KNOWLEDGE VALORIZATION

The aim of this thesis was to examine the association of biological and psychosocial risk factors on the development and course of post-stroke depression (PSD) and post-stroke apathy (PSA), and whether differences could be found between the associations with these two syndromes. This valorization paragraph describes how the results of this thesis are of societal relevance and economic application.

Mrs. K is a 69-year-old married woman who suffered from a stroke in her right hemisphere. Shortly after the stroke, her clinical symptoms were nausea and vomiting, sensations in the left corner of her mouth and in the fingers of her left hand. These symptoms were present for two weeks and then disappeared slowly. After ten weeks Mrs. K has an appointment with her neurologist. She tells him that she feels fine, and experiences no residual complaints anymore from the stroke. When the neurologist asks her husband how he experiences the situation, he answers: “My wife changed a lot since she suffered from the stroke. Since the stroke she is sleeping a lot during the day. She does not perform in any household chores and is also relatively inactive in comparison to her activities before the stroke, when she used to swim very often, which she no longer cares to do. Also, her social life is very limited at the moment. She is not interested in meeting with other people, except for our sons.”

This case describes an example of a stroke patient suffering from apathy. However, she does not report this as a complaint to her neurologist, though her husband is worried about her passive behavior and lack of interest. Will the neurologist recognize the behavior of this patient as apathy?

SOCIETAL RELEVANCE

Stroke is a leading cause of disability in the world. In the Netherlands, each year around 41,000 individuals suffer from a stroke, and currently more than 240,000 individuals are estimated to live with the consequences of stroke every day. As a result of the aging population, the prevalence of stroke will increase steadily, from 186,000 in 2011 to 343,000 in 2040. Currently, the costs associated with care for stroke patients are approximately 2.5% of the total health care costs. As the life expectancy after stroke has been increasing due to better acute stroke treatment, the number of stroke survivors dealing with the consequences of stroke is increasing as well.

The residual consequences of stroke vary between patients, but can include physical impairments (i.e. paresis), speech difficulties, visual impairment, cognitive impairment, changes in personality, and the occurrence of neuropsychiatric
symptoms. These factors all have a huge impact on stroke survivors and their caregivers, family, and other close relatives. Neuropsychiatric symptoms, like depression and apathy, occur in around a third of stroke survivors and have a negative influence on functional outcome and quality of life. As health-care professionals often do not recognize these neuropsychiatric consequences timely, several stroke survivors have unmet treatment needs.

As loss of motivation plays an important role in both apathy and depression, there is large overlap in clinical symptomatology and several studies found also overlap in risk factors between these syndromes. Despite this overlap, there is also some evidence suggesting that different risk factors may be involved in the development of PSD and PSA. However, risk factors associated with PSA are studied less frequently compared with PSD and only few longitudinal studies are available. Also, studies examining and comparing risk factors involved in the development of both PSD and PSA are scarce. Therefore, it is currently poorly understood if and how both biological and psychosocial factors have a differential influence on the development and course of PSD and PSA over time. A better understanding of the role of these risk factors is important, as for developing treatment strategies for PSD and PSA, a better understanding of the underlying pathophysiological mechanisms is required. Also, a better understanding of the etiological factors involved in these syndromes may result in better recognition, distinction, and earlier detection of PSD and PSA. Eventually, this could have a positive effect on quality of life and clinical outcome of stroke survivors, as this knowledge may help improving treatment possibilities. By providing patient-tailored care options for patients at risk for developing PSD and PSA, the prevalence of PSD and PSA will hopefully reduce, which will eventually also lower the health care costs and societal burden associated with it.

**TARGET AUDIENCE**

The findings presented in this thesis are relevant for several target groups, including stroke survivors and their relatives, health care professionals, and researchers.

The results are relevant for stroke survivors and their relatives, as the studies presented in this thesis provide more information about risk factors that are involved in the development of PSD and PSA, and also how these influence the course of PSD and PSA over time. A better explanation and psycho-education with respect to the risk of developing PSD and PSA to stroke survivors and their relatives is important, as currently a lot of them are not aware that these syndromes can develop as a consequence of their brain damage, also at a later stage during the chronic stroke phase. The current development of specialized stroke after-care
clinics, which have specific expertise regarding neuropsychiatric symptoms after stroke, like PSD and PSA, are therefore a good and promising development, as these clinics can provide this psycho-education. Therefore, we deem the findings of this thesis of particular relevance to these specialized stroke after-care clinics.

