A differential role for the hippocampus and amygdala in neuropsychiatric disorders

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There may be a differential role for the amygdala, hippocampus and possibly other temporal structures, in the development and/or the expression of psychopathology

The paper by Briellmann and colleagues¹ in this issue of *J Neurol Neurosurg Psychiatry* brings into focus an evolving trend in the literature with respect to mesial temporal structure volumes and psychopathology (see page 1226). In this study of 34 patients with temporal lobe epilepsy with hippocampal sclerosis, the authors found that a lifetime history of major depression was present in almost half of all subjects and was associated with longer duration of epilepsy and lower frequency of antecedent events. While ipsilateral hippocampal sclerosis and bilateral amygdala atrophy were seen in both depressed and non-depressed groups, there was relative preservation of the contralateral amygdala in the depressed group only.

This finding highlights an interesting trend with regard to affective illness in MRI volumetry studies—namely, preservation or even increase in amygdala volumes with the non-schizophreniform psychosis, particularly affective psychosis.² This trend is particularly interesting given that hippocampal sclerosis has been reported consistently in unipolar major depression,^{3–4} leading to experts terming it the region of interest in imaging studies (Mayberg H, 2006, keynote lecture at the 6th International Neuropsychiatry Association Congress, Sydney, Australia). It also has a parallel in epilepsy studies that have found that amygdala preservation is associated with comorbid affective illness,^{5–6} contrasting radically with the finding of hippocampal sclerosis being the underlying pathology identified in approximately two-thirds of all patients with temporal lobe epilepsy, the most common form of epilepsy. Furthermore, studies of both psychosis⁷ and anxiety⁸ in epilepsy have identified a trend of increasing amygdala volumes with increasing illness severity. Interestingly, in direct contrast, studies

of mesial temporal structure integrity in Geschwind syndrome, a specific interictal behavioural syndrome in epilepsy, have found loss of hippocampal integrity to be the neurobiological correlate.^{7–8}

These findings bring into focus many questions that have long been asked about the relative role of these structures in various neuropsychiatric disorders. Putative links between epilepsy, schizophrenia, major depression and the hippocampus have emerged from this literature, as have links between the amygdala, bipolar depression, non-schizophreniform (usually affective) psychoses and psychopathology comorbid to epilepsy. The possibility that these structures have a differential role in the development, form and content of psychopathology must therefore be considered.

While the amygdala is widely regarded as the seat of human emotion, the hippocampus is well recognised as being the storehouse of memories. It is conceivable that all human experience activates both structures, with a feedback loop between the two providing a reference point to the memory and emotions surrounding past experience. The relative preservation or even increase in amygdala volumes may reflect either a predilection for hyper-emotionality or indeed plasticity and growth of the amygdala due to hyperactivity in some hyper-emotional individuals. This is mirrored by the evidence of increased amygdala activity (in the absence of demonstrable structural change) in functional studies of human emotion.¹¹ In contrast, hippocampal sclerosis may reflect either inherently defective comparator function by this organ, or may indeed be the consequence of an overactive amygdala.

It must be pointed out that these findings are by no means ubiquitous and there are studies that fail to support

this trend. Critiques of this trend in the literature include the small sample sizes in most studies; the relative lack of normative brain volumetry data; their cross sectional nature; the highly select populations studied; the inherent fallacies in volumetry techniques; the failure to differentiate trait from state psychopathology; and the failure to exclude a myriad of confounding factors, to name a few. Nevertheless, they highlight the possibility there may be a differential role for the amygdala, hippocampus and possibly other temporal structures, in the development and/or the expression of psychopathology. Well designed prospective studies adequately powered to explore these associations are therefore necessary.

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Can stroke localisation be used to map out the neural network for yawning behaviour?

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What are the neuroanatomical structures involved in repetitive yawning during stroke?

Since the 19th century, cases of pathological yawning have occasionally been published in medical journals. In this issue of *J Neurol Neurosurg Psychiatry*, Singer *et al*¹ present the first study to focus specifically on yawning during acute stroke affecting the middle cerebral artery territory (*see page 1253*).

None of seven patients suffering from abnormal repetitive yawning had diencephalic lesions. Classically, yawning is thought to originate in archaic brain structures common to all vertebrates. It appears to be a powerful muscular stretch which recruits specific control systems, particularly the paraventricular nucleus of the hypothalamus, locus coeruleus and reticular activating system; these structures explain its ability to increase arousal. A persistent vestige of the past, yawning has survived evolution with little variation.² Singer *et al*¹ suggest that neocortical brain areas have an inhibitory effect on the paraventricular nucleus of the hypothalamus, and that in certain middle cerebral artery strokes this region is liberated, provoking repetitive yawning. This hypothesis merits discussion.

According to Lapresle,³ palatal myoclonus is the human homologue of a primitive respiratory reflex in gill breathing vertebrates, submerged but not lost, reappearing when the inhibitory system is damaged by lesions to the dentato-olivary pathway.

We coined the term “parakinesia brachialis oscitans”⁴ to describe cases of hemiplegia where the onset of yawning coincides with involuntary raising of the paralysed arm. We argued that a lesion in the internal capsule affecting an inhibitory pathway liberates certain subcortical structures that coordinate the massive inspiration of yawning and the motor control associated with quadrupedal locomotion.

In these examples, loss of cortical inhibition following stroke releases a hidden function, phylogenetically more primitive. Singer *et al*¹ do not provide evidence of such an event.

Face scratching, nose-face rubbing, yawning and sighs are automatisms frequently reported after epileptic seizures. These behaviours are also considered a characteristic pattern in healthy subjects on waking. Movement speed

EDITORIAL COMMENTARY

and repetition are the factors that vary, based on whether the context is physiological (sleep, arousal) or pathological (epileptic seizure, stroke). These behaviours are related to the brainstem and diencephalic activation that occurs when the cortex is disconnected from these areas (where the “central pattern generators” are located) by an epileptic discharge or a stroke.⁵

Adaptive behaviours depend on interactions between neural networks at various levels, requiring continuous mutual feedback. Yawning is an exterior manifestation of the tonic stimulation of the cortex by subcortical structures, particularly when the brainstem does not receive appropriate feedback from the cortex.

I agree with the conclusion reached by Singer *et al*¹: further studies are necessary to determine the exact neuroanatomical structures involved in repetitive yawning during stroke and the pathophysiological role of this behaviour.

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