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Closing gaps in brain disease — from overlapping genetic architecture to common motifs of synapse dysfunction

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Recent progress in the synaptic pathophysiology of brain diseases is reviewed. To emphasize the emergence of common motifs in synapse dysfunctions across neurodevelopmental, psychiatric and neurological disorders, conventional clinical boundaries are disregarded and a decidedly trans-diagnostic, potentially unifying view of altered synapse function is promoted. Based on the overlapping genetic architecture of brain disorders, which often converges on genes related to synaptic functions, disease-related changes in basic pre-synaptic and post-synaptic communication, neuromodulation-gated changes in Hebbian plasticity, dynamic interactions between Hebbian and homeostatic plasticity, and changes in synaptic maintenance by autophagy and glial-mediated phagocytosis are highlighted.

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All diseases of the brain impair — one way or another — its core function to generate adaptive behavior in a world of complex and ever changing environments and social interactions. In addition to maintaining this most complex biological system characterized by functional circuits on many levels [1], in itself an enormous homeostatic challenge [2], the brain must also constantly change to update its predictions about the world [3,4]. The brain circuits update by monitoring prediction errors and use them as teaching signals to drive changes in synaptic connectivity and structure [4]. Thus, by its very nature, the brain — navigating through a developmental sequence of risky and disease-prone critical phases [5] — is a moving target and never finished ('brain development is a life-long process' [6•]). This notion implies that the rules of homeostasis are not sufficient and might be widened to a concept of homeodynamics [7] — maintaining stability in the presence of constant change — a truly heroic, even somewhat paradoxical task.[1]

Brain diseases are very diverse and our mechanistic understanding is still limited. Depending on the respective age of onset — from neurodevelopmental disorders [5] to neurodegenerative diseases of old age [8] — and the functional domains affected, brain diseases have been classified into major categories and channeled into distinct clinical fields and traditions [7]. However, there is growing consensus that many brain diseases affect some of its synaptic core functions. This implies that in particular neurodevelopmental, psychiatric and neurological disorders such as cognitive impairment, autism, epilepsy and schizophrenia share substantial parts of their synaptic and circuit pathophysiology, despite manifesting within different target circuits across distinct periods of brain development, maturation and maintenance.

The current literature, highlighted in this short review, suggests a number of interacting converge points in brain diseases that are associated with the homeodynamic nature of its core synaptic processes: firstly, neuromodulator-gated synaptic function and Hebbian plasticity [9,10•] interacting with, secondly, homeostatic plasticity mechanisms [2] and thirdly, being embedded in global cellular maintenance and quality control programs [11]. Dysfunction across these domains results in unbalancing between excitation, inhibition and neuromodulation (MEI balance) within microcircuits and disturbances in frequency-band specific synchrony and coherence for long-range communication between distinct brain areas [12,13].

The dynamic synaptic proteome

Recent studies started to define the deep complexity of the synaptic core machinery. Studying pharmacologically-induced homeostatic scaling of glutamatergic neurotransmission in hippocampal neurons, Schanzenbacher

[1] My dear, here we must run as fast as we can, just to stay in place. And if you wish to go anywhere you must run twice as fast as that (Lewis Carroll; Alice in Wonderland).

et al. identified ≈300 newly synthetized, predominantly neuronal (>90%) proteins that were significantly altered with homeostatic synaptic up- or downscaling [14••]. These include subunits of the ionotropic glutamate and GABA receptors as well as proteins engaged in calcium signaling and presynaptic functions. The fact that about 150 proteins of this dynamically translated pool are known to be dysregulated in brain diseases, ranging from neurodevelopmental disorders like autism and schizophrenia to Alzheimer and Parkinson Disease (AD, PD), strongly suggests activity-dependent dynamic control of synaptic protein turnover to be one point of convergence for many brain diseases. Additional evidence for a common synaptic protein core for brain diseases comes from extensive genetic studies [15••], transcriptome analysis of human iPSC-cells [16•] and human hippocampus [17••] as well as primate brain development [18].

