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A study of the neural correlates of episodic memory and HPA axis status in drug-free depressed patients and healthy controls

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Abstract

Altered laterality of cortical activity, neuropsychological impairment and hypercortisolaemia have been shown in depression. The neural correlates of episodic memory in healthy subjects demonstrate hemispheric laterality but it is not known whether this is affected by depression and/or hypercortisolaemia. Twenty-seven drug-free depressed patients and 29 matched healthy controls were studied. Event-related potentials (ERPs) were recorded during an episodic memory test. During the study phase, subjects heard words spoken in either a male or female voice. Old and new words were presented visually during a test phase, when subjects were requested to identify words as old or new and recollect the gender of the voice for old words. Cortisol levels were measured in saliva and plasma samples. The results showed a trend for elevated salivary cortisol concentration in depressed patients. Reaction times were significantly longer in patients; however, there was no difference in memory accuracy performance between the two groups. Recollection performance was found to be negatively correlated with age, with a similar trend for cortisol concentrations. ERP activity not specifically related to episodic memory retrieval recorded 200–500 ms post-stimulus from controls showed a marked laterality, with higher voltages over the right hemisphere; however, was not seen in patients. There was significant correlation between cortisol and the laterality of the neural activity specifically related to episodic memory retrieval recorded 500–1400 ms post-stimulus in both depressed and healthy groups. These unique findings demonstrate that while the laterality of the neural correlates of episodic memory is sensitive to cortisol, it is not altered by the non-specific laterality effects seen in depression.

Keywords: Depression; Cortisol; Memory; Recognition; Evoked potentials; Asymmetry

1. Introduction

Major depressive disorder (MDD) has been associated with functional asymmetric cortical activity, as assessed by electroencephalography (EEG) (e.g. Coan and Allen, 2004; Allen et al., 2004; Davidson, 1998) and functional neuroimaging studies (e.g. Holthoff et al., 2004). In particular, asymmetry in frontal alpha power has been frequently shown in depression, with a relative increase (demonstrating less cortical activation (Laufs et al., 2003)) over the left regions (Davidson, 1998). Posterior and temporo-parietal alpha asymmetry, with relatively reduced right cortical activation, has also been reported in patients with MDD by many (e.g. Bruder et al., 1997; Kentgen et al., 2000), but not all groups (Henriques and Davidson, 1991). There is good evidence that this functional cortical asymmetry is not only state-dependent (i.e. related to depressed mood) but may also be a trait-dependant variable, since it has been shown in depressed patients, even while euthymic (Henriques and Davidson, 1990), as well as in high-risk offspring of depressed parents (Bruder et al., 2005). As such it may relate to fundamental underlying pathophysiologies of the disorder.

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Asymmetry in the electrophysiological correlates underlying episodic memory, memory for events encountered in previous study episodes, has been shown in healthy humans (Tulving et al., 1994; Baddeley, 2001).

Asymmetrical frontal and prefrontal cortex (PFC) activity, with relatively higher right hemisphere activity, has been reported in many studies of episodic retrieval (Tulving et al., 1994; Ragland et al., 2000; Bernard et al., 2001) although not all studies have demonstrated similar findings (review Cabeza and Nyberg, 2000; Mayes and Montaldi, 2001). Bernard et al. (2001) demonstrated activation in the right anterior and right inferior PFC during word recognition tasks and right dorsolateral PFC activation during stem-cued recall task. Event-related potential (ERP) data have shown differences in waveforms associated with accurate recollection when subjects are presented with a previously studied item compared to correct identification of new non-studied items (Wilding and Rugg, 1997; McAllister-Williams et al., 2002b; Alhaj et al., 2005). This "old/new" effect comprises two components: a left parietal effect, which is believed to reflect hippocampal-modulated cortical activity underlying episodic memory retrieval (Alvarez and Squire, 1994; McClelland et al., 1995), and a right frontal old/new effect, which is believed to originate from dorsolateral PFC and may reflect evaluation and monitoring processes that operate upon the products of memory retrieval (Rugg et al., 2002; Rugg et al., 1996).

