the APP cytoplasmic tail then creates a truncated APP product that is more susceptible to Aβ production. This results in a vicious cycle of Aβ production and caspase activation. In a second potential pathway, presenilin mutations initially potentiate caspase activation, which leads to caspase cleavage of the APP cytoplasmic tail and increased Aβ production. Elevated levels of Aβ then cause more caspase activation, again resulting in a vicious cycle of apoptosis and generation of Aβ. Both of these pathways link apoptosis and caspase activation with increased production of Aβ. Based on earlier findings, increased release of calcium into the cytosol (calcium dyshomeostasis) could be central to these pathways, as elevated levels of intracellular calcium have been linked to both increased production of Aβ13 and apoptosis6.

Although the results of Gervais et al.4 are certainly provocative, they are not completely consistent with some earlier findings regarding APP processing and Aβ generation. Gervais, Nicholson and colleagues report that the FAD Swedish mutation in APP creates a more favorable recognition site for caspase 6 at the N-terminus of Aβ, perhaps explaining how this mutation leads to increased production of Aβ. Citron and colleagues14 have previously shown that β-secretase cleaves just before the aspartate (aspartate) of Aβ in APP harboring the Swedish mutation. However, caspase 6 cleaves just after the aspartate (see β-secretase site with Swedish mutation in Fig. 1). Additionally, it is not immediately clear how caspase 6 would gain access to the β-secretase site, which resides in either extracellular or luminal compartments, not in the cytosol.

Another problem relates to the observation4 that Aβ generation is facilitated when most of the cytoplasmic tail of APP is removed by caspase 3 cleavage. In stark contrast to this finding, earlier studies15 have shown that truncation of the APP C-terminus actually attenuates Aβ production, suggesting that Aβ production is facilitated by the endocytic pathway. The cleavage of the APP cytoplasmic tail by caspase 3 would remove the clathrin-mediated internalization signals that reside in the C-terminus of APP. Thus, based on these earlier studies, one would have predicted that caspase 3 cleavage would reduce, not increase, Aβ production by abolishing its internalization by clathrin-coated vesicles.

In Alzheimer’s disease research, as in any active area, new and exciting findings are often shadowed by controversy. If subsequent studies ultimately confirm the provocative new data presented by Nicholson and colleagues, caspases will move one step closer to the center of the neuropathogenic cascade in Alzheimer’s disease (Fig. 1). Many would argue that there is insufficient evidence that apoptosis is the main cause of neuron death associated with Alzheimer’s disease. However, even under the assumption that apoptosis is only a minor cause of neuron death, if the small subset of neurons that die by caspases also overproduce Aβ in the process, the direct effects of apoptotic neuron death on cognition may pale in comparison to the effects of increasing Aβ production. The resulting β-amyloid deposits, together with the degenerating neurons themselves, could trigger inflammatory responses potentially capable of killing far more neurons than the original apoptotic events that initiated the process.

In the event that aberrant caspase activation is confirmed as an early initiator of the Alzheimer’s disease neuropathogenic cascade, the decision to devise therapies based on caspase inhibitors must be considered very carefully. Outside the CNS, caspases are indispensable in eliminating tumorigenic cells, which may pale in comparison to the effects of apoptotic neuron death on cognition. The CNS, caspases are indispensable in eliminating tumorigenic cells, which may pale in comparison to the effects of apoptotic neuron death on cognition. Thus, potential side effects of caspase-targeted drugs could involve carcinogenesis and/or involutional organ failure. Moreover, if Nicholson and colleagues are correct that neurons harboring activated caspases become factories for Aβ production, it may be worthwhile to consider therapeutic strategies for prodding these cells into a quick and efficient exit as opposed to sustaining their survival with caspase inhibitors.

An illusory contour, also called a subjective contour, is an apparent visual boundary that we see without a corresponding physical border in the stimuli. In this remarkable illusion called illusory contours, neurons in a visual area respond to an illusory line as if it were a real line with physical boundaries. In this remarkable combined behavioral and physiological study, the authors used a type of visual illusion called illusory contours.

An illusory contour is an apparent visual boundary that we see without a corresponding physical border in the stimuli. For example, a Kanizsa triangle (Fig. 1a) leads us to perceive a distinct triangle that is implicitly defined by a stimulus that is confined to the three corners. Somehow, the visual system appears to fill in the sides of the triangle where there are no physical lines. A second example (Fig. 1b) illustrates an illusory contour defined by interleaved line endings. A contour that connects the end points of the lines is perceived without a physical border.