This progress is matched by elegant functional studies, which by utilizing novel optogenetic tools, demonstrated the — long suspected, but only now directly demonstrated — causal role in structural synaptic spine plasticity for key brain functions like learning and memory. In a technical tour-de-force, Hayashi-Takagi *et al.* showed by selectively tagging recently potentiated spines of pyramidal layer II/III neurons in motor cortex with a photoactivatable GTPase (RAC1), which upon light-stimulation induced spine shrinkage and LTP reversal, that spine-potentiation (at an estimated population size of ca. 300 000) was necessary for motor learning [19•]. This optic erasure of memory traces on defined populations of individual potentiated spines was matched by important studies at the level of neuronal ensembles [20]. In particular, Roy *et al.* [21•], who optogenetically tagged engram cells in hippocampus and demonstrated light-mediated retrieval of memory traces in both control and AD mouse models. Furthermore, both Pascoli *et al.* [22•] and Zhu *et al.* [23] used projection-specific and input-specific optogenetically-driven depotentiation of disease-related synaptic plasticity in the context of cocaine and morphine dependence to demonstrate its causal role in drug-seeking behavior.

Disease-related plasticity at the glutamatergic synapse

Given these advances and the already strong focus on glutamatergic neurotransmission, is it not surprising that many novel insights in brain disease mechanisms were made in relation to this particular synapse type and its forms of plasticity. Apart from generic glutamatergic synapses studied in cultural systems, glutamatergic synapses in striatal medium spiny neurons (MSN), which mediate converging inputs from mainly cortical and thalamic inputs constitute one focus of attention, given their relevance for many neurodevelopmental, neurological and psychiatric diseases. The corticostriatal glutamatergic synapses on either D1R-expressing direct pathway MSN (dMSN) or D2R-expressing indirect MSN (iMSN) are of particular interest as their plasticity is controlled via important neuromodulators such as dopamine or acetylcholine [24,25]. Both are dramatically altered in brain disorders such as PD or Huntington Disease (HD). In particular, the consequences of both chronic dopamine depletion and therapeutic substitution by dopamimetics on corticostriatal synapses have been intensively studied. Recent work further highlighted the crucial role of neuromodulators in glutamatergic plasticity. Shen *et al.* defined the role of postsynaptic muscarinic type IV (M4R) receptors on dMSN, where they operate to antagonize D1R-mediated LTP [26•]. They demonstrated that M4R-signaling act downstream via RGS4 and mGLUR5-mediated endocannabinoid signaling. Their findings open the path to new and attractive treatment option of L-dopa induced dyskinesia, which is driven by aberrant plasticity in the D1R-dMSN pathway. Indeed, they demonstrated the clinical potential of a positive allosteric modulator for M4R in both rodent and non-human primate models. Importantly, Parker *et al.* showed that the plasticity of glutamatergic inputs to MSN from centromedian-parafascicular (CM/Pf) thalamic nuclei was also affected by chronic dopamine depletion in a circuit-specific manner. Using a chronic unilateral 6-hydroxydopamine (6-OHDA) rodent model, they identified a LTD-like loss of AMPA-receptors selectively from thalamostriatal synapses on D1-containing dMSN neurons and elegantly demonstrated its behavioral relevance with projection-specific chemo-genetic and opto-genetic approaches [27]. Because of its successful targeting in deep brain stimulation-based treatment of movement disorders like PD, the subthalamic nucleus (STN) is one of the most clinically-relevant downstream nuclei in the indirect basal ganglia pathway. However, the underlying synaptic processes that contribute to the dramatic pattern change of *in vivo* STN activity are not yet well understood. Here, Chu *et al.* shed new light by revealing the heterosynaptic and homeostatic interactions of cortical glutamatergic and globus pallidus (GP) GABAergic inputs in STN neurons. Again, utilizing a chronic 6-OHDA DA-depletion model, they identified the coupling between homosynaptic NMDAR-driven cortico-subthalamic LTP and NO-dependent heterosynaptic GABA-LTP [28••]. This is a conceptionally important study illustrating how disease-driven aberrant plasticity at a single synapse type might propagate throughout an entire circuit by recruiting —maladaptive mechanisms for homeostatic synaptic balance. Therefore, it might serve as an example of homeodynamic network dysfunction.

