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Latent learning in End Stage Renal Disease (ESRD)

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HIGHLIGHTS

- Neural sites underlying impairments in End Stage Renal Disease are unclear.
- Patients performed differently to controls on a latent learning task.
- Impairment is likely to be predominantly cortical in nature.
- Pattern of results implicate the involvement of the temporal lobe.

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ABSTRACT

Cognitive functions such as attention and memory are known to be impaired in End Stage Renal Disease (ESRD), but the sites of the neural changes underlying these impairments are uncertain. Patients and controls took part in a latent learning task, which had previously shown a dissociation between patients with Parkinson's disease and those with medial temporal damage. ESRD patients (n = 24) and age and education-matched controls (n = 24) were randomly assigned to either an exposed or unexposed condition. In Phase 1 of the task, participants learned that a cue (word) on the back of a schematic head predicted that the subsequently seen face would be smiling. For the exposed (but not unexposed) condition, an additional (irrelevant) colour cue was shown during presentation. In Phase 2, a different association, between colour and facial expression, was learned. Instructions were the same for each phase: participants had to predict whether the subsequently viewed face was going to be happy or sad. No difference in error rate between the groups was found in Phase 1, suggesting that patients and controls learned at a similar rate. However, in Phase 2, a significant interaction was found between group and condition, with exposed controls performing significantly worse than unexposed (therefore demonstrating learned irrelevance). In contrast, exposed patients made a similar number of errors to unexposed in Phase 2. The pattern of results in ESRD was different from that previously found in Parkinson's disease, suggesting a different neural origin.

1. Introduction

End Stage Renal Disease (ESRD) occurs when the kidneys (responsible for controlling the water and ionic balance of the body) are functioning at approximately less than 15% of their normal level. UK estimates suggest that approximately 55,000 patients are currently receiving treatment for ESRD (UK Renal Registry 14th Annual Report, [26]). In addition to the physiological problems associated with the disease, cognition is also known to be impaired in these individuals [13]. Although the exact pathophysiology of the deficit is not yet fully understood, a number of functions have been found to be impaired. Elias et al. [8] demonstrated that patients with a lower Glomerular Filtration Rate (GFR) function (standardised measure of kidney functioning) were poorer on tests of visual–spatial memory, working memory, concentration and attention. Lux et al. [17] suggested that language areas, also located in the temporal cortex, responsible for word fluency and verbal comprehension, may also be impaired in ESRD patients. Other cognitive processes found to be worse in ESRD are planning [20], attention and task-switching [11], and inhibition [29], all usually classified as executive functions and thought to be modulated by the frontal lobes [25,27]. However, more recently, there have been opposing views in the literature, suggesting that other areas, both cortical and subcortical, may be contributing to such executive tasks in ESRD [1,19]. Duke and Kaszniak [5] suggested that poorer executive functioning cannot be labelled as a solely "frontal lobe deficit": projections from frontal lobe areas to temporal, parietal and even subcortical areas may be having a modulatory effect during executive functioning tasks. Thus, at present, there is disagreement about the origin of the cognitive dysfunction demonstrated in ESRD.

At present, evidence on the neural changes underlying impairments in ESRD is limited. At this stage, it seems appropriate to initially examine broader distinctions between brain regions, with the expectation that

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this would allow more targeted investigations in the future. A key distinction often made in relation to other neurological disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD), is that between cortical and subcortical structures. Although the majority of the behavioural data in ESRD suggests a cortical impairment [16,17,24], there have also been proposals that the pattern of the impairment matches that of a subcortical deficit [12,23]. We attempted to distinguish between these possibilities with a dissociation paradigm developed by Myers et al. [21]. Elucidating the relative contributions of different brain regions to the impairments may allow firmer comparisons between ESRD and other neurological disorders.

Myers et al. [21] showed a dissociation between patients with medial temporal (cortical) and those with basal ganglia (subcortical) damage using a latent learning task. This task was split into two phases. In the first phase, two groups of participants learn to associate one stimulus with another, with one ('exposed') group being exposed to an additional uncorrelated cue. In the second phase, participants learn a new association between stimuli, in which the previously uncorrelated cue (observed by the 'exposed' group) now becomes relevant. Healthy controls exposed to such irrelevant cues in Phase 1 were slower to learn subsequent associations in Phase 2, in which the cue had become relevant, than were controls that had no prior exposure (an effect labelled 'learned irrelevance'). However, patients with medial temporal (MT) damage did not show any effect of exposure in Phase 1: both exposed and non-exposed groups learnt at the same rate. In contrast, patients with basal ganglia damage (PD patients) showed the opposite effect to the controls: patients who were exposed in Phase 1 learnt at a faster rate in Phase 2 than those who were not exposed to the initially irrelevant stimuli. One should be cautious in ascribing the differences between the groups to particular brain areas, since it is difficult to rule out the possibility of more widespread abnormality in the patient groups (an issue which we take up in the Discussion). Nevertheless, at first sight, these three distinct patterns of response suggest dissociable contributions from the medial temporal lobe and basal ganglia to learning and memory. Although the exact mechanisms underlying the different effects are not yet fully understood, they suggest that the task may be useful in identifying cortical and subcortical contributions to impairments in cognitive performance.

