This Week in The Journal

The Perils of Neuroimaging Genetics for Cognitive Traits

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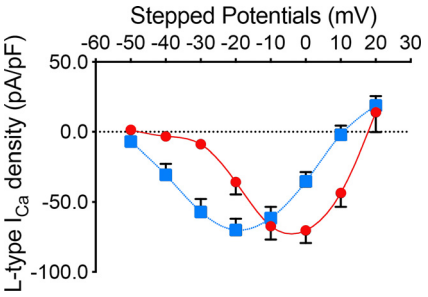
(see pages 8778 – 8787)

The risk of developing neurological or psychiatric conditions is influenced by genetic makeup. Sometimes a single mutation inevitably causes a disease, but such large effects are rare. More often, the effects of disease-linked mutations are modulated by variations in other genes, leading to variable phenotypic outcomes. But the most common gene variants have small effect sizes that can only be detected by testing thousands of people. This is especially true of genes influencing complex traits like cognitive ability and personality. These traits are influenced by tens of thousands of genetic variants, each of which has a tiny effect. To identify such variants, researchers often turn to intermediate phenotypes, such as brain structure or activity patterns, assuming that the variants will have larger, more detectable effects on these biological characteristics than on complex traits. But accumulating evidence suggests that this assumption is wrong.

With this in mind, Uddén et al. sought to replicate a study in which three single-nucleotide polymorphisms (SNPs) were found to be associated with brain activity patterns in three cortical areas as healthy subjects read or listened to sentences (Pinel et al., 2012, J Neurosci 32:817–825). To improve their chances of finding an effect in a group of 94 participants, those authors had focused on two genetic loci (*FOXP2* and *KIAA0319/TTRAP/THEM2*) in which rare mutations had previously been linked to language impairment and on three cortical areas in which activity was atypical in people with those impairments. But using a sample population four times as large, with the power to detect much smaller effects, Uddén et al. failed to replicate any of the main findings of that study. Moreover, Bayesian analysis provided substantial-to-strong support for the null hypothesis that the three SNPs have no effect on task-related activity in the three cortical areas examined. The authors conclude that effects of SNPs on brain activity measured with fMRI may be just as small as their effects on complex traits. Therefore, hundreds of subjects should be tested and care should be taken to account not only for the number of SNPs tested, but also for the number of brain areas and types of activity examined.



The current–voltage curve of L-type channels in Tg2576 neurons (blue) is shifted to the left of that in wild-type neurons (red), indicating the channels in Tg2576 neurons open at lower membrane potentials. See Ishii et al. for details.

Effects of Aβ on Ca^{2+} Channel Function in Hypothalamus

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(see pages 8816 – 8825)

Alzheimer's disease (AD) is characterized by cognitive decline accompanied by aggregation of β-amyloid (Aβ) and tau protein in the entorhinal and parahippocampal cortex. Other brain areas and functions are also affected in AD, however. For example, hypothalamic dysfunction is thought to underlie the weight loss and sleep disruption that occur in the early stages of AD and may contribute to cognitive impairment. In addition, Aβ deposits accumulate in the hypothalamus, and this area begins to atrophy in the early stages of AD. As in other brain areas, however, soluble Aβ might be responsible for hypothalamic dysfunction in AD. Indeed, previous work by Ishii et al. showed that before plaques appear in transgenic mice that overexpress an AD-linked mutant form of amyloid precursor protein (Tg2576 mice), Aβ altered the function of neurons in the hypothalamic arcuate nucleus that express neuropeptide Y (NPY) and regulate food intake. Specifically, Aβ reduced the responses of these neurons to ghrelin, which is produced by the gut and stimulates eating, and leptin, which is released by fat cells and inhibits eating.

Because the dysregulation of intracellular calcium levels contributes to AD-associated neuronal dysfunction in other brain areas, Ishii et al. hypothesized that altered calcium-channel function contributes to the depolarization of NPY-expressing neurons in Tg2576 mice. Consistent with this, intracellular calcium concentrations were higher in NPY-expressing neurons in Tg2576 mice (and in Aβ-treated wild-type neurons) than in untreated controls. This effect was likely mediated by a shift in the activation threshold of L-type calcium channels to a lower potential. Blocking L-type channels hyperpolarized the resting potential and reduced spiking in NPY-expressing neurons from Tg2576 and Aβ-treated wild-type neurons.

The ability of ghrelin to increase intracellular calcium levels—and of leptin to decrease levels—was absent in Tg2576 NPY-expressing neurons. Importantly, L-type channel blockers restored the ability of ghrelin to increase intracellular calcium levels in Aβ-treated wild-type neurons and to induce eating in Tg2576 mice. These results suggest that Aβ alters the properties of L-type calcium channels in NPY-expressing hypothalamic neurons, thus increasing the resting activity of these neurons and blunting their responses to hormones that signal hunger and metabolism. Consequential dysregulation of energy balance might exacerbate the effects of Aβ in other brain areas in AD.

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