Objectives

Uremia and associated end-stage renal disease (ESRD) is a major cause of encephalopathy. As a consequence of the extremely low glomerular filtration rate that leads to the accumulation of uremic toxins which impair brain functioning, patients with ESRD have been shown to suffer with cognitive dysfunctions, psychomotor slowing and attention/executive dysfunction in particular. Further, since cardiovascular problems (e.g. hypertension, coronary artery disease) as well as diabetes are frequently associated with ESRD, it has been posited that cognitive dysfunction in individuals with ESRD may be also linked to these comorbid conditions as well as their treatment (e.g. coronary artery bypass grafting). Although adequate dialysis reduces some of the cognitive problems associated with kidney disease, the hemodialysis itself may induce dialysis disequilibrium, cerebral ischemia or cerebral edema, producing new or amplifying already existing cognitive deficits. Importantly, following successful kidney transplantation, there is a reduction in these cognitive problems associated with ESRD and dialysis.

Similarly to these selective cognitive problems, there is evidence that some brain regions / networks are more susceptible to the effects of ESRD and dialysis than others. Based on previous research findings (including the results of our studies), it could be posited that the ESRD-related toxicity and dialysis may predominantly affect the right rather than the left hemisphere, particularly the right frontal lobe.

The right hemisphere is dominant for mediating spatial allocation of attention, hence, one of the most frequently seen behavioral disorders following right hemisphere damage is left hemispatial neglect. Although previous research suggests that the main cognitive problem in individuals with ESRD receiving dialysis is an impaired ability to sustain attention resulting from a disturbance of a phasic alertness (energizing) that affects spatial allocation of attention, spatial allocation of attention in patients with ESRD has not yet been studied.

Aim of the project

The main goal of this project is to learn if ESRD-related toxicity, dialysis as well as other disease and/or treatment related factors (e.g., cardiovascular problems) may alter spatial allocation of attention, and whether this potentially altered spatial allocation of attention is related to the reduction of cerebral arousal, as measured by electroencephalography. This study also aims at delineating a meta-model of cognitive aging that would potentially help to explain age-associated cognitive changes as well as contribute to better understanding of many activities of daily living in the elderly. Based on the assumption that processes seen in individuals with ESRD represent the accelerated processes associated with cognitive aging, this project will verify the basic elements of the proposed meta-model of cognitive aging.

Specific aims and hypothesis:

Firstly, we would like to learn if patients with ESRD (yet not receiving dialysis as well as those on dialysis), when compared to healthy controls, deviate their attempted line bisections more to the right, as seen following right hemisphere damage. Secondly, this study will test the hypothesis that, as a result of decreased hemispheric arousal, patients with ESRD present with alternations in spatial allocation of attention also in vertical plane. Thirdly, we will investigate if, due to a more pronounced dysfunction of the right hemisphere, patients with ESRD (particularly those receiving dialysis) will be more susceptible to visually presented local distractions.

Additionally, this project will not only examine physiological measures of arousal by measuring specific EEG frequency bands, but it will also help to learn if individuals with ESRD and/or dialysis have inter- or intrahemispheric as well as overall frontal-parietal asymmetries in specific frequency bands. Moreover, by measuring event-related potentials (ERP), this study will test if there are any differences in early visual ERP components between patients with ESRD and healthy controls.

The beneficial effect of kidney transplantation on some cognitive functions as well as normalization of ERPs has been reported, also by our research group. Hence, another specific goal of this project is to learn whether possible abnormalities in spatial allocation of attention in subjects with ESRD will diminish following successful kidney transplantation.

Both ESRD and aging seem to primarily affect the right hemisphere and impair functions that rely on this hemisphere. With aging there is frequently a reduced glomerular filtration rate, cardiovascular impairments as well as an increase in the prevalence of diabetes, which is frequently associated with chronic kidney disease. All these factors have been reported to contribute to the age-associated cognitive decline. Furthermore, both spatial allocation of attention, cued attention, and the alpha power lateralization during visual spatial attention change with aging. For example, older individuals show longer engagement and delayed disengagement from cues compared to younger subjects, and these alterations can be associated with changes in the early ERP components. Hence, we would like to test whether ESRD accompanied by dialysis might serve as a model for accelerated cognitive aging.

Methods

Three groups of right-handed patients with ESRD aged 21-60: 1) patients with ESRD yet not receiving dialysis, 2), patients receiving hemodialysis, 3) patients who received kidney transplant, as well as two control groups: 1) healthy demographically matched controls, 2) subjects without kidney problems aged 61-80, will be the participants of this study. In all participants relevant clinico-biochemical parameters will be measured.

General neuropsychological testing: In order to control for specific cognitive functions (general cognitive status, psychomotor and executive function) as well as depression and anxiety, all participants will undergo a brief neuropsychological assessment, in addition to the experimental tasks.

Experimental procedure: Three behavioral experiments (using line bisection tasks) as well as one additional psychophysiological experiment (using Posner paradigm), aiming at analyzing the early visual event-related potentials, have been planned.

Additionally, in all participants (during resting state) an EEG signal will be recorded, and specific EEG frequency bands will be analyzed. Also, depending on hypotheses (e.g., inter- and intrahemispheric activity differences in EEG bands), asymmetry indices will be calculated.
Statistical analyses: Depending on hypotheses, series of specific analyses have been planned, including analyses of variance with repeated measures as well as structural modeling.

Outcomes of the project
This interdisciplinary project will allow for better understanding of how ESRD-related pathological processes (including the effect of the specific treatment of this chronic condition) may impact cortical arousal and spatial allocation of attention. Moreover, this project will help to learn about some mechanisms underlying age-related decline in attention. If our hypotheses were proven, the results of this study would enable to delineate a meta-model of cognitive aging. Such model could then likely be applied to better understand cognitive functioning and the performance of the activities of daily living as well as instrumental activities of elderly individuals as well as individuals with chronic somatic conditions other than ESRD. Thus, our findings may not only influence contemporary clinical neuropsychology and neuroscience but also contribute to developmental psychology as well as health psychology.