We measured the performance of a group of ESRD patients and a matched healthy control group on the test of latent learning. Although the experimental design was the same as in the Myers et al. [21] study, the stimuli were different, allowing easier production and instruction to participants. We expected to replicate the finding of Myers et al. that healthy controls learn more slowly after prior exposure to the initially uncorrelated stimulus than after no previous exposure (in other words, show 'learned irrelevance'). Because the latent learning task has been run on other patient groups, we can compare the results of ESRD patients with those from other disorders in which the sites of damage are better understood. If the changes underlying impairments in ESRD patients are indeed cortical, their latent learning should be more like that of MT than that of PD patients.

2. Material and methods

2.1. Participants

Twenty-four patients (mean age: 67.5 years, S.D.: 13.7) were recruited from the renal unit at the Royal Berkshire Hospital, Reading, UK. ESRD patients had been receiving haemodialysis (HD) treatment three times per week for 3–5 h per treatment, for >90 days prior to testing (Kt/v > 1.4). Patients were deemed eligible for the study by the treating nephrologist who informed them about the study and obtained consent. Patients were excluded if they had any prior history of ophthalmological or neurological illness. Testing was conducted in a quiet office located on the renal ward.

Twenty-four healthy control participants (mean age: 67.8 years, S.D.: 13.1) were recruited from a research panel maintained by the University of Reading. Control participants were individually matched to patients on age, sex and education level. Participants were tested in a quiet room in the School of Psychology and Clinical Language Sciences.

2.2. Apparatus & materials

Stimuli were presented on a Toshiba 17.3″ LCD screen laptop computer using custom software written in E-Prime (v2.0). The participant was seated in a comfortable chair positioned approximately 45 cm from the screen. In addition to the primary task, all participants completed the Mini Mental State Examination (MMSE), the Instrumental Activity of Daily Living scale (IADL), the National Adult Reading Test (NART), an estimator of pre-morbid IQ, and the Geriatric Depression Scale (GDS).

2.3. Stimuli

On each trial, participants were presented with a circle (representing the back of a person's head), with a speech bubble above containing a word printed in black lowercase letters (see Fig. 1.1A). The words were taken from the list of 30 monosyllabic non-words used by Myers et al. For each participant, 15 words were randomly selected and used in Phase 1, with the remaining 15 words used in Phase 2 (see Appendix A for word list). In Phase 1 the word "melk" was the signal word, *W*, that predicted a 'happy' face, whereas all the other 14 words predicted a 'sad' face. The circle could be coloured red or green, or uncoloured (white), however, in Phase 1 the colour was unrelated to the happiness of the face. In Phase 2, either red or green was selected to be colour C+

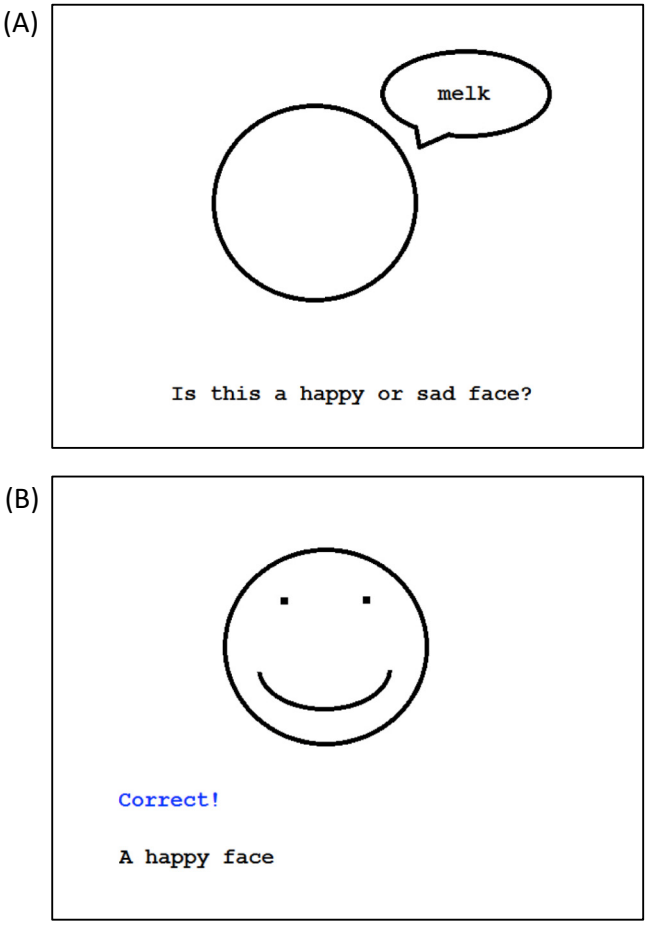

Fig. 1.1. Example of the screen appearance at: (A) the start of each trial (B) after the participant responds correctly.