Foster T. Intracellular redox state alters NMDA receptor response during aging through Ca^{2+} /calmodulin-dependent protein kinase II. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2010; 30(5):1914–24. [PubMed: 20130200]
- Buzsáki G. The thalamic clock: Emergent network properties. *Neuroscience*. 1991; 41:351–64. [PubMed: 1870695]
- Carter K, Dickerson J, Schoepp D, Reilly M, Herring N, Williams J, Sallee, Sharp J. The mGlu2/3 receptor agonist LY379268 injected into cortex or thalamus decreases neuronal injury in retrosplenial cortex produced by NMDA receptor antagonist MK-801: Possible implications for psychosis. *Neuropharmacology*. 2004; 47(8):1135–45. [PubMed: 15567423]
- Chun S, Westmoreland JJ, Bayazitov IT, Eddins D, Pani AK, Smeyne RJ, Yu J, Blundon JA, Zakharenko SS. Specific disruption of thalamic inputs to the auditory cortex in schizophrenia models. 2014; 344(6188)
- Clementz B, Sponheim S, Iacono W, Beiser M. Resting EEG in first-episode schizophrenia patients, bipolar psychosis patients, and their first-degree relatives. *Psychophysiology*. 1994; 31(5):486–94. [PubMed: 7972603]
- Corcoran C, Walker E, Huot R, Mittal V, Tessner K, Kestler L, Malaspina D. The stress cascade and schizophrenia: Etiology and onset. *Schizophrenia bulletin*. 2004; 29(4):671–92.
- Coyle J. The glutamatergic dysfunction hypothesis for schizophrenia. *Harvard review of psychiatry*. 1996; 3(5):241–53. [PubMed: 9384954]

