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Event-related potentials and reaction time can distinguish healthy aging from mild Alzheimer's disease

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PGD2S. PGD2S catalyzes the conversion of prostaglandin H₂ to PGD₂ which spontaneously converts to PGJ₂, Δ^1 PGJ₂ and ultimately 15dPGJ₂, a known apoptotic agent. The isolated native PGD2S protein showed apoptotic activity in a TUNEL assay performed on LLC-PK1 cells. A recombinant (r) form of human PGD2S was isolated from *E. coli* and polyclonal antibodies raised against it in rabbits. Western blot analysis, utilizing the rPGD2S antibody as a probe, showed a strong signal at 29 kDa in SDS-PAGE separated AD plasma. There were increases in the apoptotic indices (AI; % of cells in apoptosis) after a 2 h exposure of LLC-PK1 cells to AD plasmas (AI: 54.6 ± 3.0 , 40.2 ± 1.6), rPGD2S (AI: 22.9 ± 1.1), the end product Δ^1 PGJ₂ (AI: 22.3 ± 1.3), and camptothecin (AI: 21.3 ± 0.7), when compared to control plasma (AI: 9.4 ± 1.5), or untreated LLC-PK1 cells (AI: 7.2 ± 0.7). The cyclooxygenase (COX)-1 and COX-2 inhibitor indomethacin, the COX-2 specific inhibitor NS398, all-trans retinoic acid, and anti-PGD2S antibody all significantly ($p < 0.05$) reduced the induction of apoptosis by AD plasma (43, 58, 54, 44% reductions respectively) and rPGD2S (51, 76, 65, 59%), but not Δ^1 PGJ₂ or camptothecin. Our findings provide a novel mechanism for the expanding body of evidence that non-steroidal anti-inflammatory drugs, which inhibit the substrate for PGD2S, decrease the prevalence and retard the progression of AD; and that PGD2S might serve as a biomarker.

Poster Presentation: Brain-Behavioral Relationships II

1042 NORADRENERGIC CHANGES AND AGGRESSIVE BEHAVIOUR IN PATIENTS WITH DEMENTIA.

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In addition to cognitive impairment there are various behavioural syndromes that may be present in subgroups of Alzheimer's disease (AD) patients and it has been suggested that patients with "non-cognitive"/behavioural disturbances may have different neurochemical changes than patients with AD alone. The locus coeruleus (LC), the major source of noradrenaline (NA) projection neurons in the brain, is known to be damaged in AD. Despite substantial neuronal loss, it has been hypothesised that there is an increase in the activity of the surviving NA neurons. The integrity of the NA system was therefore investigated in patients with AD, non-AD dementia and controls and possible relationships between changes in the NA system and the presence of behavioural syndromes in AD were examined. High affinity α_2 adrenoceptor sites in three cortical regions (BA9, 21 and 46) were quantified using the full selective α_2 agonist [³H]UK14304 (bromoxidine) and NA concentration was measured by HPLC. This data was then compared with cell counts from three regions of the LC from the same patients. The α_2 adrenoceptor density (Bmax) was not found to be significantly different in the cortex (BA9, 21, 46) of AD, non-AD demented and control patients. It was found however, that there was a significant loss of LC cells in AD, the greatest cell loss occurring within the rostral portion of the nucleus (50%) with a relative sparing of caudal cells. A significant difference was also seen in the mid-temporal cortical NA concentration (31% decrease) in AD patients, although this was less pronounced than the neuronal loss from the LC. This data is consistent with a compensatory activation of the remaining LC NA neurons, which may lead to increases in both NA concentration and numbers of cortical NA terminals. There was a significant positive correlation between the presence of aggressive behaviour during the course of the illness and both magnitude of rostral LC cell loss and decreased mid-temporal NA concentration, suggesting that decreases in NA activity may lead to aggressive behaviour in a sub-group of AD patients. This study may have implications for the treatment of behavioural syndromes, particularly aggression, in AD patients.

1043 THE ASSESSMENT OF BEHAVIORAL DISTURBANCES IN DEMENTIA USING A TELEMETRIC DEVICE

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Background. The assessment of behavioral signs and symptoms in dementia (BPSSD) is a central issue to understanding the nature of the course of disease and to evaluate treatment effects in such severely demented patients. Method. Wrist motor activity was continuously recorded in 10 patients with BPSSD for three days after admission to a psychogeriatric unit. Patients were clinically assessed using BEAM-D and BEHAVE-AD scales. Results. A strong statistical association was found between mean activity levels and scores on BEAM-D and BEHAVE-AD scales. The severity of behavioral symptoms, such as wandering, aggression, and cognitive abulia, was found to account for some of the variance in mean activity levels. Conclusions. The assessment of motor activity is shown to be a valid method of assessing the severity of symptoms in demented patients. Such objective assessment of activity may

outweigh the advantages of specific description, offering opportunities for research on BPSSD, especially on the clinical assessment of severity and the effects of pharmacological and non-pharmacological treatment interventions, as well as the natural course of the disease and underlying pathologies.

