

NEUROSCIENCE

Detailed Differences

Stefan Leutgeb

Our subjective experience might tell us that events are unprecedented, even though many situations that we encounter from day to day have prominent similarities and may only differ in important detail. To form separate memories for each day and for the many events that occur within a day, it is thus necessary to keep them distinct by somewhat ignoring the similarities and emphasizing the differences. Evidence for such a process, called “pattern separation,” has been found to occur in the hippocampus—specifically, the dentate gyrus and CA3 regions—in the rodent brain (1–5). On page 1640 of this issue, Bakker *et al.* (6) report that the human dentate gyrus and CA3 regions have the same function, evidence that the contribution of the hippocampus to memory processing is common across mammalian species, including humans.

To test whether pattern separation can be found in the human medial temporal lobe, a brain region that is central to memory storage (7) (there are two lobes, one each on the left and right hemispheres of the brain, and each contains a hippocampus), Bakker *et al.* used functional magnetic resonance imaging (fMRI) to investigate the incidental encoding of visual images by human subjects. While being scanned, subjects were shown images that were initially new to them and were then repeated after approximately 30 other images had been shown. In this design, greater brain activity was seen within the medial temporal lobe during the first presentation of the images, whereas such activation was lower in these same regions when an earlier stimulus was repeated (neither observation is surprising nor unexpected for this standard procedure).

Bakker *et al.* then varied the approach, using visual stimuli that were very similar, but not absolutely identical, to those previously pre-

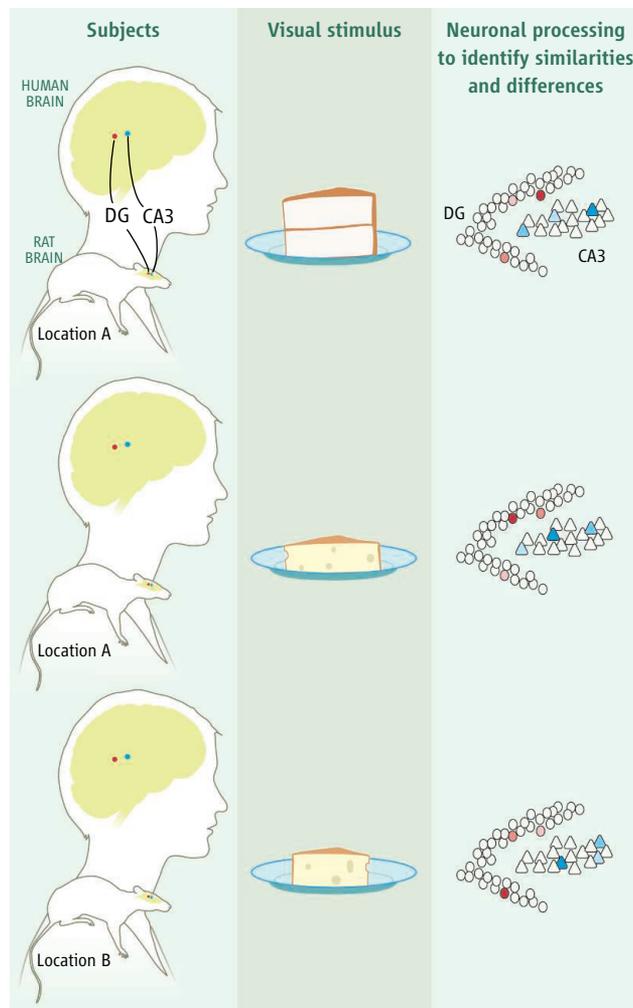
sented. If the subjects were lured into thinking that an imperfect copy was identical to a previously shown stimulus, they would respond as if it were an exact repetition. If they succeeded in detecting the small difference, they would recognize the slightly altered stimulus as new and would display brain activity of similar amplitude as during the first presentation of a visual stimulus—a so-called “novelty signal.” The authors found that only two areas embedded in the left and right dentate gyrus and CA3 regions of the hippocampus detected imperfections and responded with a novelty signal to the slightly altered replicas.

Brain imaging shows that, as in other animals, the human hippocampus has regions that help us keep our memories from becoming jumbled.

In combination with earlier studies in rodents (1–5), the current findings show a striking convergence in identifying a common function for the hippocampal dentate gyrus and CA3 regions across mammalian species. All these studies identify pattern separation processes in specific neuronal populations in these regions. However, as a consequence of not being able to resolve neuronal activity between these two subregions with the currently available technology, Bakker *et al.* have actually detected pattern separation in the combined activity signal from both areas. The relative role of either region therefore has

not yet been directly observed in humans, as it has in rodents (see the figure). Theoretical studies (applying to all mammals) have pointed to a pronounced influence of the dentate gyrus on CA3 at the time of new learning of a separate pattern (8–10), which suggests that these areas may be functionally coupled at the time of recording a novelty signal, as in the current fMRI study.

By contrast, recent studies in rodents have shown that pattern separation may not be based on a unitary network mechanism—that is, the one-on-one activation of CA3 neurons by dentate gyrus neurons—but rather might rely on two types of neuronal processing activities in these regions. The rodent dentate gyrus shows a more pronounced encoding of differences between similar sensory input patterns that occur at a single location (4). CA3 adds another layer of pattern separation that effectively distinguishes different locations by activating different neuronal subpopulations (2–4). The latter mechanism suggests that pattern separation is automatically achieved by neuronal networks that can activate a randomly selected set of CA3 neurons at each new location. If such new activation of cells is initially not bound to common sensory features (11), it is an efficient process to distinguish stimuli or events that would otherwise share a large number of common sensory features.



