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Disorders of the anterior attentional-intentional system in patients with end stage renal disease: Evidence from reaction time studies

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ABSTRACT

Objective: Dialyzed patients with end-stage renal disease (ESRD) have been reported to have several neurobehavioral impairments that are often accompanied by structural and functional abnormalities of frontal-subcortical networks. Whereas the anterior attentional-intentional systems responsible for the allocation of attention and preparation for action (intention) are mediated by these frontal-subcortical networks, these functions have not been specifically investigated in this population.
Method: Twenty-three non-demented dialyzed patients with ESRD were compared with 25 matched controls on the performance on four reaction time (RT) subtests from the ROtman-Baycrest Battery to Investigate Attention (ROBBIA). These included measures of Simple, Choice, and Prepare RTs as well as a Concentrate task.
Results: In the Prepare RT task with a warning signal presented 1 s before the onset of imperative stimulus, the patients' performance was not different than the controls; however, dialyzed patients became significantly slower than controls in the Prepare 3 s warning condition as well as on all other RT measures. Nonetheless, both groups exhibited a gradual decrease in RT with increasing interstimulus intervals, with no group difference in the number and type of errors.
Conclusions: These results suggests, that while with external preparatory stimuli, the dialyzed ESRD patients may be able to acutely increase their arousal and enhance their allocation of selective attention or action-preparation, they appear not to be able to maintain this enhanced preparatory status. Whereas these results help to elucidate a potential source of disability in this patient population, future studies will need to examine if this deficit is primarily attentional, intentional or both (arousal), as well as explore possible treatments.

1. Introduction

Patients with chronic kidney disease (CKD), particularly those with end-stage renal disease (ESRD) requiring dialysis or kidney transplant, have been repeatedly reported to suffer with cognitive dysfunctions (e.g. Dixit et al., 2013; Drew et al., 2015; Harciarek et al., 2012; Kurella, Chertow, Luan, & Yaffe, 2004; Thornton, Shapiro, Deria, Gelb, & Hill, 2007 see also Etgen, Chonchol, Förstl, & Sander, 2012; Pereira, Weiner, Scott, & Sarnak, 2005), often accompanied by functional and structural brain abnormalities (see Chen, Zhang, & Lu, 2015). The mechanisms accounting for these neurobehavioral disorders have not been fully elucidated; however, cognitive problems in patients with ESRD seem to primarily result from the extremely low glomerular filtration rate that leads to the accumulation of uremic toxins, which impair brain functioning. Further, since cardiovascular disorders (hypertension, coronary artery disease) as well as diabetes are frequently associated with ESRD, it has been posited that cognitive dysfunction in this population may be also linked to these comorbid conditions (Murray, 2008; Pereira et al., 2005) as well as their treatment (e.g., coronary artery bypass grafting) (Harciarek et al., 2010). Although adequate dialysis (Schneider et al., 2015; Umans & Pliskin, 1998) and a successful kidney transplant (Griva et al., 2006; Harciarek, Biedunkiewicz, Lichodziejewska-Niemierko, Debska-Slizien, & Rutkowski, 2011) reduce some of these cognitive disorders, hemodialysis may induce a degree of dialysis

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disequilibrium, cerebral ischemia or cerebral edema (e.g. Tuchman, Khademian, & Mistry, 2013; Walters, Fox, Crum, Taube, & Thomas, 2001), and these dialysis treatment side effects may produce additional cognitive deficits or amplify already existing ones (Kurella-Tamura et al., 2009). Thus, dialysis may further compromise these patients' quality of life and increase the risk of both dementia and death (e.g. Drew et al., 2015).

Although some individuals with ESRD, especially older patients with cardiovascular disease, may present with relatively global neuropsychological dysfunctions (e.g. Kurella-Tamura et al., 2009; Murray, 2008), most dialyzed individuals predominantly have impairments of psychomotor speed as well as attention and executive functions (Dixit et al., 2013; Harciarek et al., 2012; Post et al., 2014). Thus, the observations that these cognitive disorders in dialyzed patients with ESRD appear to be relatively selective, mainly within psychomotor, attentional and executive domains, makes the cognitive profile of dialyzed patients somewhat similar to that of individuals with diseases where there is injury to and/or dysfunction of the frontal-subcortical networks (Pereira et al., 2007). This relationship suggests that these brain regions are particularly susceptible to the effects of ESRD and dialysis. Neuroimaging research has provided support for such postulate. For example, Zheng et al. (2014) reported that patients with ESRD with minimal nephrotic encephalopathy had alterations of functional connectivity bilaterally in the middle prefrontal cortex as well as in the right superior frontal gyrus and the anterior cingulate cortex. Anatomic changes have also been reported in dialyzed individuals, predominantly within the medial prefrontal regions (see Chen et al., 2015).