- Creese I, Burt, Snyder S. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *The Journal of neuropsychiatry and clinical neurosciences*. 1996; 8(2): 223–6. [PubMed: 9081563]
- Crunelli V, David F, Leresche N, Lambert R. Role for t-type Ca^{2+} channels in sleep waves. *Pflügers Archiv: European journal of physiology*. 2014; 466(4):735–45.
- Cueni L, Canepari M, Luján R, Emmenegger Y, Watanabe M, Bond C, Franken P, Adelman J, Lüthi A. T-type Ca^{2+} channels, SK2 channels and SERCAs gate sleep-related oscillations in thalamic dendrites. *Nature neuroscience*. 2008; 11(6):683–92. [PubMed: 18488023]
- Curro Dossi R, Paré D, Steriade M. Short-lasting nicotinic and long-lasting muscarinic depolarizing responses of thalamocortical neurons to stimulation of mesopontine cholinergic nuclei. *Journal of Neurophysiology*. 1991; 65(3):393–406. [PubMed: 2051187]
- David F, Schmiedt J, Taylor H, Orban G, Giovanni D, Uebele V, Renger J, Lambert R, Leresche N, Crunelli V. Essential thalamic contribution to slow waves of natural sleep. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2013; 33(50):19599–610. [PubMed: 24336724]
- Duan AR, Varela C, Zhang Y, Shen Y, Xiong L, Wilson MA, Lisman J. Delta Frequency Optogenetic stimulation of the Thalamic nucleus Reunien is sufficient to produce working memory deficits: Relevance to schizophrenia. *Biological Psychiatry*. 2015; 77(12):1098–1107. DOI: 10.1016/j.biopsych.2015.01.020 [PubMed: 25891221]
- Earls L, Fricke R, Yu J, Berry R, Baldwin L, Zakharenko S. Age-dependent microRNA control of synaptic plasticity in 22q11 deletion syndrome and schizophrenia. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2012; 32(41):14132–44. [PubMed: 23055483]
- Fehr T, Kissler J, Moratti S, Wienbruch C, Rockstroh B, Elbert T. Source distribution of neuromagnetic slow waves and MEG-delta activity in schizophrenic patients. *Biological psychiatry*. 2001; 50(2):108–16. [PubMed: 11526991]
- Fehr T, Kissler J, Wienbruch C, Moratti S, Elbert T, Watzl H, Rockstroh B. Source distribution of neuromagnetic slow-wave activity in schizophrenic patients--effects of activation. *Schizophrenia research*. 2003; 63:63–71. [PubMed: 12892859]
- Ferrarelli F, Tononi G. Reduced sleep spindle activity point to a TRN-MD thalamus-PFC circuit dysfunction in schizophrenia. *Schizophrenia research*. 2016; doi: 10.1016/j.schres.2016.05.023
- Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, Georgieva L, Rees E, Palta P, Ruderfer DM, Carrera N, Humphreys I, Johnson JS, Roussos P, Barker DD, Banks E, Milanova V, Grant SG, Hannon E, Rose SA, Chambert K, Mahajan M, Scolnick EM, Moran JL, Kirov G, Palotie A, McCarroll SA, Holmans P, Sklar P, Owen MJ, Purcell SM, O'Donovan MC. De novo mutations in schizophrenia implicate synaptic networks. *Nature*. 2014; 506(7487):179–184. [PubMed: 24463507]
- García-Cabezas MÁ, Martínez-Sánchez P, Sánchez-González MÁ, Garzón M, Cavada C. Dopamine Innervation in the Thalamus: Monkey versus rat. *Cereb Cortex*. 2009; 19(2):424–434. [PubMed: 18550594]
- Gray KA, Yates B, Seal RL, Wright MW, Bruford EA. *genenames.org: the HGNC resources in 2015*. *Nucleic Acids Res*. 2015 Jan; 43(Database issue):D1079–85. DOI: 10.1093/nar/gku1071 [PubMed: 25361968]
- Grossman MH, Emanuel BS, Budarf ML. Chromosomal mapping of the human catechol--methyltransferase gene to 22q11.1→q11.2. *Genomics*. 1992; 12(4):822–825. DOI: 10.1016/0888-7543(92)90316-K [PubMed: 1572656]
- Guidi M, Kumar A, Foster T. Impaired attention and synaptic senescence of the prefrontal cortex involves redox regulation of NMDA receptors. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2015; 35(9):3966–77. [PubMed: 25740525]
- HGNC Database, HUGO Gene Nomenclature Committee (HGNC), EMBL Outstation - Hinxton, European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SD, UK. www.genenames.org. retrieved Aug 29, 2016
- Hughes S, Crunelli V. Just a phase they're going through: The complex interaction of intrinsic high-threshold bursting and gap junctions in the generation of thalamic alpha and theta rhythms. *Int J Psychophysiol*. 2007; 64(1):3–17. [PubMed: 17000018]

