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Excitation and inhibition imbalance – a new therapeutic target for autism and psychosis?

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Summary

In the healthy brain, homeostatic balance between excitation and inhibition maintains neural stability. However, disturbances to this balance may explain shared symptoms observed in autism and psychosis. Here we review evidence suggesting that altered levels of gamma-amino butyric acid (GABA) may underlie both disorders, providing a potential cross-diagnostic therapeutic target.

Introduction

Comorbidity between mental disorders is the rule rather than the exception. Autism and psychosis are two specific conditions that co-occur more frequently than is currently appreciated by clinical services, both as disorders (8-12%) and as traits (25-31%). Despite phenotypic similarities, such as social-communicative and emotional deficits, and unusual thinking and interests (1), diagnostic hierarchies in current clinical practice view autism and psychosis as mutually exclusive. If a person receives an autism diagnosis as a child, they are less likely to receive a psychosis diagnosis, even if new symptoms emerge. In fact, the DSM-5 and ICD-11 diagnose schizophrenia in the presence of autism only if prominent delusions or hallucinations are present.

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Declaration of interest

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Author contribution statement

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Impaired inhibitory processing in autism and psychosis

Patient and animal studies of autism and psychosis consistently report common pathophysiology involving impaired inhibitory processing in the brain. For example, in both autism and psychosis post-mortem studies report a reduction in GABA levels, due to reduced expression of the GABA synthesising enzymes GAD65 and GAD67, reduced GABA receptor subunits, and/or deficits in a specific subclass of interneuron, namely parvalbumin positive (PV+) interneurons.

Genetic studies and mouse models corroborate this thesis. Susceptibility to autism has been linked to genes encoding proteins of the neuroligin-neurexin complex, including *CNTNAP2*, which are important for inhibitory synaptic development and transmission, while susceptibility to psychosis has been linked to the DISC1 gene, implicated in the development of cortical PV+ interneurons.

This association between these psychiatric conditions and abnormal interneuron function is further supported by *in-vivo* studies. In both autism and psychosis, changes in gamma oscillations, associated with PV+ interneuron activity, have been measured using electroencephalography (EEG) and magnetoencephalography (MEG). Proton Magnetic Resonance Spectroscopy (^{1}H-MRS), which provides a means to quantify the concentration of 'unbound' GABA within a voxel of interest *in-vivo,* reveals either a reduction in GABA levels in autism, or no change, relative to controls. While comparable observations have been made in psychosis, meta-analyses report no difference in GABA-levels relative to controls. In fact, some studies report higher GABA levels, which may reflect exposure to psychopathology, duration of illness and pharmacological treatment. However, ^{1}H-MRS may provide unique *in-vivo* insight into inhibitory dysregulation in both autism and psychosis, if studies are conducted with sufficient statistical power and data quality, and appropriate control for potentially confounding variables.

Finally, autism and psychosis both co-occur with epilepsy, a third disorder characterised by major disruption to inhibitory processing, with prevalence rates reported to be 22% in autism and of 5.6% in psychosis. Taken together, post-mortem studies, animal models, *in-vivo* studies and clinical investigations present a strong case for impaired inhibitory processing in both autism and psychosis.

What are the implications of modified inhibitory function?

In the healthy brain, excitation and inhibition (E/I) are balanced at both a local and global level, a consequence of homeostatic processes that ensure neuronal excitability is maintained within a narrow dynamic range (2). E/I balance thus accounts for the temporal precision of neural computation, where signal propagation is rapidly quenched by inhibition. While E/I balance is regularly disturbed during new learning, experimental and theoretical arguments indicate a critical role for inhibitory synaptic potentiation in restoring and maintaining E/I balance (2–4), potentially via PV+ interneurons. At a behavioural and cognitive level, similar homeostatic inhibitory mechanisms may be engaged in habituation and suppression of un-attended stimuli (2).

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When subtle disturbances to E/I balance are not corrected by homeostatic mechanisms, the consequences are likely far reaching: small changes in signal gating can be amplified by unstable neural networks, resulting in profound changes to cognition. At the extreme, near persistent E/I imbalance may cause epilepsy, while more subtle perturbations in E/I balance may account for cognitive impairments observed in autism and psychosis (i.e., impaired masking of irrelevant perceptions, memories and behaviours). Such phenotypes can be mimicked in theoretical models. In the healthy adult brain when GABA levels are temporarily reduced through transcranial direct current stimulation, spontaneous memory expression and memory interference are observed (4).

However, given that E/I balance dynamically fluctuates, the precise effect of impaired inhibitory processing likely depends on neurodevelopmental stage and contextual factors. Notably, diagnostic separation of autism and psychosis has been encouraged by the distinct age of onset: early childhood in autism and late adolescence or young adulthood in psychosis. The Research Criteria Domain project addresses this concern, proposing that different symptom expressions might represent age-adjusted variation in shared dispositions, thus resulting from similar aetiology. For example, given that interneuron diversity is determined during development through an interplay between genetic and environmental factors, comparable GABAergic dysfunction during development and adulthood may affect the structure and function of neural circuits in profoundly different ways.