All health care professionals (neurologists, rehabilitation physicians, psychiatrists, general practitioners, and (neuro)psychologists) treating stroke survivors are important stakeholders as well, as they are the ones who need to inform stroke survivors about the risk of developing symptoms of depression and apathy after stroke, and which risk factors are involved in the development of these syndromes. The results of this thesis have shed more light on the risk factors that play an important role in the development and course of apathy and depression and shows that the risk factors being involved are different to some extent for PSD and PSA. More knowledge about the etiology of PSD and PSA will help to recognize these conditions by health care professionals and identify patients (timely) who are at risk to develop PSD or PSA. Better diagnostic distinction between PSD and PSA is important, as these conditions seem to benefit from different treatment strategies.

The findings resulting from this thesis are also relevant for researchers in the stroke field, as they shed more light on the biological and psychosocial factors that are involved in the etiology of PSD and PSA, which improves the understanding of the pathophysiology of these syndromes. This information is particularly important for researchers who examine possible pharmacological and psychotherapeutical treatment strategies for PSD and PSA, as the results indicate that PSA can occur as an independent syndrome, independent of PSD, and has its own associated risk factors that influence the development and course of this syndrome. In addition, the results may also be of use for researchers who work with other patient populations in which both apathy and depression are frequent (like Parkinson’s disease, Alzheimer’s disease and other types of dementia, or traumatic brain injury), as some of the associations found in this thesis might also hold for these other disease populations.

INNOVATION AND PRODUCTS

The CASPER study measured a range of 3-Tesla structural brain MRI markers, both volumetric and visual. The semi-automatic volumetric assessment of white matter hyperintensities and manual segmentation of stroke lesion tissue provided a precise measure, which made it possible to study subtle differences and also to study the role of both lesion-related markers (location, volume, laterality) and generalized background brain pathology (total cerebral small vessel disease
Addendum Knowledge valorization

burden, global brain atrophy, white matter hyperintensity volume, number of old infarcts or lacunes, and number of cerebral microbleeds). This made it possible to compare the influence of certain MRI markers on the development of PSD and PSA. The main product of this thesis is the implications that the findings have for the understanding of the pathophysiology of PSD and PSA. The findings provide evidence that both biological and psychosocial factors are involved in the development of PSD and PSA. Also, differences in associated risk factors between PSD and PSA suggest that PSA can also occur as an independent syndrome, in absence of depressive symptoms. These findings are important for researchers developing treatment strategies for PSD and PSA, as a better understanding of the complex multifactorial origin of these conditions is needed for successful treatment.

Participants of the study were updated about the study progress through newsletters. Also, the results in this thesis were presented at several international and national congresses.

IMPLEMENTATION

The clinical importance of this thesis involves the differentiation between risk factors being involved in the development of PSD and PSA, which were of both biological and psychosocial origin. The knowledge derived from the studies presented in this thesis will be the base for research into the role of biological and psychosocial predictors of PSD, PSA, and VCI. The results presented in this thesis show that it is important to consider the role of both biological and psychosocial factors, and studying their inter-relationships and interactions is another future goal, as this is needed to unravel the complex multifactorial origin of PSD and PSA. Also other biomarker data were collected for CASPER (inflammatory markers and epigenetics), which were not part of the present thesis but will be used for future studies, as these are also likely to be important factors influencing the development and course of PSD and PSA. In addition, the CASPER study joined the STROKOG consortium (https://cheba.unsw.edu.au/group/strokog), which has built a database with more than 12,000 stroke patients. This large dataset yields new opportunities for studying subtle changes, which require large datasets and will likely yield important results concerning factors associated with PSD and PSA. Also, participants of CASPER were approached for participation in our long-term follow-up study, for which we are currently collecting data. For this study, we are collecting data at 3 years post-stroke. These long-term data can provide interesting findings with respect to PSD and PSA as potential risk factors for mortality and the development of vascular dementia.
HOW COULD MRS. K BENEFIT FROM THE RESULTS OF THIS THESIS?

The neurologist of Mrs. K has read some articles on apathy after stroke and realizes that this is a frequent complaint after stroke, which is often confused with depression. He administers a semi-structured questionnaire based on DSM-5 criteria to find out if Mrs. K has depressed feelings, but that was not the case. The neurologist explains to Mrs. K and her husband that apathy is a frequent complaint after stroke and that it is sometimes part of a depressive disorder, but not necessarily. He tells them that there are currently no pharmacological treatment options for apathy available. He advises the husband to keep motivating Mrs. K to stay active and to help her setting goals, because that is difficult for her. The neurologist also decides to refer them to a neuropsychologist, who can help the couple dealing with this new situation.