Neuropsychological impairments, including in learning and memory, have been reported in patients with MDD (Veiel, 1997; Christensen et al., 1997; Elliott, 1998). However, reports of such impairments have been inconsistent and it has been argued that this could be due to the characteristics of both patients studied and memory tests employed (Burt et al., 1995; Austin et al., 1999). Previous studies of episodic memory in depression have focused on item recognition. However, it is not clear whether retrieval of the "source", or the context in which the information was acquired, is impaired in patients with MDD. In the only previous study that tested "source retrieval" in depression, performance of 12 hospitalised patients was found to be similar to that of healthy controls (Degl'Innocenti and Backman, 1999).

Neuroendocrine studies have demonstrated hypercortisolaemia in a substantial proportion of depressed patients (Holsboer, 2000). Abnormally high levels of cortisol have been suggested as a possible explanation of neuropsychological impairments associated with depression (McAllister-Williams et al., 1998). The hippocampus and prefrontal cortex, which are known to play an important role in episodic memory, are cortisol-sensitive (Lupien and McEwen, 1997; McEwen et al., 2002) and it has been argued that hypercortisolaemia may lead to the hippocampal and PFC atrophy seen in depression in MRI studies (Sheline et al., 1996; Bremner et al., 2000; Bell-McGinty et al., 2002; Ballmaier et al., 2004). Cortisol administration to healthy volunteers has been shown to impair episodic memory (Newcomer et al., 1999; de Quervain et al., 2000; Wolf et al., 2001) and lead to qualitative changes over frontal scalp regions in the electrophysiological correlates of retrieval (McAllister-Williams et al., 2002a).

The normal hemispheric laterality in healthy subjects seen with certain neurocognitive tasks, such as visuospatial functions, has been shown to be modified or absent in patients with MDD (Henriques and Davidson, 1997). However, it is not known if this is the case regarding the neural correlates of episodic memory. Administration of cortisol or a synthetic glucocorticoid prednisone in healthy subjects has been shown to alter the laterality of alpha EEG, increasing right frontal activation (Tops et al., 2005; Schmidt et al., 1999). It is unclear whether cortisol dysregulation, which is known to modulate the neural circuitry of episodic memory retrieval and is believed to play an important role in the pathophysiology of depression, plays a part in any alteration in the laterality seen with episodic memory in depressive illnesses.

The aim of the current study was to investigate the lateralisation of the neural correlates of episodic memory using an ERP technique in drug-free depressed patients compared to matched controls. Furthermore, we aimed to evaluate the association between cortisol level, episodic memory performance and hemispheric asymmetry. It was hypothesised that depressed patients would show longer response times, worse episodic memory performance and abnormality in the cortical activation, leading to a decrease in the right temporo-parietal and the left anterior activities during episodic retrieval. This change in asymmetry was postulated to be correlated with cortisol levels in depressed patients.

2. Materials and methods

Twenty-seven patients (16 females) with a diagnosis of unipolar depressive disorder according to DSM-IV and 29 healthy controls (13 females) took part in this study. DSM-IV diagnosis of depression was verified using the semi-structured interview schedule (SCID) administered by a research psychiatrist. Depressed patients and healthy controls were recruited from the community by advertisements in the local papers. The inclusion criteria required that all participants had an IQ of 90 or more as assessed by the National Adult Reading Test (NART) to ensure that they comprehended the task instructions. It was also required that they were fluent in English in order to be familiar with all the words used in the episodic memory task. Participants had to have normal (or corrected normal) vision and hearing and be right-handed as assessed using Briggs' modification of Annett's (1967) handedness inventory (Briggs and Nebes, 1975). Both patients and controls were excluded if they had used any psychotropic medication within the previous 6 weeks. Patients meeting the diagnostic criteria for additional psychiatric disorders (including personality disorder and substance misuse) were also excluded from the study. Patients with psychotic symptoms were also not included in the study. Controls