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Short communication

Transcranial Doppler ultrasonography in the assessment of neurovascular coupling responses to cognitive examination in healthy controls: A feasibility study

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HIGHLIGHTS

- Classical cognitive tests do not consider the neurovascular coupling (NVC) response.
- NVC has not been previously challenged with novel paradigms from cognitive tests.
- Transcranial Doppler (middle cerebral artery) validated novel paradigm responses.
- Novel paradigms elicited similar responses to more established paradigms.
- Clinical assessment of cognitive loss could be improved with matched NVC testing.

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ABSTRACT

Background: We tested the hypothesis that paradigms from the Addenbrooke's Cognitive Examination (ACE-III), including those that had not been studied using TCD previously (novel) versus those which had been (established), would elicit changes in CBF velocity (CBFv).
New method: Healthy subjects were studied with bilateral transcranial Doppler (TCD), beat-to-beat blood pressure (Finapres), continuous electrocardiogram (ECG), and end-tidal CO_2 (nasal capnography). After a 5-min baseline recording, cognitive tests of the ACE-III were presented to subjects, covering *attention* (SUB7, subtracting 7 from 100 sequentially), *language* (REP, repeating words and phrases), *fluency* (N-P, naming words), *visuospatial* (DRAW, clock-drawing), and *memory* (MEM, recalling name and address). An event marker noted question timing.
Results: Forty bilateral data sets were obtained (13 males, 37 right-hand dominant) with a median age of 31 years (IQR 22-52). Population normalized mean peak CBFv% in the dominant and non-dominant hemispheres, respectively, were: SUB7 ($11.3 \pm 9.6\%$, $11.2 \pm 10.5\%$), N-P ($12.7 \pm 11.7\%$, $11.5 \pm 12.0\%$), REP ($12.9 \pm 11.7\%$, $11.6 \pm 11.6\%$), DRAW ($13.3 \pm 11.7\%$, $13.2 \pm 15.4\%$) and MEM ($13.2 \pm 10.3\%$, $12.0 \pm 10.1\%$). There was a significant difference between the dominant and non-dominant CBFv responses ($p < 0.008$), but no difference between the amplitude of responses.
Comparison with existing methods: For established paradigms, our results are in excellent agreement to what has been found previously in the middle cerebral artery.
Conclusions: Cognitive paradigms derived from the ACE-III led to significant lateralised changes in CBFv that were not distinct for novel paradigms. Further work is needed to assess the potential of paradigms to improve the interpretation of cognitive assessments in patients at risk of mild cognitive impairment.

1. Introduction

By 2050, 135.5 million people are predicted to be living with dementia worldwide (Robinson et al., 2015); cognitive impairment having a great impact not only on the patient, but also on their relatives, carers and health care providers. Previous studies have shown an association between cerebral haemodynamic abnormalities and

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cognitive decline (Meel-van den Abeelen et al., 2014; Keage et al., 2012).

Neurovascular coupling (NVC) refers to the changes in cerebral blood flow (CBF) in response to brain activation, and is carried out by the components of the neurovascular unit; endothelial cells, neurons, pericytes and astrocytes. Transcranial Doppler ultrasound (TCD) is a non-invasive tool used to continuously monitor CBF velocity (CBFv) in major vessels such as the middle cerebral artery. The technique has a good temporal, but poorer spatial, resolution in comparison with other methods used to measure CBF, including functional magnetic resonance imaging (fMRI). However, advantages of using TCD are its ability to be used at the bed-side, and the ability of subjects to be in the seated position whilst carrying out tasks such as writing.

Cognitive batteries are widely used clinically in the diagnosis of cognitive impairment, including dementia and mild cognitive impairment (MCI). CBFv and NVC responses to questions commonly used in the diagnosis of cognitive impairment have not been studied in detail to date; previous studies having largely investigated the responses to individual cognitive tasks which are not widely used to aid the diagnosis of dementia (Keage et al., 2012).

The Addenbrooke's Cognitive Examination-III (ACE-III) is a validated tool, with an excellent sensitivity and specificity for diagnosing dementia, which is routinely used in clinical practice (Hodges 2011; Hsieh et al., 2013). The examination takes approximately 25 min to complete and comprises questions from five cognitive domains (attention, fluency, language, visuospatial and memory).

