

EDITOR'S CHOICE

COGNITION: belief and uncertainty

Is there a neurology correlate to belief? That is, is there a specific region or process that "decides" whether something is true, whether verifiable or not? And is this the same pathway that determines the belief that something is untrue, or that it is not possible to decide? Sam Harris and colleagues from the UCLA brain mapping centre set out to answer these questions by studying the functional MRI activation patterns of 14 healthy people judging written statements as "true", "false" and "undecidable". These included, amongst others, propositions about maths ("1.257 = 32608.5153"), geography ("California is larger than Rhode Island"), facts ("Eagles are common pets") and religion ("A personal God exists, just as the Bible describes"). The first finding was that subjects were much quicker to respond to say a statement was true (3.26 seconds) and slower when they thought it was false or were uncertain (3.7 seconds). The authors like to argue that the brain seems disposed to accept statements as true, with more neurological "effort" required for disbelief. We are all gullible it seems.

When comparing activation patterns of belief versus disbelief (that is the belief that something is false), a discrete region of ventromedial prefrontal cortex was found to be associated with belief. Turning the tables, the left inferior frontal gyrus, anterior insula, dorsal angular cingulate and superior parietal lobules were correlated with disbelief. Uncertainty was associated with a positive signal in the anterior angular cingulate. What to make of all of this? Well, firstly it is interesting that different types of belief (mathematical, religious) elicited a similar brain activation, and further in a region associated with linking factual knowledge to emotions. Perhaps there is a "reward" or "pleasure" in something that is true. In contrast, the anterior insula, involved in the disbelief map, is associated with perception of pain or disgust. The anterior angular cingulate, activated with uncertainty, is involved in resolving response conflict.

It is easy to overinterpret such imaging studies and cleverer souls than I will have to ruminate over the experimental paradigm before we get too carried away. But, as a scientific romantic, it is hard to resist the conclusion that humans are built to love truth and hate what is false. Now, where have I heard that before? – *AJC*

Harris S, Sheth SA, Cohen MS.

Functional neuroimaging of belief, disbelief, and uncertainty.

ANNALS OF NEUROLOGY

2008 Feb;63(2):141-7.

NEUROGENESIS: Neural stem cells and behaviour

In Nature Neuroscience the group of Alvarez-Buylla et al have expanded on the observation that Sonic hedgehog is important for the proliferation and maintenance of adult neural stem cells in the subgranular zone in the hippocampus. They demonstrate that Sonic hedgehog signalling is essential for expanding the neural precursors in this region during perinatal development to establish the adult stem cell population that carries on turning over throughout life. This effect of Sonic hedgehog requires a factor known as Kif3a, which is a subunit of kinesin-II involved with microtubular proteins. The reason why this is essential for the formation of the stem cell pool is that this protein is important for the motor machinery necessary for assembling primary cilia. If they remove Kif3a, the capacity to make radial astrocytes and the production of the hippocampal precursors is lost, and thus adult neurogenesis fails in this region. Whilst they have no functional data to address what the consequences may be of not having this factor expressed in development, there is some interesting speculation in this paper about the link between certain forms of mental retardation and dysfunctional cilia.

In a related article in Nature, Zhang et al have explored more explicitly what exactly adult neurogenesis is all about in terms of what functions does it serve in the adult brain. In this paper they have used a series of ingenious strategies with various knock-out mice to investigate what drives neurogenesis. They first demonstrate that the orphan nuclear receptor TLX is a marker and necessary factor in neural precursor cell proliferation. They demonstrate this in vitro by showing that knocking out this critical receptor reduces proliferation by 80%. They then turn to a series of in vivo studies where using micro

arrays, they showed that there were significant gene differences in TLX knock out mice versus a conditional knock out model when the gene was left on. They then switched neurogenesis off in the brain using this conditional mouse model and showed there was no major changes in the morphology of the hippocampus and that neurogenesis could still be switched on to some extent by physical activities such as running. Furthermore they were able to demonstrate that whilst neurogenesis was reduced in these conditional knock out mice, there was no change in the fate of neural precursor cells in terms of how many survived and differentiated into neurons. They went on to demonstrate that there were no deficits in contextual fear learning in contrast to reports from other groups. They did however find major deficits in spatial learning using a Morris water maze test. They therefore have demonstrated that this orphan receptor is critical in the genesis of neurons in the adult hippocampus and that this neuronal population seems to be important in spatial learning. Of course those cells which do not contain this receptor and form a separate population may perform some rather different function, but as to what this is remains a mystery. – *RAB*

Han Y-G, Spassky N, Romaguera-Ros M, Garcia-Verdugo JM, Aguilar A, Schneider-Maunoury S, Alvarez-Buylla A.

Hedgehog signalling and primary cilia are required for the formation of adult neural stem cells.

NATURE NEUROSCIENCE

2008;11:277-84.

Zhang C-L, Zou Y, He W, Gage FH, Evans RM.