Another pressing need in the field is to relate the complex and overlapping genetic landscape of brain diseases to synaptic and circuit dysfunctions. This might also address the puzzling questions why different mutations in the same gene — such as in SHANK3, coding for a

postsynaptic density scaffold protein enriched in the striatum — lead to different clinical phenotypes with distinct ages of onset. Here, Zhou *et al.* carried out a rigorous comparison of two different missense mutations in exon 21 inducing premature stop codons in SHANK3 [29•]. They found that — due to differences in mRNA stability of the two distinct missense mutants — only the ASD-related SHANK3 mutant led to complete absence of SHANK3 protein and early dysfunction in striatal glutamatergic transmission with ASD-associated behavioral impairments. In contrast, in adult medial prefrontal cortex (mPFC), the partial protein function of the schizophrenia-related SHANK3 mutant apparently prevented full compensatory expression of SHANK1 and SHANK2, as was the case with the ASD-related SHANK3 mutant. This failure of compensatory expression resulted in adult-onset synaptic defects in mPFC. This study emphasizes the need and value for detailed celltype-specific functional analysis of disease-related mutants at defined times of brain development and maturation.

Presynaptic impairments

While one strong focus still remains on the dynamics of postsynaptic aspects of glutamatergic transmission, presynaptic key functions, novel and important synapse-type specific players such as CNTNAP4 for GABAergic and dopaminergic neurotransmission were also discovered [30]. Cao *et al.*'s investigation of LoF-mutations in synpaptojanin1 (SJ1), which are associated with early-onset PD, revealed that the resulting deficit in PIP2-dephosphorylation and in turn shedding of vesicle-associated endocytosis mediators led to an accumulation of clathrin-coated vesicles. Interestingly, analysis of a mutant SJ1 knock-in mouse model revealed — apart from the expected dysfunction of the nigrostriatal dopamine system — a pronounced impairment of inhibitory compared to excitatory synapses with a resulting shift in E/I balance leading to a severe epileptic phenotype [31]. The presynaptic core machinery of activity-dependent and calcium-dependent neurotransmitter vesicle release is also under powerful control of presynaptic neurotransmitter receptors that - in analogy to the postsynaptic side — are important targets of brain diseases and relevant for both the generation or buffering of clinical phenotypes. In an elegant study monitoring disease-related changes in presynaptic neurotransmitter release directly, Borgkvist *et al.* showed that as a response to 6-OHDA-mediated dopamine depletion in a PD rodent model and in turn reduced stimulation of D1Rs on GABAergic striatonigral terminals, the tonic function of presynaptic GABA-B receptors was suppressed [32], again likely to be a result of homeostatic plasticity. This partial compensation of the presynaptic D1R-GABA-B receptor balance on striatonigral terminals reduced some of the dysfunction resulting from DA depletion, but at the same time sensitized the system to dopamimetic therapy. This work illustrates well how new homeostatic setpoints in response to brain diseases might come with a price of reduced stability and altered response to therapeutic interventions. Homeostatic control to balance between two neurotransmitters (E/I Balance) is also operative for axo-axonal synapses as recently demonstrated for presynaptic GABAergic terminals on glutamatergic Ia afferents in the spinal cord by Mende *et al.* [33]. They demonstrated that glutamate release from Ia terminals controls the synthesis of both GAD65 and GAD67, key enzymes for producing the neurotransmitter GABA, in axo-axonal GABAergic terminals via different signaling pathways including presynaptic mGLUR type 1 receptors and BNDF signaling.