The possibility of matching the ACE-III results to corresponding NVC responses has considerable potential to improve assessment of individuals at risk of MCI, particularly in the identification of cognitive losses of vascular origin. However, whilst some of the ACE-III questions can be regarded as equivalent to cognitive paradigms that have been previously adopted in NVC studies, such as the N-back and naming words, the majority of the questions involved in its five domains have not been validated regarding their ability to elicit an equivalent NVC response as quantified from the CBFv change following neural activation (Moody et al., 2005; Vermeij et al., 2014). As a first step towards creating a NVC-based 'mapping' to the ACE-III battery, we tested the hypothesis that it is feasible to use TCD to assess CBFv responses in the MCA to paradigms contained within the ACE-III. We also tested the hypothesis that paradigms which had not been studied previously (novel), such as simply drawing a clock, would be able to elicit a detectable change in CBFv similarly to more established protocols. For these purposes, we selected five representative questions, one for each of the ACE-III's main domains.

2. Methods

This observational, cross-sectional study took place over a four-month period. Ethical approval was obtained from the University of Leicester (Reference: 5355). Healthy controls were recruited via the University of Leicester by means of poster and email invitation and formally consented. Inclusion criteria were age $\geq$18 years and willingness to comply with all study requirements. The exclusion criteria included females who were pregnant, lactating or planning a pregnancy during the course of the study as well as being unable to comply with the study requirements. The experiment took place in the Cerebral Haemodynamics in Ageing and Stroke Medicine (CHIASM) laboratory at the Leicester Royal Infirmary, which is of controlled temperature and free from distraction.

Volunteers were asked to abstain from large meals, strenuous exercise, nicotine, caffeine and alcohol for four hours prior to the recordings. CBFv was recorded bilaterally with TCD (Viasys Companion III) in the MCA, together with heart rate (3-lead ECG), beat-to-beat blood pressure (BP) using arterial volume-clamping of the digital artery on the non-dominant hand (Finometer, Finapres Medical Systems; Amsterdam, the Netherlands) and end-tidal CO_2 via nasal cannula, (Salter Labs, ref. 4000; Capnocheck Plus). TCD probes were held in place using a head-frame. Signals were sampled at 500 samples/second and stored in the PHYSIDAS data acquisition system.

Four separate recordings were performed in each subject, comprising a five-minute baseline recording during which participants sat quietly with their eyes open, followed by three separate recordings which divided the ACE-III questions into the following sections: 'A' (4 attention, 3 memory and 2 fluency paradigms), 'B' (6 language paradigms) and 'C' (4 visuospatial and 1 memory paradigm). Each recording began and ended with a one-minute baseline recording and there was a thirty-second rest between individual questions to enable CBFv to decrease following previous stimulation. An event-marker was used to note question timings and the brachial BP (UA767 BP monitor) of the dominant arm was measured prior to each recording for calibration of the Finometer device. The entire protocol took ninety minutes from set up to completion, but individual paradigm durations varied according to how long each subject took to complete each of the tasks. There were no requirements for any follow up sessions.

Following these measurements, data editing software (RBP) was used to determine which recordings were suitable for further analysis. Firstly, the raw signals were visually inspected and linear interpolation was used to remove non-physiological spikes (<100 ms) in the individual CBFv waves. A median filter was used to remove smaller spikes and all signals were low-pass filtered (20 Hz) with a zero-phase Butterworth filter. The beginning and end of each cardiac cycle were detected on the ECG and mean values of CBFv and BP, as well as heart rate and end-tidal CO_2, were obtained for each heart beat. Standard polynomial interpolation, followed by re-sampling at 5 Hz, was performed to obtain signals with a uniform time base (Moody et al., 2005).

After this analysis of the four recordings from each volunteer, files containing the groups of participants with good-quality data were created from which population average responses could be determined using the saved events marker timings as the point of synchronism. The population average responses were assessed bilaterally, in the dominant and non-dominant hemispheres, and were normalized to the fifteen-seconds immediately preceding that particular question. In addition to the population averages, the standard error of the mean (SEM) was also calculated at each sample point.

One question from each domain was analysed in this feasibility study; subtracting seven from one hundred and subsequent answers repeatedly (attention, SUB7), naming words beginning with 'P' (fluency, N-P), repeating words and phrases (language, REP), clock-drawing (visuospatial, DRAW) and recalling a previously learned name and address (memory, MEM).

3. Statistical analysis

For each question, a graph of the population average bilateral CBFv changes with time was plotted and the peak CBFv responses to questioning were determined, as well as the largest SEM at the point of occurrence. In addition to the calculation of population mean and SEM at each sample point, that is every 0.2 s within a 60 s window of observation, the peak value of each normalized CBFv response was extracted for both right and left MCA as the averaged CBFv value from the 10 s surrounding these peaks. A repeated measures 2-way ANOVA was performed (see Appendix A) on the averaged peak values to test for differences amongst