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Slowing with end-stage renal disease: Attentive but unprepared to act

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ABSTRACT

Dialyzed patients show longer response latencies to stimuli than healthy controls. This study was designed to learn if this abnormal latency may be related to an impairment in the networks that mediate the allocation of sensory-attention (inducing a delay in stimulus recognition-awareness) and/or an impairment of intentional motor preparation (inducing a delay in action-initiation). Dialyzed patients with end-stage renal disease and matched healthy controls were assessed using reaction time tasks from the ROtman-Baycrest Battery to Investigate Attention (ROBBIA) and event-related potentials (ERPs) to help elucidate the possible attentional and/or intentional brain mechanisms that may account for this slowing. The following ERP components were analyzed for single attentional and intentional processes: response preparation (Contingent Negative Variation); perceptual preparation (P1); selective attention and monitoring (P300/Late Positive Potential). Patients (vs. controls) had a decreased ability to sustain response preparation under the condition of a long (3 s) but not a short (1 s) preparation period. This action-intentional deficit was, however, not accompanied by impaired perceptual preparation and monitoring. Future research may investigate whether deficits observed in dialyzed patients can be reduced with treatments such as kidney transplantation.

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1. Introduction

Frontal lobe networks are critical for organizing and supervising a variety of cognitive, perceptual and behavioral functions (Brunner et al., 2015; Stuss et al., 1995; Stuss et al., 2002). Whereas injury to orbitofrontal cortex may result in disinhibition of emotional responses (e.g. Rascovsky et al., 2011), damage or dysfunction of the left dorsolateral cortex may cause a selective disorder of task setting, and damage to the right dorsolateral cortex may impair monitoring (see Stuss and Alexander, 2007). Further, it has been demonstrated that an injury or dysfunction of medial and superior frontal cortex as well as the supplementary motor area may result in impairments of action-initiation including failures to act (akinesia) or a delay in initiating an action (hypokinesia) (Heilman et al., 2012; Heiferman et al., 2014). An additional action-intentional deficit observed in patients with frontal lobe dysfunctions, especially of the right hemisphere, is motor impersistence, the inability to maintain an action or series of actions over a period of time (Fisher, 1956; Kertesz et al., 1985). The process of response initiation and maintenance has also been called 'energization' (Stuss and Alexander, 2007).

There is growing evidence that frontal networks (e.g. fronto-basal ganglia-thalamic and fronto-temporal networks) that mediate executive functions are particularly sensitive to metabolic and endocrine disorders such as hepatic encephalopathy (Meyer et al., 2006) and hypothyroidism (Samuels, 2014). Frontal dysfunction accompanied by executive and attentional problems, can also occur with the accumulation of uremic toxins related to the extremely low glomerular filtration in patients with chronic kidney disease (CKD), and especially those with end-stage renal disease (ESDR) requiring dialysis (see Pereira et al., 2007). For example, recent neuroimaging data obtained from patients with minimal nephrotic encephalopathy revealed reduced functional connectivity in the medial prefrontal, right superior frontal and anterior cingulate cortices (Chen et al., 2015; Zheng et al., 2014). Although some patients with ESRD may show a variety of different neuropsychological deficits (e.g. Kurella-Tamura et al., 2009; Murray, 2008), most well-dialyzed individuals present mainly with psychomotor slowing as well as attentional and executive dysfunction (Dixit et al., 2013; Harciarek et al., 2012; Post et al., 2014). In a recent study using the ROtman-Baycrest Battery to Investigate Attention (ROBBIA), it has been demonstrated that dialyzed patients do not suffer from a dysfunction of the entire frontal-executive system encompassing the processes of energization,

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monitoring, and task setting (see Stuss and Alexander, 2007) but rather develop a selective attentional-intentional disorder characterized by difficulties in response initiation and maintenance-persistence (Harciarek et al., in press). Although the exact mechanisms of these selective disorders have not been fully elucidated, they may result from an impairment of the preparatory intentional activation of the motor system as well as the maintenance of this activation over a period of time.

Previous studies have shown that event-related potentials (ERPs) may provide particularly useful indicators of the three processes included in the anterior (frontal-subcortical) attentional-intentional system (i.e. energization, task setting, and monitoring, Stuss and Alexander, 2007). For example, electroencephalographic (EEG) derived contingent negative variation (CNV) has been shown to be related to the neuronal excitability that occurs with motor preparation prior to the initiation of an action (e.g. Damen and Brunia, 1994; Gomez et al., 2003; Rektor et al., 2004; Ulrich et al., 1998;). Additionally, source localization studies revealed that the CNV reflects the engagement of premotor and motor areas (Nagai et al., 2004; Rektor, 2002) and a fronto-parietal network (Gomez et al., 2003). Preparation can also be sensory-attentional and the P1 component of ERPs has been shown to be an electrophysiological indicator of the allocation of visuospatial attention, with an increase of P1 amplitude representing enhanced processing in the extrastriate visual cortex (Mangun et al., 1993). For example, Van Voorhis and Hillyard (1977) requested that healthy participants attend to a specific location and presented visual stimuli in that location as well as outside that location. They found that the P1 had a greater positive amplitude when the target was presented in the attended location than when it was presented outside the attended location. The P300 and late positive potential (LPP) are often used to investigate attention, with higher amplitudes indicating greater selective attention (Michalowski et al., 2009, in press; Polich, 2007; Schupp et al., 2000). In addition, using a dual-task paradigm, Donchin and collaborators (1986) have demonstrated that the P300 amplitudes are more pronounced when higher perceptual/cognitive resources need to be engaged to maintain an appropriate performance level. Moreover, P300 and LPP amplitudes are commonly observed to be increased after infrequent and target stimuli than after frequent and non-target stimuli, but in the presence of impaired monitoring this enhancement is not observed (Dujardin et al., 1993; Verleger et al., 2005).

