Improving pattern separation and cognition

Valorisation Addendum

Relevance & Audiences

Cognitive impairment is a common feature in many neurological and psychiatric conditions, like Alzheimer's disease (AD), dementia, schizophrenia, post-traumatic stress disorder (PTSD) and aging. Cognitive deficits include a wide variety of different symptoms which can affect multiple types of mental functions in different levels of severity depending on the nature of the underlying condition. The intricate nature of cognitive functions and inter-personal differences between patients makes it difficult to study cognitive impairments. Therefore, many of the mechanisms serving cognitive function are not fully understood yet. Our cognitive abilities enable us to perform many of the tasks important in day-to-day living. Therefore, cognitive impairments can have a great impact on everyday functioning of the patient and their quality of life. Hence, it is important to study different types of cognitive impairments to gain a better understanding of its underlying mechanisms and ultimately develop targeted treatments which can ameliorate cognitive impairments.

The studies in this dissertation have mainly focused on pattern separation, a specific type of cognitive function that entails the ability to discriminate between two highly similar but slightly different memory formations. Given that most people constantly move around in the same environments, seeing the same surroundings, the same people and the same objects on a very regular basis. One can imagine that pattern separation is of high importance to even the simplest aspects of day-to-day living. Impaired pattern separation has a severe impact on memory function, leading for example to difficulties in making a distinction between situations. Next to a decreased memory function, this can affect judgment and decision making which has a negative influence on the long-term outcome and chances of recovery for the patient.

Pattern separation has been found to be impaired in diseases like schizophrenia, PTSD and AD. Schizophrenia is a disabling psychiatric disorder that affects about 1% of the population worldwide. While schizophrenia is most known for its positive and negative symptomatology, cognitive deficits are also an important symptom category. In recent history, the importance of cognition in schizophrenia patients has been under-acknowledged and all available treatment strategies focus on the treatment of positive and negative symptoms. However, it was found that the extent of cognitive deficiencies is the best predictor of functional outcome when compared to the positive and negative symptomatology. Therefore, the development of treatment for cognitive impairments will have a substantial beneficial effect on the functional outcome and quality of life of patients. Furthermore, it will also lessen the significant and long-lasting health, social and financial burden for

the patients, their families, caregivers and the wider society. In addition to the social and economic benefits, amelioration of cognitive impairment would re-establish a patient's ability to function independently which has a major positive influence on recovery and chances of re-lapse.

Pattern separation impairment is of specific interest in the treatment of cognitive deficits in schizophrenia. It has been proposed that this particular impairment leads to the exacerbation of some of the more pronounced positive and negative symptoms, or might even be the underlying cause of the disease. The disability to judge situations and overgeneralization of potential threats increases anxiety and paranoia. This could lead to the development and sustenance of the commonly seen psychotic beliefs, which make schizophrenia such a debilitating disorder. Development of a treatment which could tackle all these symptoms at once would be of high benefit to both patients and society.

In addition, pattern separation impairments have been found to occur in a wide variety of psychiatric diseases. In AD for instance, it has been found to be one of the first cognitive abilities to be impaired in the early stages of the disease. This highlights the fundamental nature of pattern separation processing and its importance to support overall cognitive function. A cognitive enhancer that could ameliorate pattern separation dysfunction could not only benefit schizophrenia or AD patients, but improve the outcome of a broad spectrum of patients suffering from different psychiatric diseases. The 5-HT1AR sub-population has been studied widely in this respect, due to its distribution through the brain and wide involvement in many mechanisms important to cognition. However, most of the drugs that (partially) target 5-HT1AR's only show moderate results in their memory and cognition enhancing effects, due to the differentiating effects that stimulation of 5-HT1AR's can have based on their location within the brain. In this dissertation a novel type of 5-HT1AR agonists was studied in their ability to enhance cognition and specifically pattern separation processing. These 'biased' agonists have the ability to specifically target either the pre-synaptic autoreceptors or post-synaptic heteroreceptors, enabling the ability to specifically target the receptors that show beneficial effect without the opposing effect of the other sub-group.