Memory is in the details. The dentate gyrus (DG) and CA3 regions in the human and rodent brain function in distinguishing stimuli (or events) that may otherwise seem similar. In rodents, two distinct processes in the DG and CA3 select different neuron activation patterns for each sensory input and location.

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It is not yet clear what the precise cellular mechanisms are, in humans or other animals, that generate novel and separate neuronal firing patterns (the composition of electrical impulses that neurons discharge when excited by a stimulus) for images that share a striking number of common features. However, the mechanisms require that neuronal firing is initially not strongly influenced by the large number of visual features that are shared between similar images (12). It also remains to be determined whether neuronal processes that accentuate differences between sensory inputs in humans could be mechanistically related to those that select new, random neuronal firing patterns for spatial locations in rodents.

If such strong pattern separation is not available in other cortical architectures of the brain, it could be one of the defining processes that make the hippocampus and its

connected regions in the medial temporal lobe essential for automatically recording detailed memories in humans and other mammals. It will therefore be important to address whether any related separation of sensory inputs also occurs outside of the medial temporal lobe, although such processes might be more difficult to identify if they are not bound to novelty signals in the same way as in the hippocampus. Conversely, it will be important to find how pattern separation and novelty signals might be integrated in the dentate gyrus and CA3 and across the entire medial temporal lobe to give rise to memory for detailed differences but still let us see the big picture. Although these questions are challenging to address even in animal models, the findings of Bakker *et al.* have paved the way for a new category of imaging studies that can investigate neuronal network mechanisms in the human brain.

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ATMOSPHERIC CHEMISTRY

Rethinking Ozone Production

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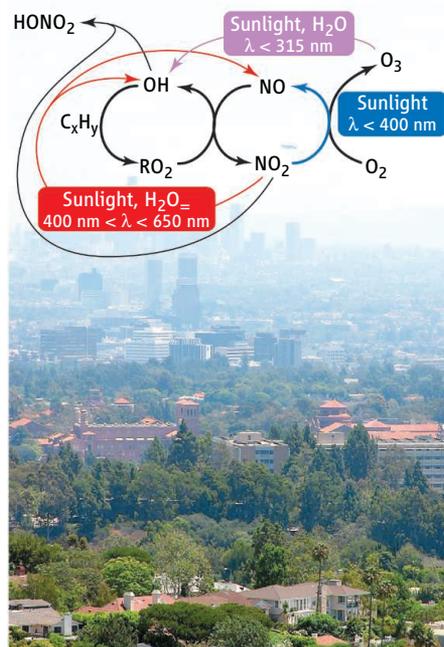
More than a hundred million people live in cities that fail to meet international standards for air quality. Efforts to improve conditions in these urban areas have usually focused on reducing emissions of reactive hydrocarbons (such as unburned gasoline vapors), nitrogen oxide free radicals (NO and NO₂, together known as NO_x), and primary and secondary sources of particulate matter (such as diesel smoke and sulfur dioxide). Control strategies have changed over time in response to evolving understanding about atmospheric photochemistry and the impact of urban emissions on air quality downwind of cities (1, 2). The results reported by Li *et al.* on page 1657 of this issue (3) may require another rethinking of these control strategies.

There are three essential ingredients for producing ozone, O₃, in urban atmospheres: sunlight, NO_x, and hydrocarbons (see the first figure). Ozone production chemistry is initiated when hydroxyl free radicals, OH, are produced from water vapor. Classical theory suggests that the O-H bond in water is broken by excited-state oxygen atoms produced in the

photolysis of ozone. In the atmosphere, OH oxidizes hydrocarbons to produce peroxy radicals, RO₂ (where R is a hydrogen atom or carbon-containing fragment). In the presence of NO_x, the RO₂ radicals convert NO to NO₂; subsequent photolysis of NO₂ yields O₃. When sufficient amounts of NO are available, the chemistry is catalytic: For each OH produced from water, many hydrocarbons can be oxidized and large amounts of ozone produced. However, when NO₂ levels become high, the loss of OH to nitric acid, HONO₂, slows the reactivity, and the rate of ozone production drops. As a result, in many cities, including Los Angeles, ozone levels are generally higher on weekends, when NO₂ levels are lower due to the lack of truck traffic.

Li *et al.* add another level of complexity to the story. In laboratory experiments, they show that excited-state NO₂ (denoted NO₂^{*}) may also break the O-H bond in water, yielding OH and HONO. NO₂^{*} is produced in the atmosphere when NO₂ absorbs sunlight between 400 and 650 nm. Li *et al.* find that for typical urban conditions, 1 in 10,000 of the NO₂^{*} molecules produced reacts with H₂O to produce OH and HONO. Despite this low efficiency, the rate of OH production from NO₂^{*} in urban atmospheres can be comparable to the classical OH source (ozone photolysis). The amount of OH produced from NO₂^{*}

Laboratory data suggest that atmospheric models are missing a source of hydroxyl, which plays a central role in tropospheric ozone production.



Ozone chemistry. When NO and NO₂ are present, O₃ is produced in the catalytic oxidation of hydrocarbons by the OH radical. Classical theory suggests that the chemistry is initiated when OH is produced after the photolysis of ozone in the presence of water vapor (purple). Li *et al.* find that the O-H bond in water can also be broken by excited-state NO₂ (red). This chemistry increases the amount of OH and thus O₃ production.

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