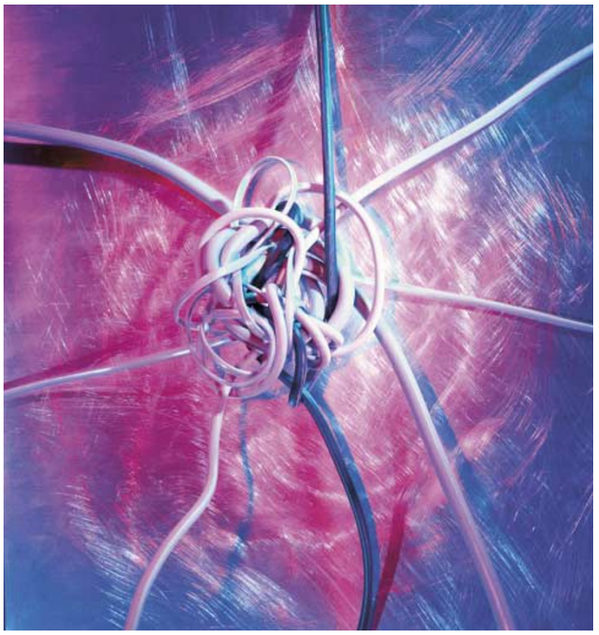
NEURODEGENERATIVE DISORDERS

Tying up loose ends



It's always a bonus for researchers when apparently separate pathways for pathogenic mechanisms in fact conveniently and neatly intertwine. A report by Lipton and colleagues in *Science* shows how two proposed mechanisms for nerve-cell death are intimately linked, and should therefore help to direct therapies aimed at treating neurological disorders.

It had been known that the nerve-cell damage that triggers their demise during stroke, Alzheimer's disease and other neurodegenerative diseases not only occurs from inside the cell but externally too. The best-characterized nerve-cell-death pathways occur inside cells, but in terms of external mechanisms, two observations had previously been made — levels of matrix metalloproteinases (particularly MMP9) are elevated in neurodegenerative disorders, and nitric oxide (NO) can modulate the activity of proteins (in a manner that can be described as being analogous to phosphorylation) by reacting with cysteine thiols to form an *S*-nitrosylated derivative.

Now, Lipton and colleagues show that these two events are linked. They found that NO switches on the over-expression of MMP enzymes, which, in turn, chew up the environment that surrounds nerve cells.

Initial *in vitro* analysis showed that NO can directly activate MMP9 and induce neuronal apoptosis. To confirm their results *in vivo*, Lipton and colleagues used mass spectrometry to characterize the events during focal ischaemia (the lack of blood supply owing to the occlusion of an artery) and reperfusion (the return of blood to an ischaemic region, which is also accompanied by tissue damage). This showed that MMP9 is activated by *S*-nitrosylation of a cysteine residue followed by further oxidation to a sulphinic- or sulphonic-acid derivative. This latter step is particularly interesting, as it is irreversible, which would explain the permanent pathophysiological activation of MMP9 that has been

EMOTION

Attention to detail

Is emotion processed automatically? According to the prevailing view, the processing of faces with emotional content can occur without attention. In a paper published in *Proceedings of the National Academy of Sciences*, Pessoa *et al.* argue against this standpoint, presenting evidence that brain regions that respond differentially to emotional faces do so only when sufficient attentional resources are available.

Psychophysical studies indicate that visual processing outside the focus of attention is attenuated and can even be abolished. But is this true of emotional stimuli? Previous studies have indicated that emotional expressions can be processed automatically — that is, without attention. Pessoa *et al.* considered that the failure of these studies to detect an effect of attention on emotional processing might have been due to the failure of competing tasks to divert sufficient attention away from the emotional stimulus. To address this possibility, the authors used functional magnetic resonance imaging to measure activations in brain areas that are involved in emotional processing, and

examined how these responses were modulated by attention. Importantly, they chose a competing task that would exhaust subjects' attentional resources.

A fearful, happy or neutral face was presented at the point of fixation for 200 ms, and bars were presented in the left and right periphery. In 'attended' trials — with the focus of attention on the face — subjects were asked to indicate whether the face was male or female; in 'unattended' trials, they had to comment on whether the bars were of similar orientations. Pessoa and colleagues found that, in attended trials, fearful and happy faces produced greater activations in the amygdala than neutral faces. Several other brain regions, including the fusiform gyrus, responded differentially to emotional stimuli in attended trials. However, when attention was arrested by the competing task, differential responses to emotional faces were eliminated. So, the processing of emotional expressions, like that of other visual stimuli, seems to be modulated by attention.

