RNA interference, benzenoid volatiles accumulated in petunia petal cells from ongoing biosynthesis in amounts that were sufficient to disrupt cell membranes. The inherent toxicity of plant volatiles to living tissue is a reminder that despite their pleasant odors, these perfumes may be active in plant defense. Many floral volatiles play a role in warding off unwanted visitors, such as nectar-robbing ants (8).

The discovery of PhABC-G1 should stimulate the search for other cell components involved in volatile trafficking in plants. Given their potential toxicity, these compounds may be transported in vesicles from their site of synthesis to the plasma membrane to minimize contact with other cell components (5). After plasma membrane passage, volatiles must still traverse the cell wall before reaching the cuticle and wax layers on the surface. For lipophilic volatiles, passage through the hydrophilic cell wall may be facilitated by association with proteins similar to lipid transfer proteins, which are known to mobilize cutin and wax biosynthesis precursors (9).

At an early stage of evolution, volatile organic compounds may have been passively released from plants by simple diffusion through membranes. However, the work of Adebesin et al. shows that an ATP-driven membrane transporter has been recruited for volatile emission in petunia petals and likely in many other species and organs as well. The investment of energy and protein machinery in volatile emission makes sense because active transport proteins can export volatiles at faster rates than diffusion and may prevent the toxic buildup of products in cells allowing for faster biosynthetic rates. The resulting increases in emission rate may have in turn allowed plants to increase the transmission range of their volatiles, target new receiver organisms, and add new functions to their volatile communication systems. Active transport proteins should also enable tighter controls on volatile emission rates, which might have permitted plants to convey volatile-encoded messages with greater precision.

**REFERENCES**


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**SCIENCE**

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**Rejuvenating brain plasticity**

Can the potential to change be restored in the adult brain?

By Vassilis Kehayas and Anthony Holtmaat

What if we could unlock the potential of the brain to change at will? Could we then rejuvenate old brains? On page 1352 in this issue, Blundon et al. (1) demonstrate that with a pharmacological intervention, the brain’s cortical plasticity in adult mice could be restored to an extent that is normally seen only in juveniles. The findings should spur research into noninvasive therapies to treat conditions relating to perceptual deficits.

In the mammalian cerebral cortex, largely specialized areas receive information related to their corresponding sensory modalities. Within these areas, the external world is represented in a neatly organized topographic map. In the auditory cortex, for example, neurons in the rostral part are preferentially activated by high-frequency sounds and in the caudal part by low-frequency sounds (see the figure). During an animal’s early postnatal life, known as the critical period for cortical map plasticity, the organization of this map highly depends on sensory experience (2, 3).

In most animal species, the ability to change topographic maps largely comes to a halt relatively shortly after birth, for good reasons. After the appropriate circuits are fixed in place, it would be unnecessary to preserve the potential for large-scale changes because the sensory world (such as the gamut of experienced sounds) will remain largely stable. At this stage, only small-scale changes in local cortical networks are still observed upon experience and learning (4, 5).

It would be useful, though, if we could re-instate the brain’s potential to undergo large-scale changes. For example, in pathological conditions in which the connections between the sensory organs and the cortex are severed, unlocking such plasticity could accelerate recovery. There have been various attempts to induce cortical map plasticity in adult animals. One successful approach consists of pairing a sensory stimulus with activation of the nucleus basalis (6, 7). The nucleus basalis, which is located in the basal forebrain, is a major source of the neurotransmitter acetylcholine for the cortex. Acetylcholine has been implicated in attention and learning, and its release into the cortex is necessary for plasticity induction with this pairing protocol (8). However, direct activation of nucleus basalis requires invasive surgery.

Previous work has shown that acetylcholine promotes synaptic depression or potentiation (9, 10), phenomena that are thought to underlie forms of map plasticity (11). It was proposed that acetylcholine mediates both effects by increasing release of the neurotransmitter acetylcholine (6, 7). However, direct activation of the nucleus basalis requires invasive surgery.