- Hulme S, Connelly W. L-type calcium channel-dependent inhibitory plasticity in the thalamus. *Journal of neurophysiology*. 2014; 112(9):2037–9. [PubMed: 24623510]
- Jahnsen H, Llinás R. Ionic basis for the electro-responsiveness and oscillatory properties of guinea-pig thalamic neurones in vitro. 1984; 349:227–247.
- Javitt D, Zukin S. Recent advances in the phencyclidine model of schizophrenia. *The American journal of psychiatry*. 1991; 148(10):1301–8. [PubMed: 1654746]
- Kanyshkova T, Pawlowski M, Meuth P, Dubé C, Bender R, Brewster A, Baumann A, Baram T, Pape H, Budde T. Postnatal expression pattern of HCN channel isoforms in thalamic neurons: Relationship to maturation of thalamocortical oscillations. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2009; 29(27):8847–57. [PubMed: 19587292]
- Kielland A, Bochorishvili G, Corson J, Zhang L, Rosin D, Heggelund P, Zhu J. Activity patterns govern synapse-specific AMPA receptor trafficking between deliverable and synaptic pools. *Neuron*. 2009; 62(1):84–101. [PubMed: 19376069]
- Kirov G, et al. De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Molecular psychiatry*. 2011; 17(2):142–53. [PubMed: 22083728]
- Knyazev GG. EEG delta oscillations as a correlate of basic homeostatic and motivational processes. *Neuroscience & Biobehavioral Reviews*. 2012; 36(1):677–695. DOI: 10.1016/j.neubiorev.2011.10.002 [PubMed: 22020231]
- Kobrynski L, Sullivan K. Velocardiofacial syndrome, DiGeorge syndrome: The chromosome 22q11.2 deletion syndromes. *Lancet (London, England)*. 2007; 370(9596):1443–52.
- Korb E, Finkbeiner S. Arc in synaptic plasticity: From gene to behavior. *Trends in neurosciences*. 2011; 34(11):591–8. [PubMed: 21963089]
- Lavin A, Grace A. Dopamine modulates the responsivity of mediodorsal thalamic cells recorded in vitro. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 1998; 18(24):10566–78. [PubMed: 9852593]
- Lein ES, et al. Genome-wide atlas of gene expression in the adult mouse brain. *Nature*. 2006; 445(7124):168–176. DOI: 10.1038/nature05453 [PubMed: 17151600]
- Lisman J, Pi H, Zhang Y, Otmakhova N. A thalamo-hippocampal-ventral tegmental area loop may produce the positive feedback that underlies the psychotic break in schizophrenia. *Biological psychiatry*. 2010; 68(1):17–24. [PubMed: 20553749]
- Lodge D, Grace A. Aberrant hippocampal activity underlies the dopamine dysregulation in an animal model of schizophrenia. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2007; 27(42):11424–30. [PubMed: 17942737]
- Ma TM, Abazyan S, Abazyan B, Nomura J, Yang C, Seshadri S, Sawa A, Snyder SH, Pletnikov MV. Pathogenic disruption of DISC1-serine racemase binding elicits schizophrenia-like behavior via D-serine depletion. *Molecular Psychiatry*. 2013; 18(5):557–67. [PubMed: 22801410]
- Micó JA, Rojas-Corrales MO, Gibert-Rahola J, Parellada M, Moreno D, Fraguas D, Graell M, Gil J, Irazusta J, Castro-Fornieles J, Soutullo C, Arango C, Otero S, Navarro A, Baeza I, Martínez-Cengotitabengoa M, González-Pinto A. Reduced antioxidant defense in early onset first-episode psychosis: A case-control study. *BMC Psychiatry*. 2011; 11(1)doi: 10.1186/1471-244x-11-26
- Moghaddam B, Krystal J. Capturing the angel in “angel dust”: Twenty years of translational neuroscience studies of NMDA receptor antagonists in animals and humans. *Schizophrenia bulletin*. 2012; 38(5):942–9. [PubMed: 22899397]
- Nagalski A, Puelles L, Dabrowski M, Wegierski T, Kuznicki J, Wisniewska M. Molecular anatomy of the thalamic complex and the underlying transcription factors. *Brain structure & function*. 2016; 221(5):2493–510. [PubMed: 25963709]
- Narayanan B, Soh P, Calhoun V, Ruaño G, Kocherla M, Windemuth A, Clementz B, Tamminga C, Sweeney J, Keshavan, Pearson G. Multivariate genetic determinants of EEG oscillations in schizophrenia and psychotic bipolar disorder from the BSNIP study. *Translational psychiatry*. 2015; 5
- Neto L, Schadrack J, Berthele A, Zieglänsberger W, Tölle T, Castro-Lopes J. Differential distribution of metabotropic glutamate receptor subtype mRNAs in the thalamus of the rat. *Brain research*. 2000; 854:93–105. [PubMed: 10784111]