This study provides us with clues to the route of emotional processing by the amygdala and other brain regions. Pessoa *et al.* contend that the main pathway for the processing of emotional expressions is not an automatic, subcortical one; rather, they suggest that processing proceeds from the primary visual cortex to extrastriate areas, including the fusiform gyrus, and then to the amygdala.

Rebecca Craven

References and links

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WEB SITES

MIT Encyclopedia of Cognitive Sciences: http://cognet.mit.edu/MITECS/ emotion and the human brain

observed in cerebral ischaemia and reperfusion.

The authors say that this NO-activated MMP mechanism "confers responsiveness of the extracellular matrix to nitrosative and oxidative stress", which are found in several conditions, including cerebral ischaemia and neurodegenerative diseases. The extracellular proteolytic cascades that are triggered by MMPs can disrupt the extracellular matrix, contribute to cell detachment and lead to anoikis (apoptosis due to cell detachment from the substrate). So, the authors conclude that preventing NO-activated MMP activity could be a novel way of tackling neurodegenerative diseases.

Simon Frantz,
Associate Editor (News),
Nature Reviews Drug Discovery

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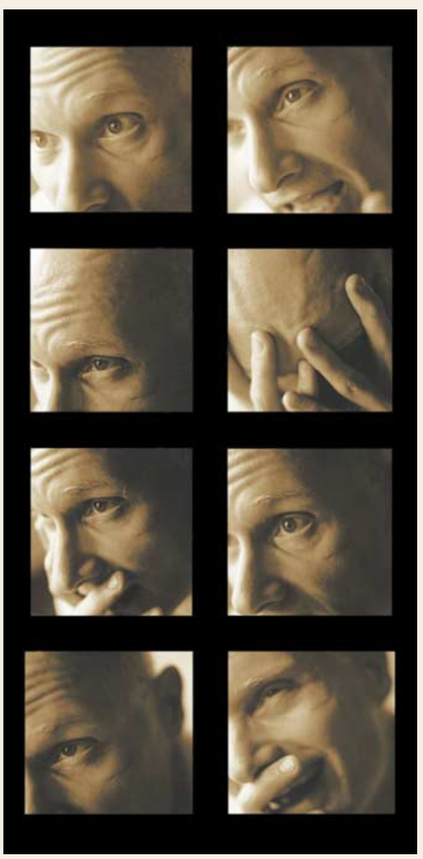

Courtesy of the Kobal Collection.

DEVELOPMENT

To branch or not to branch?

Dendrites come in a wide variety of shapes and sizes, ranging from a solitary process with no branches to an elaborately branched arborization. Because dendritic morphology is a vital factor in determining the pattern of inputs that a neuron will receive, its development has been the subject of many investigations. In neurons that are fated to produce branched dendrites, the structure of the arborization is controlled by a complex array of cell-intrinsic and cell-extrinsic factors. However, according to a new report in *Science*, the initial decision — to branch or not to branch — might be made at the flick of a genetic switch.

During development of the *Drosophila* peripheral nervous system, external sensory organ precursor (ESOP) cells divide to give two cells, one of which (IIB) generates a multidendritic (MD) neuron and a neuronal precursor called IIIB. The IIIB cell divides once more to generate an external sensory (ES) neuron and a glial cell. Although the MD and ES neurons are closely related by lineage, their dendrites could not be more different — the ES neuron has a single unbranched dendrite, whereas the multidendritic MD neuron, as its name implies, has a complex dendritic tree.

From a genetic screen that was designed to find mutations that cause defects in dendrite development, Moore *et al.* identified a gene that they named *hamlet* (or *ham*), after Hamlet's "To be or not to be" soliloquy in Shakespeare's play. This mutation caused ES neurons to adopt all the molecular and morphological characteristics of MD neurons. Conversely, ectopic expression of the HAM protein in the IIB precursor transformed its MD progeny into an ES neuron with a single dendrite.

The *ham* gene is expressed in the IIIB precursor, but not in the MD neuron, and its expression is maintained in the ES neuron as it differentiates, consistent with a role in preventing elaboration of the dendritic arborization in ES neurons. However, it is possible that HAM controls more fundamental aspects of neuronal identity, and that its effects on dendrite development are secondary. To find out, the authors expressed HAM in postmitotic MD neurons. They found that they could generate cells that continued to express MD-specific genetic markers, but had a single unbranched dendrite. So, in cells that are already committed to the MD lineage, HAM can suppress dendritic branching without completely switching the fate of the cell.

The *ham* gene seems to encode a transcription factor, which presumably initiates a cascade of events that culminates in the suppression of dendritic branching. The identification of the downstream targets of HAM should provide a fruitful line of research for the future. Genes with similar sequences to *ham* have been identified in higher organisms, including humans, so it will be interesting to see whether the binary switch from branched to unbranched dendritic morphology has been conserved during evolution.

Heather Wood

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