Translational control in synapses

In addition to pinpointing individual signaling processes (low-level players), brain disease-genes also code for regulatory hub proteins involved in maintenance and quality control of larger families of downstream proteins. Apart from controlling metabolic pathways or epigenetic DNA modifications, local control of synthesis, delivery and turnover of synaptic proteins is another essential feature. In particular, mRNA-binding proteins such as FMRP exerting essential multi-gene translational control of synapse function have received sustained attention due to their key role in brain diseases like fragile X syndrome [34–36]. While the role in tuning mGluR-dependent synaptic depression has been elucidated, recent studies identified novel and important FMRP-interaction partners and intervention strategies [37,38]. Here, Pasciuto *et al.* identified enhanced expression and function of the alpha-secretase ADAM10 upon loss of FMRP in a fragile X mouse model [6•]. They found that ADAM10-dependent elevated APP-processing was driving enhanced but immature spinogenesis and synaptic dysfunction.

Macroautophagy and glial-mediated phagocytosis in synapses

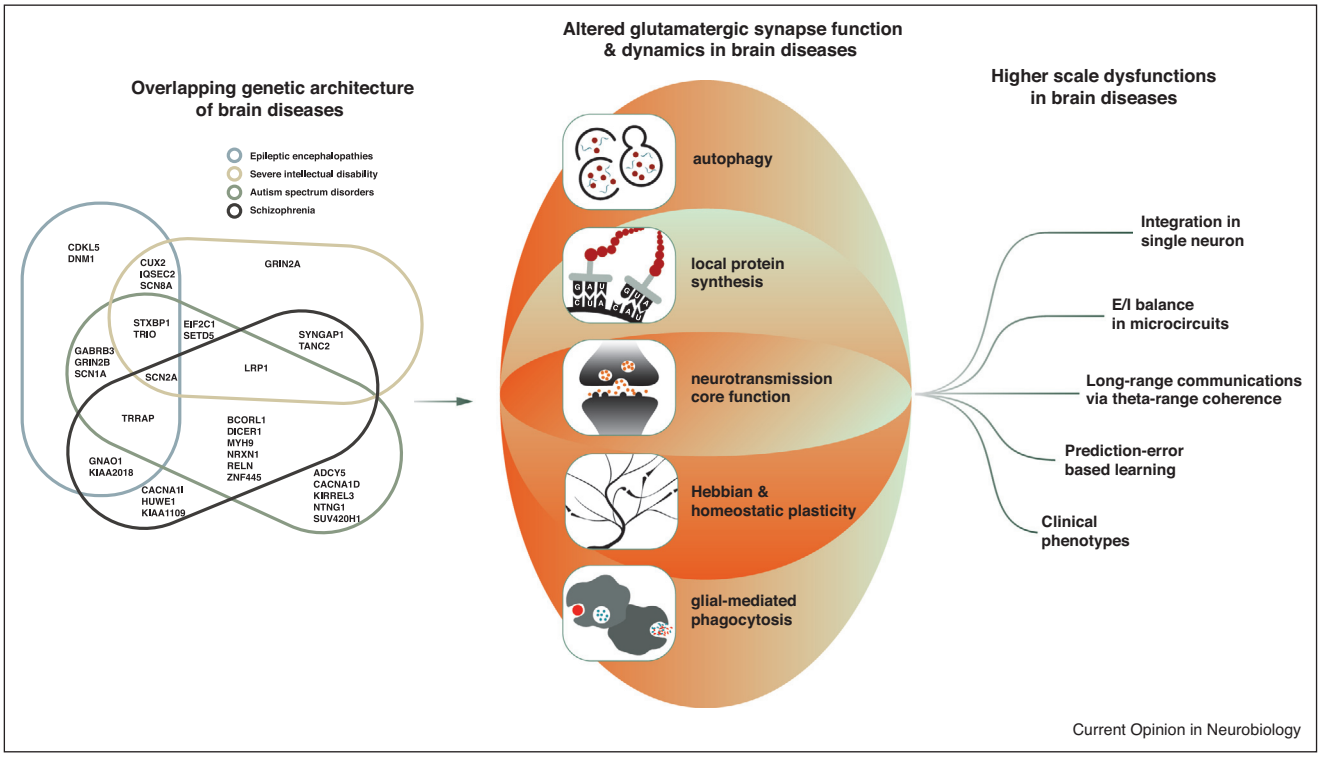
Moreover, recent studies highlighted the importance of neuronal autophagy as well as astroglial and microglial-mediated phagocytosis in particular for synaptic turnover (synapse formation and pruning) during critical phases of brain development, adult maintenance as well as aging [39]. Tang *et al.* identified a deficit in cortical synaptic pruning during adolescence in brain of ASD patients, which was associated with indicators for reduced activity of macroautophagy and elevated mTOR signaling [40•]. Indeed, they demonstrated that mice with genetically reduced autophagy activity (ATG7 KO) displayed typical behavioral features of ASD. Soukup *et al.* demonstrated that phosphorylation of endophilinA by LRKK2, which is a major PD disease gene, controls presynaptic macroautophagy. The perturbation of endophilinA phosphorylation in both directions leads to neurodegeneration in model systems [41].