Furthermore, the precise neural pathway affected by reduced inhibition may lead to changes in perception and memory either via over-weighting sensory input or over-weighting prior expectation. Over-weighting bottom-up processes might result in hyper-sensitivity, taking the form of sensory over-load as commonly seen in autism. An over-weighing of top-down processes may result in positive psychotic symptoms, with delusions and hallucinations described as a prediction error generated via a mismatch between predictions generated from prior knowledge and received sensory input. Together, these two defects could explain changes in behaviour (e.g. difficulties with social-emotional and face-processing; social withdrawal) (see Fig. 1).

Trans-diagnostic integration

Investigating the neural processes that underpin the phenotypic overlap could provide important mechanistic insight into the co-occurrence of autism and psychosis and ultimately lead to a significant re-conceptualisation in the way we classify and treat these two conditions. What we currently need is greater diagnostic and prognostic clarity to improve treatment efficacy, specifically considering the diagnostic uncertainty in the early illness stages and the absence of explicit NICE guidelines for comorbid psychosis and autism.

A trans-diagnostic approach will aim to explain shared and distinct symptoms. This may eventually address whether autism and psychosis should be understood as separate disorders that sometimes co-occur, or a unitary condition where shared risk factors and pathogenetic mechanisms are modulated by neurodevelopment to otherwise disrupt the same inter-neuron subtypes and synapses.

Pharmacological implications and other challenges

For both autism and psychosis developing new treatments that target early pathophysiological mechanisms and elements of the phenotype that we are currently unable to treat, is crucial. Based on findings from clinical research studies, the GABAergic system has been targeted with some potential for improving clinical symptoms (5), especially social cognition. For example, GABAA and GABAB receptor agonists (Clonazepam, Baclofen) have yielded promising behavioural effects in mouse models, reversing social deficits. In addition, Bumetanide, a diuretic that reinforces GABAergic inhibition, improves emotional face processing in adolescents with autism. While these studies show promising results, evidence for other GABAergic drugs such as Tiagabine, Riluzole and Vigabatrin is still limited and controversial. Further challenges come from established psychotropic drugs acting on $GABA_A$ receptors, such as Diazepam, where paradoxical reactions are observed in some individuals with autism (e.g. increasing anxiety and aggression).

In addition to pharmacological manipulations, a number of other alternative treatments have been proposed that involve modulating cortical excitability. For example, transcranial magnetic stimulation - a method that increases cortical excitability - was found to increase working memory network connectivity in healthy individuals but results have yet to be replicated in clinical samples. Insulin-like growth factor 1 restores neuronal plasticity by reducing cortical GABA levels, and was found to reduce social impairment and repetitive behaviours in individuals presenting with autism symptoms. Lastly, certain neurosteroids that enhance GABAA receptor function may be effective in subgroups of children with autistic traits.

Conclusion

Co-occurrence of autism and psychosis traits represents a significant clinical problem, specifically in the early stages of illness where there is significant diagnostic ambiguity. Despite some distinct phenomenological differences, both disorders appear to be characterised in part by GABAergic alterations which might be associated with cognitive deficits that might in turn impact on other, more diagnosis-specific symptoms, such as sensory hyper-sensibility and positive psychotic symptoms. A number of therapeutic avenues have been tested that show varying degrees of promising results, but what is missing from the literature is an exploration of people presenting with both clinically relevant autism and psychosis to explore shared and distinct disease-related and therapeutic mechanisms.

Outlook

Outlook In humans, recent advances in *in-vivo* neuroimaging include the development of functional ^{1}H-MRS, ^{1}H-MRS imaging, and more accurate measures of GABA with high field imaging. When combined with other imaging modalities, such as functional Magnetic Resonance Imaging, GABA levels can be related to neural mechanisms that underlie cognitive traits. These potentially powerful techniques may establish more nuanced measures of the pathophysiology underlying phenotypes attributed to E/I imbalance, across neurodevelopment. If combined with clinical studies that assess patients with homogeneous

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symptoms as opposed to a common diagnosis, these imaging tools may reveal unique insight into the shared pathophysiology underlying autism and psychosis. In parallel, advances in mouse genetics and optical imaging can characterise the microcircuit mechanism, including the contribution of different interneuron subtypes. Together these measures have the potential to establish stratification markers across patients diagnosed with autism and psychosis, to tailor treatment in a manner that redefines contemporary diagnosis.