- Notomi T, Shigemoto R. Immunohistochemical localization of Ih channel subunits, HCN1-4, in the rat brain. *The Journal of comparative neurology*. 2004; 471(3):241–76. [PubMed: 14991560]
- Purcell S, et al. A polygenic burden of rare disruptive mutations in schizophrenia. *Nature*. 2014; 506(7487):185–90. [PubMed: 24463508]
- Ripke S, et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014; 511(7510):421–427. DOI: 10.1038/nature13595 [PubMed: 25056061]
- Santoro B, Chen S, Lüthi A, Pavlidis P, Shumyatsky GP, Tibbs GR, Siegelbaum SA. Molecular and functional heterogeneity of Hyperpolarization-Activated pacemaker channels in the mouse CNS. *The Journal of Neuroscience*. 2000; 20(14):5264–5275. [PubMed: 10884310]
- Schobel S, Lewandowski N, Corcoran C, Moore H, Brown T, Malaspina D, Small S. Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. *Archives of general psychiatry*. 2009; 66(9):938–46. [PubMed: 19736350]
- Schulman JJ, Cancro R, Lowe S, Lu F, Walton KD, Llinás RR. Imaging of Thalamocortical Dysrhythmia in Neuropsychiatry. *Frontiers in Human Neuroscience*. 2011; 5doi: 10.3389/fnhum.2011.00069
- Seeman P, Lee T. Antipsychotic drugs: Direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science (New York, NY)*. 1975; 188(4194):1217–9.
- Siekmeier PJ, Stufflebeam SM. Patterns of spontaneous Magnetoencephalographic activity in schizophrenic patients. no date; 27(3)
- Venables NC, Bernat EM, Sponheim SR. Genetic and disorder-specific aspects of resting state EEG abnormalities in schizophrenia. 2008; 35(4)
- Su P, Li S, Chen S, Lipina TV, Wang M, Lai TK, Lee FH, Zhang H, Zhai D, Ferguson SS, Nobrega JN, Wong AH, Roder JC, Fletcher PJ, Liu F. A dopamine D2 receptor-DISC1 protein complex may contribute to antipsychotic-like effects. *Neuron*. 2014; 84(6):1302–16. [PubMed: 25433637]
- Trossbach SV, Bader V, Hecher L, Pum ME, Masoud ST, Prikulis I, Schäble S, de Souza Silva MA, Su P, Boulat B, Chwiesko C, Poschmann G, Stühler K, Lohr KM, Stout KA, Oskamp A, Godsavage SF, Müller-Schiffmann A, Bilzer T, Steiner H, Peters PJ, Bauer A, Sauvage M, Ramsey AJ, Miller GW, Liu F, Seeman P, Brandon NJ, Huston JP, Korth C. Misassembly of full-length Disrupted-in-Schizophrenia 1 protein is linked to altered dopamine homeostasis and behavioral deficits. *Molecular Psychiatry*. 2016; doi: 10.1038/mp.2015.194
- Walsh T, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science (New York, NY)*. 2008; 320(5875):539–43.
- Wolosker H, Blackshaw S, Snyder SH. Serine racemase: A glial enzyme synthesizing d-serine to regulate glutamate-n-methyl-d-aspartate neurotransmission. 1999; 96(23)
- Zhang Y, Buonanno A, Vertes R, Hoover W, Lisman J. NR2C in the thalamic reticular nucleus; effects of the NR2C knockout. *PloS one*. 2012a; 7(7)
- Zhang Y, Llinas RR, Lisman JE. Inhibition of NMDARs in the nucleus Reticularis of the Thalamus produces Delta Frequency bursting. *Front Neural Circuits*. 2009; 3(20)
- Zhang Y, Yoshida T, Katz D, Lisman J. NMDAR antagonist action in thalamus imposes δ oscillations on the hippocampus. *Journal of neurophysiology*. 2012b; 107(11):3181–9. [PubMed: 22423006]
- Zhu J, Shang Y, Zhang M. Mechanistic basis of MAGUK-organized complexes in synaptic development and signalling. *Nature reviews. Neuroscience*. 2016; 17(4):209–23. [PubMed: 26988743]
- Zimmerman E, Grace A. The nucleus Reuniens of the Midline Thalamus gates Prefrontal-Hippocampal modulation of Ventral Tegmental area Dopamine neuron activity. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2016; 36(34):8977–84. [PubMed: 27559178]

Fig. 1. Nineteen risk genes for schizophrenia may affect delta generation in the thalamus

