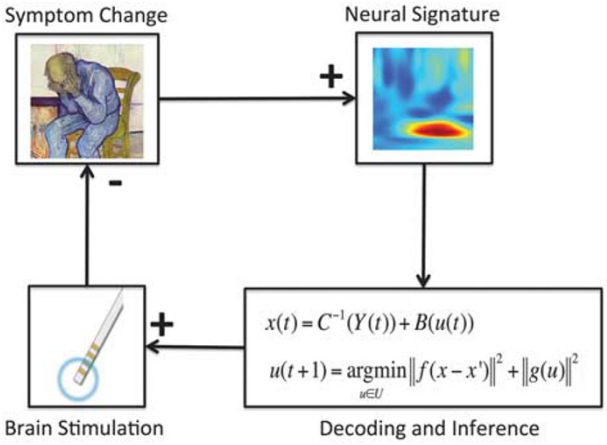

Figure 1. Schematic of closed-loop DBS control. A change in psychiatric symptoms (likely a dimensional construct such as negative mood, over-generalized fear or hyper-arousal) leads to a stereotyped change in neural activity. This is detected by a neural decoding algorithm, which automatically adjusts brain stimulation parameters according to a pre-defined transfer function. The resulting change decreases the symptom level, which stabilizes the system in a homeostatic loop.

circuit-based endophenotypes, analogous to research domain criteria constructs. For instance, preliminary data suggest that DBS response at the ventral striatum target may depend on changes in fronto-cingulate activity evoked by Stroop-like tasks (Widge *et al*, 2015). This cross-diagnostic approach may be broadly useful in dissecting DBS' mechanisms of action.

Second, neural plasticity can help. A recent surprise from BCI studies is that models are helpful, but not always necessary. A motivated subject can learn to skillfully control a prosthetic limb or an internal neurostimulator, even if the mapping between neural firing and device behavior does not match 'natural' input–output relationships. As the user trains with the BCI, the brain re-maps its firing patterns to match the device's control scheme (Moritz and Fetz, 2011). In effect, the decoded patterns become a readout of the user's intention—what he/she wants the device to do at that moment. For a prosthetic limb, this is an instantaneous motion command. For psychiatry, it would be a stimulator command. For instance, one could place a recording electrode in an area that contains emotion-related signals, then link the amplitude of a DBS intervention to the intention-modulated signals in that area. The patient's signals in the recorded area would then 'tune' the DBS intervention as needed. We recently showed that rodents can learn to use prefrontal cortex signals in precisely this fashion to activate DBS-like stimulation (Widge and Moritz, 2014). Similar strategies may be useful for modulating fear behaviors in anxiety disorders, using fronto-limbic networks as targets (Besnard and Sahay, 2015).

DBS remains an interesting technique, and closed-loop approaches may make it more useful for a broader group of patients. Despite recent clinical trial failures, the prospects for psychiatric DBS may be brighter than ever.

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Heteroreceptor Complexes and their Allosteric Receptor–Receptor Interactions as a Novel Biological Principle for Integration of Communication in the CNS: Targets for Drug Development

The receptor–receptor interaction field began with the studies on the

neuropeptide–monoamine receptor–receptor interactions in membrane preparations in the early 1980s, which altered especially the affinity of the monoamine receptor subtypes. It was proposed that their interactions in the plasma membrane took place in postulated heteroreceptor complexes of GPCRs which could involve the participation of adapter proteins (Fuxe *et al*, 2014). Now the receptor field in the CNS has expanded and includes not only the monomers but also homo and heteroreceptor complexes with receptor assemblies of unknown stoichiometry and geometry together with adapter proteins (Figure 1) as novel targets for treatment of neurological and mental diseases. In the beginning bivalent compounds were developed like norbinaltorphimine to obtain selective opioid receptor antagonists (Portoghese, 1992).

It is of high interest that dopamine D_2R receptors form higher order homoreceptor complexes at physiological expression levels in living cells as was demonstrated using protein complementation assays combined with resonance energy transfer (Guo *et al*, 2008). Also, it was demonstrated that allosteric mechanisms are in operation between protomers of D_2R homodimers that modulate their activation (Han *et al*, 2009). Using a functional complementation assay it became possible to evaluate the D_2R homodimeric functional unit and directly study their receptor-G protein interactions. The evidence suggests an asymmetrical activated D_2R homodimer where the second D_2R protomer inhibits signaling.