In this dissertation it was shown that the cognitive performance of rodents can be improved by specifically targeting post-synaptic 5-HT1A heteroreceptors. In summary, it was shown that:

1. A biased post-synaptic 5-HT1AR agonist (F15599) can improve pattern separation performance in healthy rats when given both acutely and chronically;
2. Chronic biased post-synaptic 5-HT1A heteroreceptor stimulation enhances hippocampal plasticity;
3. That chronic exposure to a pre-synaptic 5-HT1AR agonist (F13714) will desensitize the pre-synaptic autoreceptors and restore the initial acute impairment.
4. That acute administration of a post-synaptic 5-HT1AR agonist ameliorates a pattern separation deficit in a pharmacological rat model for schizophrenia
5. That acute administration of a post-synaptic 5-HT1AR agonist ameliorates a behavioral flexibility deficit in a pharmacological rat model for schizophrenia

The possibility to study the behavioral effects of differently located 5-HT1ARs separately is a major benefit of these biased agonists. This dissertation demonstrates that there can be benefits in separately targeting these sub-populations and that it will provide us with new insights into the mechanisms of these receptors. This brings us one step closer to unravelling the 5-HT1AR system mechanisms and diseases associated with a dysfunction in this receptor population. Increasing our knowledge on the exact mechanisms will contribute to the development of successful treatments of psychiatric disease.

Post synaptic 5-HT1A heteroreceptors are expressed on many types of non-serotonergic neurons with a high distribution in area's important to memory and cognition, activation has many (indirect) effects on different signaling cascades. It was shown that specifically targeting this sub-population of receptors is potentially more effective than using a non-biased 5-HT1AR agonist in the treatment of pattern separation, because it circumvents the impairing effects of autoreceptor stimulation. It was shown that chronic stimulation of post-synaptic 5-HT1ARs with F15599 did not lead to desensitization to the treatment. Implying that this drug potentially can be given as a long-term treatment, without a decrease in its behavioral benefits.

Furthermore, it was shown that chronic treatment with F15599 enhances hippocampal plasticity measures, illustrating that chronic post-synaptic 5-HT1AR stimulation also has structural effects which support its beneficial behavioral effects. As enhanced hippocampal plasticity has been linked strongly to enhanced memory function, the beneficial effects might not be limited to pattern separation. These findings are also of interest to the investigation of other cognitive modalities which are influenced by 5-HT1AR function and the symptomatic treatment of cognitive dysfunctions.

Therefore, the results from these studies are of interest for the pharmaceutical industry. Developing new symptomatic treatments for schizophrenia, AD or other neurological or psychiatric disorders that show impaired cognition, is commercially interesting and has great societal impact. The industry has appropriate financial resources and infrastructure organization to bring a new drug to the market. Of note, research on the biased 5-HT1AR agonists is a collaboration with Neurolixis (Dana Point, USA).

In summary, the results of the studies described in this dissertation are of importance to patients, their family and caretakers, governments (reduction in medical costs) and pharmaceutical industries.

Activities/Products & Innovation

An innovation derived from this dissertation is the development of the Object Pattern Separation task. This novel task allows for easy, effective and efficient pre-clinical screening of spatial pattern separation-enhancing drugs, which can be of interest to the pharmaceutical industry.

An actual product that can be further developed based on these studies is the use of the biased 5-HT_{1A}R agonist F15599 in the treatment of schizophrenia related cognitive impairment. This dissertation showed there is an implication that treatment with F15599 might ameliorate both pattern separation and set-shifting impairments in schizophrenia patients. Since F15599 has already been approved for safe administration in humans, a next logical step would be to administer the treatment in a clinical trial to schizophrenia patients. If this treatment would prove to be effective in humans, this would be the first treatment available specifically for cognitive impairment in schizophrenia. This would not only be of high benefit to patients suffering from the disease but would also have high financial benefits for to the company being first-to-market with this type of treatment. The pharmaceutical industry would also have the financial resources and infrastructure to set-up the required clinical studies and bring this treatment to market. Furthermore, follow-up studies with these biased compounds could lead to new indications to be patented. For a whole spectrum of psychiatric diseases that show pattern separation dysfunction or other types of cognitive dysfunction.

In conclusion, the findings that the biased agonist F15599 can enhance spatial pattern separation processes and can be given chronically has shown the potential of biased 5-HT_{1A}R agonists as a treatment for cognitive deficits in schizophrenia patients. Furthermore, the application of these biased agonists is also a promising strategy for the treatment of other cognitive impairments in psychiatric diseases and a way to enhance the knowledge of the specific mechanisms of receptor sub-populations.