The analyses of EEG/ERP recordings have also been used to delineate neuronal correlates of attention/executive disorders in patients with CKD. For example, previous EEG research in this population showed a nonspecific EEG slowing, indexed by a reduced alpha and increased theta power, that may indicate problems with energizing/vigilance-arousal (Bourne et al., 1975) and lower P300 amplitudes indicating reduced monitoring ability (Weissenborn and Lockwood, 2015). However, other studies have shown that the EEG/ERP abnormalities in this population may result from uncontrolled anemia, and when this was taken into account, CKD patients showed higher alpha frequency power in the eyes-closed resting condition (Röhl et al., 2007) and similar P300 amplitudes to those of the healthy controls (Madan et al., 2007; Sagalés et al., 1993). Hence, the interpretation of many previous EEG/ERP results in patients with CKD remains unclear. Moreover, to our knowledge there has been no study designed to specifically investigate the neurophysiological basis of the attentional or intentional deficits observed in dialyzed patients with ESRD, who are particularly at risk for cerebral dysfunction that may produce new or amplify already existing cognitive deficits as well as induce a substantial and sustained decline in functional status (Kurella-Tamura et al., 2009).

While addressing the limitations of previous EEG/ERP studies in the CKD population, the goal of the present study was to investigate the attentional and intentional systems in dialyzed patients with ESRD by using ERP recordings, which could provide a more direct insight into the dynamics of the networks mediating sensory-attention and action-intention. Specifically, by measuring the EEG signal during the patients' performance on several timed reaction tasks derived from the ROBBIA, this study was designed to determine whether dialyzed patients differ from demographically matched healthy controls in respect to the specific ERP components that have been shown to be associated with the following attentional-intentional processes: motor response preparation (CNV), perceptual preparation (P1) as well as selective attention and monitoring (P300 and LPP). Considering our previous behavioral findings demonstrating that patients with ESRD who are undergoing dialysis have particular problems with initiating and maintaining an appropriate action preparation (Harciarek et al., in press), we expect that this selective deficit in dialyzed individuals would be accompanied by significantly smaller CNV and/or P1 amplitudes, and especially in those tasks that require the participant to maintain their preparatory activity for longer periods of time. Moreover, this CNV and/or P1 reduction is expected to result in longer response latencies. At the same time, shortening the gap between the warning and the imperative stimuli should help to overcome these preparatory deficits and may cancel CNV and/or P1 differences between patients and controls. However, based on previous studies (Harciarek et al., in press; Madan et al., 2007; Sagalés et al., 1993), there is no reason to expect that the action-intentional and/or sensory-attentional deficits in ESRD patients would be accompanied by impaired selective attention and monitoring abilities, as indexed by the P300 and LPP amplitudes.

2. Material and methods

2.1. Participants

Sixteen right-handed adult patients with ESRD who were being treated with dialysis and 15 right-handed demographically matched healthy control individuals participated in the present study. Patients were recruited at three dialysis stations in Gdańsk, Poland: 1) the Department of Nephrology, Transplantology, and Internal Medicine, Medical University of Gdansk, 2) NZOZ Diaverum, 3) 7th Navy Hospital. The healthy control participants, who were without history of kidney disease (GFR > 90 ml/min/1.73 m^2, as determined by blood testing conducted a day before the experiment), were recruited from a pool of Gdańsk citizens. The two groups did not differ in terms of the overall cognitive status (Mini-Mental State Examination) as well as the level of anxiety and depression (Hospital Depression and Anxiety Scale) (see Table 1). None of the participants had malignancies or clinically evident cerebrovascular disease, uncontrolled hypertension, uncontrolled diabetes, uncontrolled anemia, mental retardation, speech or learning disabilities, psychiatric disorders, used a psychoactive medication, had dementia, alcohol abuse, clinically relevant visual or hearing difficulties, or other major organ failure (e.g., liver, cardiac, pulmonary disease). Also, none of the patients was converted from peritoneal dialysis nor was transplanted, and all had received hemodialysis for a minimum of one year. Detailed clinical group characteristics are presented in Table 1.

2.2. Procedures

Each subject was evaluated at approximately the same time of the day (from 9 am till 12 pm $\pm$ 1 h). Patients were tested ~24 h before their second hemodialysis session of their weekly dialysis cycle that includes three dialysis sessions, one session every two days. Before testing, each subject was asked to provide written informed consent and underwent a neurological, cardiac and hematological evaluation. Additional blood samples were obtained from patients shortly before their second weekly dialysis session (~20–24 h after the neuropsychological testing). The study protocol was approved by the institutional ethics committee at the Institute of Psychology, University of Gdańsk.

All participants were tested in a dimly lit and sound-attenuated room at the Institute of Psychology, University of Gdańsk with the following reaction time tasks (RTT) from the ROtman-Baycrest Battery to Investigate Attention (ROBBIA): 1) Simple RTT, 2) Choice RTT, 3) Prepare RTT (Stuss et al., 2005). All these tasks required the participants

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