The allosteric receptor–receptor interactions in heteroreceptor complexes give diversity, specificity and bias to the receptor protomers due to conformational changes in discrete domains leading to changes in receptor protomer function and their pharmacology (Fuxe *et al*, 2014; George *et al*, 2014). The discovery of the adenosine $A_{2A}R$-D_2R heteroreceptor complexes in the dorsal striato-pallidal GABA neurons with antagonistic $A_{2A}R$-D_2R receptor–receptor interactions reducing D_2R signaling (Figure 1) led to the development of $A_{2A}R$ antagonists for treatment of Parkinson's disease (Fuxe *et al*, 2014). The motor complications found with levodopa such as dyskinesias and wearing off phenomena can involve a reorganization of these heteroreceptor complexes involving also a disbalance with $A_{2A}R$ and D_2R homoreceptor complexes. Increased knowledge of the changes in the heteroreceptor complexes and their function in neurological and mental diseases may lead to the discovery of novel therapeutics.

Neurotrophic and antidepressant effects of 5-HT in brain may, in part, be mediated by activation of the 5-HT1A receptor protomer in the hippocampal and midbrain raphe fibroblast growth factor receptor 1 (FGFR1)-5-HT1A heterocomplexes enhancing the FGFR1 signaling (Borroto-Escuela *et al*, 2015). The FGFR1-5-HT1A heteroreceptor complex likely represents a