In particular, dysregulation of complement-driven (C1q-C3) phagocytosis has entered a central stage in

brain diseases inducing the loss of synaptic communication. This pathway, most active during early developmental waves of synaptic circuit refinement, showed also enhanced later activity in a mouse model of Rett Syndrome [42] or in response to viral encephalitis [43]. In addition, genetic risk variants of the complement gene C4A (MHC class III gene) have been identified for schizophrenia, leading to enhanced expression and likely to higher rates of synaptic pruning [44••]. Finally, oligomeric A-beta also re-activated the complement C1q-mediated synaptic pruning pathway at an early pre-plaque stage of a genetic AD mouse model [45].

In conclusion, recent progress in defining the synaptic pathophysiology of brain diseases might help to outline a general framework (Figure 1) that integrates research data into a coherent context. The emerging overlapping genetic architecture of brain diseases provides a strong emphasis to study glutamatergic synapse function on multiple levels. Even for central core functions — such as the composition of AMPA-R protein complexes [46] — new discoveries are still made and the protein machinery and detailed regulation of their biogenesis are just beginning to be understood [47]. These synaptic core functions are embedded in multiple, interactive layers, which together determine the dynamic turnover of neurotransmitter receptors as well as entire synapses. For the inner shell, which orchestrates Hebbian and homeostatic plasticity of the synapse, the first comprehensive analysis of locally synthetized proteins revealed a complex but at the same time highly disease-relevant cast of about 150 proteins. It will take a major research effort to move from this list of players to an understanding of the rules of dynamic interactions among them. In any cases, the in depth-studies of neuromodulation-gated synaptic plasticity continue to be a fertile ground to better define brain diseases and identify new treatment options. The outer layer contains more global cellular maintenance and quality control processes like autophagy and glial-mediated phagocytosis of synapses, which also appear to be dysregulated across many different brain diseases. Outside this converging point of synaptic dysfunction in brain diseases, where the role of disease-related genetic variants can be directly evaluated, another major challenge in understanding brain diseases looms: How dysfunctions of individual synapses scale up to impairments on the respective levels of cellular integration [48••], microcircuit function including E/I balance [49•,50], of long-range communication using frequency-selective coherence [12] and — eventually — on the behavioral level, which determines the diversity of clinical phenotypes. However, the increasing definition of circuit-level dysfunctions in brain diseases, beyond the scope of this review, provides an increasingly rich substrate for future scale-crossing studies to

Figure 1



Overlapping genetics of brain diseases converge on common motifs of synapse dysfunction, which scale to higher level impairments ranging from cellular to clinical phenotype (left panel was adapted from Zhu *et al.*, 2013, Nature Neuroscience 17:773–81).

eventually bridge the multiple gaps between genes, synapses, cells, circuits and clinical phenotypes.

Conflict of interest statement

Nothing declared.

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