A role for adult TLX-positive neural stem cells in learning and behaviour.

NATURE

2008;451:1004-9.

REHABILITATION: Can you feel me touching you; can you feel you touching you?

Despite the importance of sensation for hand function, this aspect of sensorimotor control is a rather neglected area in rehabilitation. Sensory testing of patients with stroke is usually fairly cursory and is limited to determining whether a few stimuli are detected. Studies using careful testing procedures and using a number of different modalities of stimulation have found that up to 65% of stroke patients have impaired somatosensory detection. But detection alone is only part of the picture. In order to be useful, incoming sensory information must be detected, discriminated and located. A fuller understanding of impairment in sensory processing is important for developing new strategies for rehabilitation.

Some interesting findings about enhancement of somatosensory perception have recently been reported in the JNNP. Valentini et al have analysed sensory performance in a sample of 39 stroke patients. The patients were tested, blind-folded, using a Semmes-Weinstein pressure monofilament (a calibrated nylon fibre attached to the end of a hand held rod). Testing with these filaments allows the pressure to be carefully controlled but also means that the stimulus is somewhat remote from the hand it is held in. The researchers compared performance of detection, intensity rating and location when the stimuli were applied conventionally by a tester and when the filament was held in the patient's unaffected hand. In this latter condition, called 'self touch', the patient's hand was positioned and moved by the tester to reduce proprioceptive cueing. A sample of unimpaired control subjects were also tested but with a finer filament to avoid ceiling effects. These healthy volunteers were able to detect stimulations with a probability of 50-70%.

No advantage of 'self touch' was seen in the unimpaired control group. However the stroke patient group had significant and reliably improved detection, intensity estimation and location when the stimuli were delivered via the 'self touch' method. The effect was found in more than half of the patients and in both left and right hemisphere strokes. It was more frequent in patients with right hemisphere strokes, but no correlation was found between the sensory enhancement and visual hemispatial inattention.

The enhanced appreciation for touch could have been due to proprioceptive cueing, but the authors discount this. Their strategy to have the tester move the patient's limb in the self touch condition would only have partially reduced the proprioceptive information available, but if the proprioceptive element was important in enhancing performance surely the effect would have been seen in the unimpaired control group too. Instead the authors suggest that the 'self touch' enhancement is due to modulation of attention. This may explain the increased frequency in the right hemisphere patients, however further investigation will be needed to confirm any attentional mechanism. Let's hope the findings will provoke renewed attention from rehabilitation practitioners and researchers both for improving the quality of sensory assessments and for testing new ideas for therapy. – *AJC*

Valentini M, Kischka U, Halligan PW.

Residual haptic sensation following stroke using ipsilateral stimulation.

JOURNAL NEUROLOGY, NEUROSURGERY AND PSYCHIATRY

2008;79:266-70.

NEURODEGENERATION: Progranulin: a promising growth factor?

The gene, GRN, which codes for progranulin is associated with 17q-linked frontotemporal dementia FTD with ubiquitin-immunoreactive inclusions. Progranulin is a 593 amino acid glycoprotein containing 7.5 cysteine-rich tandem repeats and is the precursor of granulin proteins. Progranulin is a secreted growth factor found in many tissue types and has been found to be important in development, wound repair, inflammation and tumorigenesis and while it is highly expressed in neurons of the cerebral cortex, its function in the central nervous system is yet to be clarified. Patients with GRN mutations have variable phenotypes although usually present with frontal variant FTD (fvFTD). Le Ber et al have now carried out a detailed study examining the clinical, neuropsychological and brain perfusion characteristics of patients with progranulin mutations to illustrate the highly variable phenotypes and neuropsychological profiles associated with these mutations and provide further evidence that clinical phenotype is a poor predictor of the underlying histopathology.

The authors have examined GRN in 502 patients out of which 352 had fvFTD. They have identified 18 mutations of which 7 were novel in 24 families including 32 symptomatic mutation carriers. GRN mutations presented with a variety of phenotypes with again 63% of the carriers having fvFTD whilst the remaining 37% had a variety of clinical diagnoses including primary progressive aphasia (PPA), corticobasal degeneration (CBD), dementia with Lewy body (DLB) or Alzheimer's disease (AD). Using DNA extracted from peripheral blood from the 502 patients the authors have looked for deletions of the GRN gene which might be responsible for the partial loss of functional progranulin. After sequencing, it was observed that in patients with either fvFTD or FTD-MND no mutations were present and further analysis showed no copy number variation.