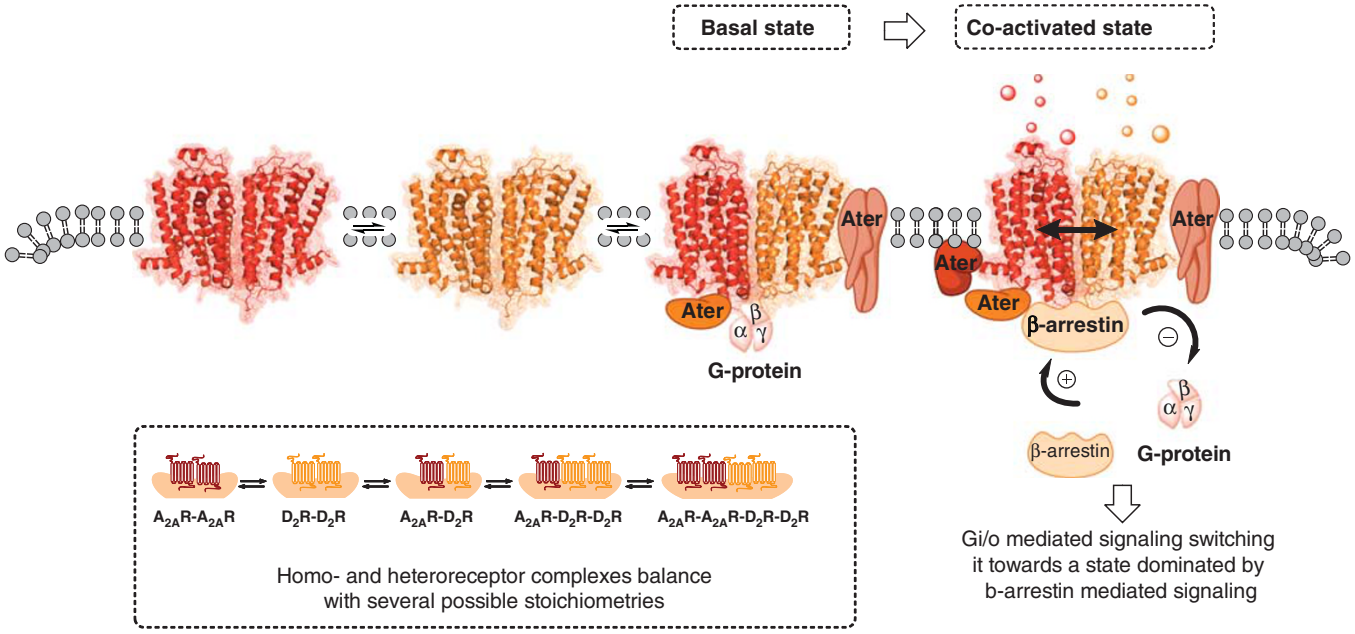

Figure 1. Illustration of the antagonistic allosteric receptor–receptor interactions in the $A_{2A}R$-D_2R heteroreceptor complexes with several possible receptor stoichiometries from heterodimers to higher order heteromers of various types (heterotrimer and heterotetramer are shown; lower part) with the participation of adapter proteins (Ater). These proteins may participate in the mediation of the allosteric interaction by eg, guiding the receptors towards each other through a scaffolding function. Such actions may also regulate the time of the heteromerization from being transient to becoming more stable and long lasting. The major allosteric interaction appears to be an antagonistic $A_{2A}R$-D_2R interaction by which the agonist-activated $A_{2A}R$ protomer inhibits the D_2R protomer recognition (reduced affinity) and Gi/o mediated signaling. D_2R protomer becomes switched towards a state dominated by beta-arrestin-mediated signaling (far right). The heterocomplexes are in balance especially with the corresponding $A_{2A}R$ and D_2R homoreceptor complexes (upper part) but also with other collocated D_2R heterocomplexes and $A_{2A}R$ heterocomplexes (not shown) in the synapses and their extrasynaptic regions in the striato-pallidal GABA neurons. Although not shown, the adapter proteins also participate in modulating the organization and function of the $A_{2A}R$ and D_2R homodimers and their higher order homoreceptor complexes.

novel target for antidepressant drugs and offers a new strategy for treatment of depression.

Taken together, GPCR heteroreceptor complexes and their receptor–receptor interactions represent a new fundamental principle in molecular medicine for integration of transmitter signals in the plasma membrane. A novel understanding of the molecular basis of CNS diseases is given together with new strategies for their treatment by targeting heteroreceptor complexes based on a new pharmacology with combined treatment, multi-targeted drugs and heterobivalent drugs. Our perspective on the future of research on heteroreceptor complexes is the further development and employment of multiple techniques for use in cellular models, brain tissue and *in vivo* studies to understand their role in discrete brain circuits. The advancement of the proximity ligation assay will be of special importance as will be the development of selective heterobivalent compounds for the heterocomplexes.

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Hippocampal Neurogenesis and Memory Clearance

We are constantly forgetting. For a moment, consider what you have done today. It might be relatively straightforward, for example, to recall your journey to work. Similarly, you might recall easily the people you encountered and conversations you had, even with a fair degree of clarity. We keep a good record of these ordinary, everyday events. But what about memories of similar, everyday activities that occurred a week ago? Or a month or a year ago? Unless something extraordinary occurred, it is unlikely that you can recall much of what happened, and certainly not in any great detail. This reflects the fact that while we are continuously encoding our experiences, the vast majority of these encoded experiences (or memories) are 'cleared away' and only a small portion ultimately retained. The hippocampus is thought to be the automatic encoder, with the cortex serving as the final repository for the fraction of memories that are successfully consolidated (Wang and Morris, 2010). But how are memories cleared from the hippocampus?

Recent work has identified one likely clearance mechanism. In the hippocampus, new cells are continuously generated in the subgranular zone of the dentate gyrus. Most of these new cells differentiate into granule cells and migrate into the granule cell layer, where, after a few weeks, they synaptically integrate into the hippocampal circuitry. There has been plenty of interest in how these newly generated neurons might facilitate the formation of new memories (eg, by increasing the mnemonic capacity or facilitating certain types of computations carried out by the dentate gyrus, such as pattern separation) (Christian *et al*, 2014). However, as new cells integrate into the hippocampus they necessarily remodel existing circuitry. This remodeling may degrade memories already stored in those circuits (or at least render them difficult to access) (Deisseroth *et al*, 2004; Weisz and Argibay, 2012). We recently provided experimental support for this prediction (Akers *et al*, 2014). Voluntary exercise increases hippocampal neurogenesis in adult mice. We found that running-induced increases in neurogenesis led to forgetting of established contextual fear and spatial memories. While running induces a number of physiological changes, the forgetting effects appeared to depend on elevated neurogenesis, since genetically attenuating this consequence of running prevented forgetting. Furthermore, pharmacological (eg, memantine, fluoxetine) and genetic (conditional deletion of p53 from neural progenitors) interventions that artificially elevate hippocampal neurogenesis, when introduced after training, similarly weakened existing hippocampus-dependent memories, suggesting that running-induced forgetting is mediated by a neurogenic mechanism.

There are two important implications of these findings. First, not only do they tell us about how forgetting normally occurs, but perhaps additionally they hint at an important functional consequence of ongoing neurogenesis in the adult hippocampus. Established memories interfere with encoding of new memories, especially when the new and established memories are in conflict with one another. By continuously clearing hippocampal memories, ongoing neurogenesis may serve to minimize this form of proactive interference