Fig. 1. Illusory contour stimuli. (a) Kanizsa triangle. A triangular shape is perceived even though only the three corners are physically present. (b) Illusory contour defined by interleaved line endings. A contour that connects the end points of the lines is perceived without a physical border.

angle occluding three circles.

Nieder and Wagner first tested the owls' perception of illusory contours using behavioral techniques. This is not easy, as step-by-step training is required to familiarize animals with the required tasks. First, the owls had to learn to discriminate a triangle or square outlined in white on a black background. In this initial stage, the birds had to ignore overlaid white stripes that would later define an illusory contour. Once they learned to discriminate the shapes reliably, the outlines were removed, and the triangle and square shapes were defined instead by offsetting the white stripes within the shape (as in Fig. 1b). The owls were almost equally good at discriminating these shapes whether they were defined by real or illusory contours. The animals spontaneously generalized the discrimination of real contours to illusory contours without additional training, as they were rewarded randomly on illusory contour trials.

The authors then recorded responses from neurons in the visual Wulst in two other awake, behaving owls. The Wulst is a lamina structure similar to the primary visual cortex of mammals, but it lacks the convoluted sulci and gyri of mammalian cortex. The area of the visual Wulst that Nieder and Wagner studied receives direct input from the thalamus and is roughly equivalent to the primary visual cortex of mammals. Illusory contour stimuli (Fig. 1b) and real lines elicited very similar responses when they were swept across a neuron's receptive field, although the responses were somewhat weaker for the illusory contour stimuli. Neurons appeared to respond to comparable orientations for real lines and illusory contour stimuli, although this was not investigated systematically. These results show that highly complex visual processing has already occurred early in the visual pathway, possibly only two synapses away from the retinal ganglion cells.

Nieder and Wagner are not the first to demonstrate neural responses to illusory contour stimuli. Von der Heydt et al. postulates that neurons that respond to illusory contours do so by combining the outputs of multiple end-stopped neurons. End-stopped neurons are thought to have an additional inhibitory zone at one end of the excitatory zone for a line stimulus, so that they respond well to a terminated line but not to an extended line. A neuron might detect illusory contours by collecting information from multiple end-stopped cells (or 'line-ending detectors') whose receptive field positions and spatial alignment are matched to a stimulus such as Fig. 1b. Note that in von der Heydt's model, the mechanism that responds to illusory contours does not respond to real contours, or vice versa, because the optimal real line orientations for the two mechanisms are orthogonal to each other (as illustrated in Fig. 1b).

Therefore, it seems that a neuron that responds to both illusory and real contours must combine the output of two separate detection mechanisms.

Interestingly, this hybrid structure that combines signals from illusory and real contour processing pathways is very similar to that proposed for the processing of second-order stimuli. A second-order stimulus is a type of texture-defined pattern in which local differences in texture define a border, even though there is no difference in the average luminance (brightness) across this border. As with illusory contours, neurons that respond to second-order stimuli also seem to respond to first-order borders defined by...
The origin of confabulations

Schnider and Ptak suggest that confabulation in amnesic patients results from their failure to suppress currently irrelevant information.

Episodic memory is the system that we use to retain specific autobiographical memories from our own past. It is clear from the study of neurological patients that episodic memory is distinct from semantic memory, which we use to store knowledge. In organic amnesia, which can arise from a variety of different diseases, patients can lose access to the details of virtually all incidents in their lives except for those occurring in the last few seconds. Yet their general knowledge and knowledge of the significance of objects and of word meanings can be preserved, even though they fail to remember the details of any specific incidents from the period when the information was acquired.

Organic amnesia results from the loss of the episodic memory trace or—on some accounts—of the indices for those memories; it is often associated with damage to the hippocampus. There is, however, another class of episodic memory deficit, namely the confabulatory disorders, which are much less well understood than organic amnesia. Confabulations can occur in patients with a number of etiologies, but they are most closely associated with the effects of aneurysms of the anterior communicating artery. If the aneurysm ruptures, it can cause lesions of the ventromedial frontal lobes and the basal forebrain. How such lesions could lead to confabulations has been unclear. On page 677 of this issue, however, Schnider and Ptak present striking new evidence that such patients are unable to suppress associations that are irrelevant to the current memory task, but are simply brought to mind by the situation.

Most confabulating patients perform poorly on many measures of memory,