Among the various results presented in this study it is interesting to note that Parkinsonism was frequent in the patients (41%), which fits with the observation of striatal lesions in GRN mutation carriers as well as the presence of visual hallucinations (25%) and motor apraxia (25%), both of which probably have an origin in the posterior parietal cortex and supplementary motor cortex. Episodic memory disorders were frequent (89%) while results show that hypoperfusion was observed in the hippocampus, parietal lobes and posterior cingulate gyrus and frontotemporal cortices. These results associated with GRN mutations are interesting in the sense that they again show how a single "genetic" disorder can have a variety of clinical representations and pathological profiles. Thus whilst all these mutations are responsible for a progranulin haploinsufficiency, there must be other factors that interact with this to explain the variation of the clinical presentation and pathology. – **CA Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, Hahn-Barma V, van der Zee J, Clot F, Bakchine S, Puel M, Ghanim M, Lacomblez L, Mikol J, Deramecourt V, Lejeune P, de la Sayette V, Belliard S, Vercelletto M, Meyrignac C, Van Broeckhoven C, Lambert JC, Verpillat P, Campion D, Habert MO, Dubois B, Brice A; French research network on FTD/FTD-MND.**

Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study.

BRAIN

2008;131:732-46.

Journal reviewers

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EPILEPSY: How long to treat epilepsy?

When do you stop AED? In adults the decision is generally made on a mixture of medical evidence and social factors; are you going to have a baby or do you drive for a living? The MRC drug withdrawal study has been the benchmark used in making decisions regarding AED withdrawal for nearly two decades. This is a smaller study but nevertheless provides up-to-date information, which has both confirmatory and new elements. As a sign of the times, the consent form was drawn up by a legal representative to include possible claims from injuries arising as a result of seizures. Patients were included after at least two years of seizure-freedom. In fact two thirds had been seizure-free more than five years and as patients were only on monotherapy, this was a cohort of patients with milder epilepsy than in the MRC study. Amongst the exclusion criteria were juvenile myoclonic epilepsy or a very active EEG in patients with idiopathic generalised epilepsy. One hundred and sixty patients were randomised to either withdrawal or no withdrawal and followed up for a median of 47 months for patients on medication and 41 months for patients off medication. Additional data were recorded, including neuropsychological assessment, EEG, quality of life assessment. Relapse rates in the first twelve months were 7% of those on medication and 15% of those withdrawing medication. At the end of the twelve month double-blind period, of the 72 seizure-free patients in the non-withdrawal group, 62 chose to taper medication. This is a surprisingly large number and meant that almost as large a cohort stopped medication at the end of a year as were randomised to initial withdrawal. Their outcome over the next year was similar. Relapse rate was greatest in the first year after withdrawal and around 80% remained seizure-free at 36 months in both groups. On an intention to treat basis this means that the two arms are comparable but I don't think it answers the question of whether staying on medication carries a lower risk of relapse than coming off it in the longer term, since from one year onwards more or less the same number in both arms were actually continuing treatment. Numerous factors did not predict seizure-freedom, including age, gender, partial or generalised epilepsy, MRI, or duration of seizure-freedom. A normal neurological examination and seizure freedom on carbamazepine were associated with a significantly lower risk of relapse on withdrawal. Since carbamazepine is generally a first-line drug, those patients on it are likely to have had the easiest to control epilepsy. The patients in this study demonstrated a small but significant improvement in a range of neuropsychological tests after drug withdrawal.

So what can one conclude from this study. Firstly, in selected patients with easy to control epilepsy, drug withdrawal carries only a 20% risk of recurrence over three years. However, we can't really say what would happen if the patients stayed on the drugs over that time as a comparator. The only thing we can say is that in the first year the withdrawal group had a relapse risk of about 15%, compared to 5% in the continuation group. Secondly, withdrawal of long term medication in this study (but not all studies) is associated with an improvement in cognitive testing which is difficult to relate to activities of daily living. But the bottom line for the patient asking if their seizures will come back is only a slightly more educated: "I don't know." – **MM**

Erikssen J, Gulbrandsen, B, Gjerstad L.

Consequences of antiepileptic drug withdrawal: A randomized, double-blind study (Akershus study).

EPILEPSIA

2008;49:455-63.

EPILEPSY: Another cause of epileptic confusion

These investigators retrospectively analysed patients in whom continuous EEG monitoring had identified thirteen critically ill patients who experienced cyclical seizures with a periodicity of 30 seconds to twenty minutes, recurring for hours. The patients ranged in age from 12 weeks to 79 years and had a wide range of causes of seizures including hypoxic ischaemic injury, posterior reversible leucoencephalopathy syndrome, Ohtahara syndrome and lead poisoning. The mean interseizure interval was 7.6 minutes and the median 6.7 minutes and cycling lasted up to 48 hours with a mean if 7.9 hours and median 3 hours. Clinical state ranged from confusion to coma. Interestingly the ictal onset was left sided in 9, diffuse in 2 and right sided in 2 patients. Clearly this pattern will only be recognised if there is continuous EEG monitoring, as in many cases it would be over, before a routine EEG could be arranged. How many patients have I unknowingly seen with this problem? – **MM**

Friedman D, Schevon C, Emerson R, Hirsch L.

Cyclic electrographic seizures in critically ill patients.

EPILEPSIA

2008;49:281-7.