Although the results are interesting, it is a pity that the logic of using knock-in approaches was not continued with the *APP* gene. Using a humanized knock-in *APP* sequence would have mimicked the human situation even better. Nevertheless, the results strongly support the pathogenic role of Aβ43 *in vivo*: the substantial rise in soluble and insoluble Aβ43 apparently caused memory impairment, even in young mice. Notably, relative and absolute levels of Aβ42 and Aβ40 were unchanged in the animals. Thus, the authors concluded that the Aβ43 species might trigger an early Alzheimer's disease–related memory loss in these animals. Finally, Saito *et al.*[3] demonstrate a correlation between the steady-state levels of Aβ43 generated by cells expressing different familial presenilin 1 mutant proteins and age of onset in people with the corresponding familial Alzheimer's disease. A similar correlation was found before with Aβ42 (ref. 9), but the new result strengthens the hypothesis that Aβ43 contributes to Alzheimer's disease.

Although this suggestion logically follows the experimental results, one must be cautious regarding extrapolation to human Alzheimer's disease for several reasons. First, despite the confirmed presence of Aβ43 in amyloid plaques of human sporadic Alzheimer's disease and familial inherited Alzheimer's disease associated with APP and presenilin mutations[10], its concentration is several-fold less than that of Aβ42 (ref. 11), a predominant species in plaques. Second, Aβ43, let alone its longer precursors, is highly hydrophobic and does not easily leave the cell membrane environment[11]. Thus, the role of Aβ43 might still be indirect, driving neurotoxicity mostly by acting as a seed that interacts with the more abundant Aβ species. The role of the cell membrane and lipids in this process also remains poorly understood[12]. Finally, the amyloidogenicity of Aβ43 and Aβ42 has not been extensively compared[10,13]. Other questions raised by work of Saito *et al.*[3] are the extent to which Aβ43 could contribute to the formation of Alzheimer's disease–relevant toxic Aβ conformers, such as human brain-derived dimers[5] or amylospheroids[6], and whether Aβ43 species may drive both sporadic and familial Alzheimer's disease.

Mechanistically, the question remains how exactly the clinical mutations affect the length of the Aβ peptides. This will need careful measurements of kinetic parameters of the γ-secretase enzyme and determination of the effect of the mutations on those properties. Such work is only possible with *in vitro* assays. However, the authors did make a series of intriguing observations in their *in vivo* experiments. For instance, Aβ43 accumulation was associated with Aβ46 accumulation in homozygous presenilin 1 R278I fibroblasts, corroborating a previously proposed model of tripeptide-wise APP cleavage[11,14] (**Fig. 1**). In addition, Saito *et al.*[3] investigated an interesting allelic series of fibroblast mutant cell lines. From those experiments, it emerged that the production of Aβ43 is lower in heterozygous cells that contain one disease allele and one wild-type allele than in cells that contain one disease allele and one knockout allele. The authors suggest that intermediary cleavage products of the consecutive Aβ processing, such as Aβ43, can be transferred to the wild-type allele for further processing (**Fig. 1**). In the absence of the wild-type allele, processing stops at the Aβ43 form, which is therefore released more abundantly. However, further support for this idea can only come from detailed *in vitro* kinetic studies.

In conclusion, this study points to the importance of qualitative changes in the Aβ peptide spectrum, as opposed to quantitative changes in total Aβ peptide release, for our understanding of Alzheimer's disease and the role of Aβ peptides in neurodegeneration. The apparent paradox that loss of function of γ-secretase resulting from clinical mutations[15] can lead to decreased total Aβ peptide generation while still causing amyloid plaques and Alzheimer's disease can only be resolved if it is accepted that qualitative changes in the Aβ peptides are more important than quantitative changes. This has obvious implications for drug development.

COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details accompany the full-text HTML version of the paper at www.nature.com/natureneuroscience/.

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Reward and autoreceptors

Both natural rewards and addictive drugs increase extracellular dopamine (DA) in the striatum. Although studies have found that DA receptors are involved in addiction, the results are conflicting. Susceptibility to drug addiction is correlated with reduced availability of striatal D_2 receptors, yet D_2 receptor knockout mice show reduced responses to drugs of abuse. These contradictory results may arise because there are two populations of D_2 receptors. Most D_2 receptors are postsynaptic, responding to DA release from striatal dopaminergic neurons. However, D_2 receptors are also expressed presynaptically on DA-releasing neurons (autoreceptors), which exert negative feedback. Previous genetic and pharmacological studies have not been able to differentiate between these two populations of D_2 receptors. On page 1033, Bello and colleagues dissect the selective role of D_2 autoreceptors and find that deleting D_2 autoreceptors increases DA synthesis and release, resulting in increased sensitivity to cocaine.

The authors created mice lacking D_2 receptors only in DA-releasing neurons (autoDrd2KO mice). Striatal dopaminergic neurons in autoDrd2KO mice did not show inhibitory currents in response to D_2 agonists. This lack of negative feedback was accompanied by increased DA synthesis and release. AutoDrd2KO mice were hyperactive, and hypersensitive to cocaine. They exhibited increased cocaine-seeking in a conditioned place preference procedure and worked harder for a food reward in an operant conditioning procedure, suggesting that the role of D_2 autoreceptors extends to natural rewards.

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