1044 PREFRONTAL ACTIVATION DURING DEEP AND SHALLOW INCIDENTAL ENCODING OF FIGURATIVE AND NON-FIGURATIVE DRAWINGS

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The objective of this PET study were to investigate the prefrontal activation pattern during incidental episodic encoding of visuo-spatial material under a levels of processing manipulation. Material and Methods: 15 males (average age 25). Measurements of PET-rCBF were acquired, each subject was scanned in 6 different states repeated twice. The subjects were instructed to view the figurative and non-figurative drawings attentively and to subjectively rate their pleasantness (deep processing) or their graphical quality (shallow processing). The PET images were analysed with SPM99b. The SPM[t] (160df) was threshold at $t = 3.35$ ($p < 0.0005$). Results: In the main effect contrast of deep vs. shallow, a left dorsolateral inferior frontal region and a bilateral left-dominant frontopolar, anterior medial frontal region. In shallow vs. deep, two right dorsolateral PFC regions were activated. Comparing the main effect of figurative vs. non-figurative, a similar frontopolar, anterior medial frontal region was activated. In addition, two smaller clusters in the left inferior frontal region were observed. In the reverse contrast, non-figurative vs. figurative, smaller activated clusters centered on the right middle frontal and the right inferior frontal regions as well as the anterior cingulate region. The only PFC region where the factors deep/shallow and figurative/non-figurative interacted significantly was in the bilateral frontopolar, anterior medial superior frontal region. This interaction is related to the fact that the increased activity in deep versus shallow encoding is greater when the subjects are encoding figurative compared to non-figurative drawings. Conclusions: In this PET study of incidental episodic encoding of visuo-spatial material elaborate meaning-based processing yielded left-lateralised PFC activations while surface-based processing yielded right PFC activations. These effects were independent of whether the stimuli were figurative or non-figurative. Comparing figurative vs. non-figurative stimuli, the PFC tended to be more activated on the left, while in the non-figurative vs. figurative comparison, the PFC tended to be more activated on the right.

1045 EVENT-RELATED POTENTIALS AND REACTION TIME CAN DISTINGUISH HEALTHY AGING FROM MILD ALZHEIMER'S DISEASE.

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Objective: To examine the utility of multivariate measures of event-related brain potentials and reaction time (RT) to accurately classify healthy elderly subjects and mild Alzheimer's disease (AD) subjects. Background: Studies using the detection of a rare target stimulus have found group differences in RT and brain potentials (P300 and readiness potential, or RP) between AD and elderly controls. However, these individual measures do not have the requisite sensitivity or specificity to be useful for defining an individual as having AD. The purpose of the present experiment was to determine if a multivariate approach using RT, RP, and P300 would improve sensitivity and specificity. Methods: We studied healthy controls ($n = 18$; M age 69.7 ± 7.7), and AD patients ($n = 11$; M age 72.0 ± 9.0 ; Mini-mental status = 23.3 ± 2.9). Healthy controls were screened using a battery of neuropsychological tests. In the target detection task subjects listened to a sequence of 300 tones. Frequent (1000 Hz; $n = 240$) and target (2000 Hz; $n = 60$) tones were presented in a random order. The subject's task was to quickly press a button when a target was presented. Behavioral measures were reaction time and accuracy. EEG was continuously recorded from 7 sites using standard techniques. Evoked potentials to target and frequent tones were averaged off-line. Linear discriminant analysis was used to predict group membership (AD or control) for each subject on the basis of their RT, RP, and P300 latency. Results: There were significant univariate differences in reaction time ($p > .01$), RP amplitude ($p > .02$), and P300 latency ($p < .01$) between controls and AD. Median z-scores for AD relative to controls were 1.4 (RT), -1.1 (RP), and 1.6 (P300 latency). Discriminant analysis showed 81.8 % sensitivity (correctly classified AD) and 100% specificity (correctly classified controls). Conclusions: We identified significant differences between healthy controls and AD patients on three measures using a task that is easy to perform. The combined use of RT, RP, and P300 latency was capable of distinguishing mild AD patients from age-matched subjects with a high degree of accuracy. The method may have promise for distinguishing normal aging from early AD.