Maastricht University

Finding the way forward

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Summary

One in four people will experience a stroke in their lifetime, and many survivors will face long-term cognitive impairments. Currently, effective treatments for post-stroke cognitive impairment (PSCI) are limited, underscoring a critical unmet medical need. A promising therapeutic approach under investigation is the inhibition of the enzyme phosphodiesterase type 4 (PDE4). The primary objective of this doctoral dissertation was to evaluate the effects of the PDE4 inhibitor roflumilast on PSCI, utilizing standard neuropsychological tests, questionnaires, and daily digital home-based assessments. This was studied in a randomized placebo-controlled trial (RCT) and an open-label extension (OLE) study, both part of the ROSTMEMA trial. Furthermore, previous research has demonstrated that subjective and objective memory problems often do not correlate, which can impact the ecological validity of memory assessments. As a result, the second aim of this dissertation was to investigate the relationship between subjective and objective memory complaints and to potentially close the gap between the two by employing virtual reality (VR).

Chapter 1 provides a general introduction to the topics, rationale, and relevant background literature.

Chapter 2, describes the results of our ROSTMEMA trial. This double-blind randomized placebo-controlled phase 2 trial included 100 community-dwelling participants. The study tested whether three months of oral once-daily intake of 100 µg roflumilast improves cognition in PSCI patients. Half of the participants received the roflumilast treatment, the other half received a placebo. Participants were between 41 and 70 years old, had a stroke at least one year ago, and dealt with memory complaints due to this stroke. The complaints were objectified using the 15-word Verbal Learning Task (VLT). Participants had to score below the normative score (corrected for age, gender, and education) to participate. The primary outcome was the VLT delayed recall score. Additional effects of roflumilast were measured with neuropsychological tests assessing daily memory function, attention, mental flexibility, and concentration. The results indicated a larger response in the roflumilast group for the memory tests on the final endpoint with promising effect sizes. When correcting for baseline imbalances with an adjusted analysis the results after three months of

treatment were significant on the VLT and another test measuring daily memory function (Rivermead Behavioral Memory Test: RBMT). The drug proved to be safe and well-tolerable since reported adverse events were similar for the placebo and roflumilast groups. Our study was the first study to report improved memory performance in chronic stroke patients (>1 year post-stroke) following pharmacological treatment. It demonstrated that roflumilast has the potential to improve memory performance and suggest the need for a further multicenter phase III study. This could include methods to minimalize potential placebo- and practice effects, a lower dosage and longer treatment duration to further explore the potential of the drug.

Participants who were in the placebo group in the RCT, were asked to participate in the OLE study to further evaluate the effects, safety and tolerability of roflumilast. The results of this study are presented in **Chapter 3**. Forty-two participants completed the OLE study. Analysis of the results revealed a significant improvement in verbal episodic memory performance on the immediate recall of the VLT and the immediate and delayed recall of the RBMT. The results of the OLE study provided further experimental evidence that chronic roflumilast treatment significantly enhances memory performance in PSCI patients. Moreover, the study has confirmed the safety and tolerability of this drug.

During the ROSTMEMA trial, all participants completed daily digital home-based assessments. The results of these daily assessments are described in **Chapter 4**. Often studies assessing drug effects use traditional cognitive assessments, typically at fixed time points. These assessments fail to account for the impact of daily mental states, fatigue, and intraindividual variability, thereby raising concerns about their ecological validity. To overcome these concerns, we utilized a daily digital home-based assessment to examine the effects of the PDE4 inhibitor roflumilast on cognitive performance, as well as the relationship between mood, fatigue, and cognitive function in chronic stroke patients. Due to technical issues, the data of some participants could not be included in this study, thus data from 78 participants were analyzed. The primary outcomes of this study were scores on the Cogstate Brief Battery (CBB), assessing focused attention, working memory, psychomotor speed, and visual learning. For the current study, an additional test was included to assess visuospatial learning and executive functioning. Effects were estimated through mixed

regression models. Both groups demonstrated overall improvement over time, with significant treatment effects observed in psychomotor function and focused attention. The roflumilast group showed a significantly greater and faster improvement compared to the placebo group following chronic treatment. However, no significant effects were found for visual learning, working memory, or visuospatial memory. Mood and fatigue were not significantly associated with cognitive performance. The daily digital home-based assessment offered nuanced insights into cognitive changes over time. Future studies employing daily digital home-based assessment should incorporate more cognitively demanding tests to avoid floor- and ceiling effects and to better challenge participants. Additionally, future research on chronic roflumilast treatment should broaden the range of cognitive domains assessed. Beyond verbal episodic memory, attention and psychomotor function should be prioritized to further investigate the therapeutic potential of roflumilast.

As described above, previous research has demonstrated that subjective memory complaints (SMCs) and objective memory problems (OMPs) often do not correlate, which can impact the ecological validity of memory assessments. Therefore, in **Chapter 5** we investigated the relationship between subjective and objective memory complaints, to potentially close the gap between these two. We used virtual reality (VR) to create a sensory-rich environment. The impact of other common stroke symptoms, namely sensory hypersensitivity (SHS) and fatigue, was considered. PSCI patients were compared with healthy controls. The same inclusion criteria as for the ROSTMEMA trial were maintained for the stroke survivors with the exception that they scored above the normative score on the VLT (and were therefore excluded from participating in the RCT). Memory performance was evaluated using the VLT. Additionally, we measured subjective memory complaints (SMCs) with the Everyday Memory Questionnaire, and assessed fatigue and sensory hypersensitivity (SHS) over the past month using a fatigue questionnaire and the Multi-Modal Evaluation of Sensory Sensitivity (MESSY). A total of 31 chronic stroke patients and 32 healthy controls participated. The findings revealed that memory performance declined in a sensory-rich environment compared to a neutral one, although this decline did not significantly differ between the groups. Notably, fatigue and SHS were linked to the level of SMCs in stroke patients, but no such relationship was found in healthy controls. Furthermore, in stroke patients

there was a significant negative correlation between SMCs and memory performance in a sensory-rich environment, but not in a neutral one. In conclusion, our study suggests that in stroke patients, fatigue and SHS are associated with SMCs, and that using a sensory-rich VR environment could provide a more ecologically valid means of assessing SMCs. However, caution is advised in interpreting these findings due to the lack of gender- and age-matched controls and potential selection bias.

Chapter 6 unifies the preceding chapters through a discussion of the main findings alongside methodological strengths and considerations, leading to potential clinical implications and future directions. The following conclusions could be drawn from the research presented in this dissertation. The proof-of-concept phase II trial demonstrates that three months of roflumilast treatment (100 µg q.d.) has the potential to improve memory performance in PSCI patients. Additionally, digital home-based daily assessments suggested possible benefits of roflumilast for psychomotor function and focused attention. No significant safety or tolerability concerns were reported. Roflumilast may be a promising treatment option for PSCI. These findings support the need for a phase III trial, incorporating long-term follow-up, measures to control for possible placebo- and practice effects, an extended treatment duration, and an evaluation of effects of lower dosages. Moreover, in both clinical practice and research, greater emphasis should be placed on connecting objective cognitive deficits to the real-life challenges patients face. More ecologically valid methods to quantify these subjective complaints could include high-frequency testing and sensory-rich virtual reality (VR) environments. Such methods provide a more immersive and realistic way of assessing cognitive function with neuropsychological tests.