In the thalamus, inhibitory cells of the nRT interact with excitatory relay cells of thalamic nuclei. For ease of visualization, risk genes that affect glutamatergic function (NMDA hypofunction), dopamine hyperfunction, and delta generation are placed against different background colors. The lower-left inset shows the layout of the nRT. Genes are **1)** *TT*-type calcium channel (*CaV3.3*); **2,3)** *L* L-type calcium channel (*CaV1.2* alpha subunit or *CaVB2* beta subunit); **4)** *SERCA* sarcoplasmic/endoplasmic reticulum Ca transporting ATPase (*ATP2A2*); **5)** *HCN1* hyperpolarization-activated, cyclic-nucleotide gate K channel 1 (*HCN1*); **6)** *GRM3* glutamate receptor metabotropic 3; **7)** *D2* dopamine receptor D2 (*DRD2*); **8)** *DGCR8* DiGeorge critical region 8; **9)** *COMT* catechol-O-methyl transferase; **10)** *Serine racemase* (*SRR*); **11)** *GSTT2* glutathione-S-transferase theta 2; **12)** *MSRA* methionine sulfoxide reductase A; **13)** *DISC1* disrupted in schizophrenia 1; **14)** *ARC* activity-regulated cytoskeleton-associated protein; **15)** *GluA1* glutamate ionotropic AMPA receptor 1 (*GRIA1*); **16)** *ErbB4* erb-b2 receptor tyrosine kinase 4; **17)** *SAP-97* synapse-associated protein 97 (*DLG1*); **18)** *PSD-93* postsynaptic density protein 93 (*DLG2*); **19)** *CHRNA3* Cholinergic receptor nicotinic alpha 3 subunit. Also shown are *GluA4*, *DAO*, *NR2C* and *NR2A*, which are relevant to thalamic function, but have not been strongly implicated in the disease by genetic studies. *DAO*-amino acid oxidase; *GluA4* glutamate ionotropic AMPAR subunits; *NR2A* or *NR2C* glutamate ionotropic NMDA receptor subunits; neuregulin is shown in this figure because of its role in the control of thalamic function (Ahrens et al., 2015). *SOM* somatostatin interneuron. The list at bottom right gives the symptoms of SZ that may be linked to thalamic dysfunction in SZ: attentional gating (Behrendt, 2003), hyperactivation of CA1 (Schobel et al., 2009; Zhang et al., 2012b), elevated delta power (Clementz et al., 1994), delta jamming (Duan et al., 2015), and lowered auditory input (Chun et al., 2014). Note that the proportions in this figure do not reflect the actual sizes of the nRT and thalamic relay nuclei. Also note that, while some of these genes

displayed in the nRT are also present in relay nuclei, and vice versa, we only show where the genes are preferentially expressed.

Table 1

List of schizophrenia risk genes implicated in delta generation

Action Group	Risk Gene	Locus*	Reference
Delta Generation	CACNA1i	22q13.1	Ripke et al.,2014; Narayanan et al., 2015
	CACNA1c	12p13.33	Ripke et al.,2014
	CACNB2	10p12.33	Ripke et al.,2014
	ATP2A2	12q24.11	Ripke et al.,2014
	HCN1	5p21	Ripke et al.,2014
	GRM3	7q21.12	Ripke et al.,2014
Dopaminergic Regulation	DRD2	11q23.2	Ripke et al.,2014; Narayanan et al., 2015
	DGCR8	22q11.21	22q11 Deletion; Chun et al. 2014
	COMT	22q11.21	22q11 Deletion
NMDAR Hypofunction Related	SRR	17p13.3	Ripke et al.,2014
	GSTT2	22q11.23	22q11 Deletion
	MSRA	8p23.1	Narayanan et al., 2015; Kirov et al., 2012
	DISC1	1q42.2	Narayanan et al., 2015
General Glutamatergic Function	ARC	8q24.3	Kirov et al., 2012; Fromer et al., 2014
	GluA1 (GRIA1)	5q33.2	Ripke et al.,2014
	ErbB4	2q33.3-q34	Walsh et al., 2008
	DLG1	3q29	Kirov et al., 2012; Fromer et al., 2014
	DLG2	11q14.1	Walsh et al., 2008; Kirov et al. 2012; Fromer et al., 2014
	CHRNA3	15q25.1	Ripke et al.,2014

* All loci were obtained from the HUGO Gene Nomenclature Committee (HGNC Database; Gray et al. 2015)