Based on the prefrontal lobe's multiple reciprocal connections with other brain areas (see Weinberger, 1993), the frontal lobes are critical in organizing and supervising cognition and behavior, the central executive. Further, there is now strong and converging evidence indicating that different region of the frontal cortex support different supervisory processes (Brunner et al., 2015; Stuss, Shallice, Alexander, & Picton, 1995; Stuss, Binns, Murphy, & Alexander, 2002; Stuss et al., 2005; Vallesi, 2012; Vallesi, Shallice, & Walsh, 2007). For example, Poppen (1939) and Dandy (1946) (see Freemon, 1971) described patients who during their surgery had their anterior cerebral arteries "sacrificed" on both sides of their brain. These arteries supply much of the medial and superior frontal lobes including the supplementary motor area and the cingulate gyrus. As a result of this surgery with damage to these areas, these patients became akinetic and mute. Also, Heiferman et al. (2014) provided evidence that damage to supplementary motor areas could induce this akinetic disorder. Patients with mild forms of akinesia may be able to initiate movements, but may be slower to initiate responses than normal people; a disorder called hypokinesia (Heilman, Watson, & Valenstein, 2012). Further, Fisher (1956) described a disorder where patients were impaired at maintaining an action (e.g., eye-closure together with tongue-protrusion) over a period of time, and called this disorder "motor impersistence." Subsequently, Kertesz, Nicholson, Cancelliere, Kassa, and Black (1985) reported that motor impersistence appears to be most often associated with a right frontal lesion. These disorders of action-initiation (akinesia and hypokinesia) as well as the failure to persist at an action (impersistence) have been called "action-intention disorders" (Heilman et al., 2012). Stuss and Alexander (2007) have used the term "energization" to denote the process of initiation and sustaining of any response.

In a series of studies studying patients with focal lesions using ROBBIA (ROtman-Baycrast Battery to Investigate Attention), Stuss et al. (2005) reported that, when compared to other frontal and non-frontal regions, damage to the superior medial parts of the frontal lobe (particularly in the right hemisphere) appeared to produce a selective deficit in "energization" (see also Stuss & Alexander, 2007). In the same study, they also demonstrated that left dorsolateral frontal lesions typically resulted in a relatively selective impairment of setting a stimulus-response association (task setting), whereas lesions to right dorsolateral frontal areas tended to selectively impair the function of monitoring. The dominant role of the right lateral frontal lobe in monitoring has also been confirmed in a more recent transcranial magnetic stimulation study by Vallesi et al. (2007). As a result, Stuss and Alexander (2007) proposed that these three processes (i.e. energization, task setting, and monitoring), allowing for the functional fractionation of the frontal lobes, constitute the anterior attentional system.

Despite the increasing number of research reports supporting the existence of a relationship between renal and cerebral functions (see Murray, 2009), and the fact that patients with ESRD receiving hemodialysis often have neurobehavioral disorders (e.g. Pereira et al., 2005), the nature of cognitive impairment in dialyzed patients has not been completely identified. Furthermore, although dialyzed individuals with ESRD frequently present with medial fronto-subcortical abnormalities (Chen et al., 2015), a reduction of cortical arousal (Röhl, Harms, & Pommer, 2007), psychomotor slowing, as well as attentional and executive dysfunction (e.g. Harciarek et al., 2011; Pereira et al., 2007), the specific attentional as well as action-intentional processes of the anterior attentional-intentional system in this population have never been investigated. Previous studies (e.g., Dixit et al., 2013) as well as our clinical observations indicate that, although dialyzed patients often need more time to complete a cognitive task, they do not typically commit errors on measures like the Trail Making Test or Digit Symbol Test. Thus, it could be posited that ESRD and/or chronic dialysis may primarily affect the process of energization-intention, and not adversely influence monitoring as well as not impairing the ability to learn how to perform the task, or what Stuss and Alexander (2007) called "task setting". Hence, this study was designed to investigate the functioning of the anterior 'supervisory' attentional-intentional system of dialyzed patients with ESRD.

2. Methods

2.1. Participants

The participants enrolled in this study were right-handed, native Polish speakers. Detailed demographic and clinical group characteristics are presented in Table 1.

The sample size for this study was determined by power analysis conducted using G*Power software. For split-plot ANOVA $2\times(3)$ and a desired effect size $\eta^2 \sim 0.15$, the a priori test power analysis revealed that, with $\alpha = 0.05$ and the test power $1 - \beta = 0.90$, the expected sample size of 24 would enable the detection of a meaningful interaction effect, whereas a sample of 12 observations would allow the detection of a meaningful within-subject effect.

2.1.1. Individuals with ESRD receiving dialysis

Twenty-four patients with ESRD who agreed to participate in this study were randomly recruited from a total of 187 individuals receiving dialysis at three local 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. However, 1 person was excluded from the analyses since she received an emergency phone call from her husband, and she had to immediately return home without completing her testing. Thus, 23 dialyzed patients between 21 and 65 years of age, who had no malignancies or clinically evident cerebrovascular disease (e.g., stroke) as reflected by their history, had no uncontrolled hypertension, uncontrolled diabetes, anemia, mental