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References

1. Hommer RE, Swedo SE. Schizophrenia and Autism-Related Disorders. Schizophr Bull. 2015; 41 (2) 313–4. [PubMed: 25634913]
2. Barron HC, Vogels TP, Behrens TE, Ramaswami M. Inhibitory engrams in perception and memory. Proceedings of the National Academy of Sciences of the United States of America. 2017; 114 (26) 6666–74. [PubMed: 28611219]
3. Vogels TP, Sprekeler H, Zenke F, Clopath C, Gerstner W. Inhibitory Plasticity Balances Excitation and Inhibition in Sensory Pathways and Memory Networks. Science. 2011; 334 (6062) 1569–73. [PubMed: 22075724]
4. Koolschijn RS, Emir UE, Pantelides AC, Nili H, Behrens TEJ, Barron HC. The Hippocampus and Neocortical Inhibitory Engrams Protect against Memory Interference. Neuron. 2019; 101 (3) 528. [PubMed: 30581011]
5. Foss-Feig JH, Adkinson BD, Ji JL, Yang G, Srihari VH, McPartland JC, et al. Searching for Cross-Diagnostic Convergence: Neural Mechanisms Governing Excitation and Inhibition Balance in Schizophrenia and Autism Spectrum Disorders. Biological Psychiatry. 2017; 81 (10) 848–61. [PubMed: 28434615]

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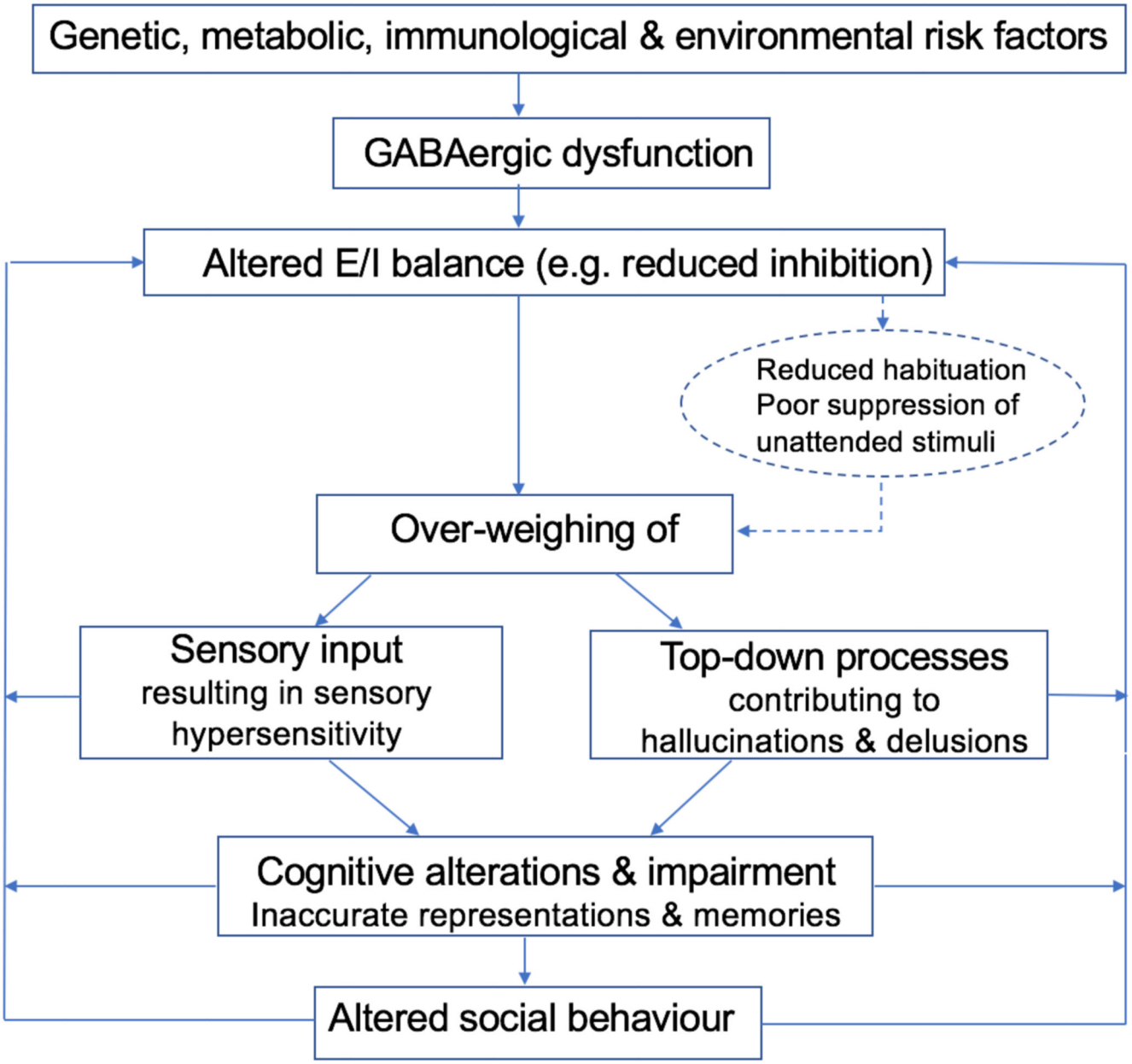

Figure 1. Aetiological model of symptomatology in autism and psychosis elicited by GABAergic dysfunction.