Unlocking auditory plasticity

Sound is paired with an A1 receptor antagonist (FR194921) to expand the cortical representation of a target sound frequency (green area), a phenomenon that is mediated by the increase of synaptic plasticity at thalamocortical connections.

**Target sound**

9.8 kHz

**Auditory cortex**

**A1 receptor**

**Glutamate receptor**

**Glutamate**

**Adenosine**

**Presynapse**

**Postsynapse**

**Thalamus**

**Cortical map plasticity**

Adult mouse

FR194921

5 kHz

9.8 kHz

35 kHz

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mimic glutamate from the thalamus, a deep brain structure that relays sensory information to the cortex. Acetylcholine achieves this by diminishing the signaling from presynaptic adenosine A1 receptors (A1Rs) on the thalamic neuronal projections to the cortex. A1R is a member of the adenosine receptor family, which is thought to be a target of caffeine.

Blundon et al. exposed mice to repeated stimulation with a pure-tone sound (the target sound frequency) for more than 5 days, while simultaneously rendering the A1R signaling inactive with various genetic and pharmacological strategies. Among others, the authors used FR194921, which is a blood-brain barrier-permeable and specific A1R antagonist (12). In all cases, they observed a proportional increase in the cortical area that preferentially responded to the target sound frequency. Importantly, this effect could be achieved only if A1R signaling was suppressed in the auditory thalamus but not in the cortex.

To verify that cortical map plasticity could also be detected in individual neurons, the authors measured tone-evoked activity in individual cortical neurons over time, using a genetically encoded sensor of calcium transients. Suppression of A1R signaling in thalamocortical neurons led to an overall shift in the proportion of neurons responding preferentially to the target frequency. Conditional A1R gene deletion in auditory thalamus increased sound frequency-discrimination in a prepulse inhibition experiment, indicating that their auditory perception had changed.

The fact that cortical map plasticity could be induced in adult animals by suppressing A1R signaling suggests that this is a mechanism that is related to the demarcation of the critical period for map plasticity. Indeed, Blundon et al. found that both the expression of an enzyme that produces adenosine [5'-nucleotidase ecto (NT5e)] as well as adenosine itself increase in the thalamus of wild-type adult mice but not in the cortex. Not surprisingly, disruption of NT5e expression in the auditory thalamus also led to enlarged representations of the target sound. This effect was reversed when the metabotropic glutamate receptor-5 (expressed by cortical neurons) was blocked, in line with previous observations (9, 10).

Conversely, auditory cortical map plasticity in young animals, which can normally be produced by tone exposure alone, was prevented when they were treated with an A1R agonist.

Blundon et al. convincingly show that suppression of adenosine signaling in thalamic projections to the auditory cortex facilitates map plasticity and alters basic perception in adult animals. Together with previous work, this further establishes the role of thalamic activity in defining the critical period for map plasticity. Importantly, the findings of Blundon et al. may open avenues for noninvasive alterations of cortical map plasticity after the closing of its critical period.

The findings will also prompt research to further investigate the circuit-level mechanisms that are involved in this type of cortical plasticity. For example, what is the role of inhibitory circuits? The authors found proportionally more neurons that responded to the target tone, rather than an increase in individual neurons’ responses. This suggests that the excitatory cortical circuit is in part affected indirectly and raises the possibility that disinhibition is involved, which would be congruent with previous findings that blocking inhibition unlocks synaptic potentiation (10, 13).

Furthermore, it will be interesting to test whether other sensory systems are susceptible to the same type of plasticity. The thalamocortical pathway of the auditory system is distinct in some respects. For example, the auditory cortex represents a higher-order node in the network in comparison to other sensory cortices because the thalamocortical information it receives has gone through more synapses (14) and may be transformed in more diverse ways (15). Additionally, thalamocortical synaptic plasticity in auditory cortex involves distinct postsynaptic mechanisms (9, 10). Insights into the mechanistic underpinnings of this type of cortical plasticity will benefit the development of noninvasive methods to increase plasticity specifically in targeted cortical areas for clinical applications.

**REFERENCES AND NOTES**


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