Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Diaschisis: An Old Concept Brought to New Life

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Review of Ishii, Kubo et al.

Diaschisis, a Greek term meaning "split throughout," was introduced to neurology in 1914 by Monakow. This concept suggests that damage in one focal area of the brain can affect distant brain regions. Diaschisis was originally described in patients with ipsilateral paralysis following focal brain lesions (Finger et al., 2004). With the advent of brain imaging techniques, we now know that focal damage can result in large connectivity abnormalities in the brain (for review, see Carrera and Tononi, 2014). Traditionally, the concept of diaschisis was applied to acute brain injuries, as seen in head trauma or stroke. However, a similar phenomenon may occur in developmental disorders, as illustrated in recent work published in *The Journal of Neuroscience* (Ishii, Kubo et al., 2015).

Ishii, Kubo et al. (2015) used *in utero* electroporation in mice to ectopically express genes related to neuronal migration, inducing the formation of focal neuronal heterotopias (focal areas of ectopic tissue) (Ishii, Kubo et al., 2015). The presence of these heterotopias persisted long after birth. Although these heterotopias were located in the somatosensory cortex, their presence resulted in early gene activation in the medial prefrontal cortex (mPFC) and in disruption of behavior associated with the mPFC. No direct connections were found between the somatosensory cortex and the mPFC, suggesting that dysregulation in the mPFC may have been the result of disrupted circuitry, reminiscent of diaschisis.

Furthermore, even though the lesion was isolated to a relatively small region of the somatosensory cortex, Ishii, Kubo et al. (2015) found that the animals had decreased threshold for seizure induction as well as deficits in spatial memory and decreased social dominance, both features associated with the prefrontal cortex. When the abnormal cells in the somatosensory cortex were stimulated through DREADD (designer receptor exclusively activated by designer drug) technology, the overt behavioral differences were rescued.

The authors indicate that their results are important for understanding the neurological and behavioral aspects of individuals with distinct heterotopias, which are associated in the patient population with increased seizure susceptibility and cognitive dysfunction. However, the results obtained from their study have the potential to be even more widespread in their applicability and may demonstrate how mutations in a few neurons, or a small area of the brain, can lead to widespread cognitive dysfunction.

One disorder, for which this knowledge may be particularly applicable is tuberous sclerosis complex (TSC). TSC is caused by heterozygous mutations in *TSC1* or *TSC2* and is marked by a high incidence of benign tumor growths in various organ systems, including the brain, liver, and kidney. These tumor growths are postulated to develop as a result of somatic loss of function in the second allele of either *TSC1* or *TSC2*, resulting in complete loss of function of the gene product, a phenomenon called loss of heterozygosity (LOH). LOH has consistently been demonstrated in kidney tumors (Henske et al., 1996, 1997). The other hallmark of TSC is a constellation of neurological symptoms, including cortical and cerebellar tuber formation, seizures, intellectual disability, and autism.

The cause of brain involvement in TSC is an active area of research. Although the LOH model is the prevailing model for the peripheral pathogenesis of TSC, LOH has not been detected in the brains of most patients with TSC (Henske et al., 1996). This suggests that either an alternate mechanism is responsible for brain/neurological manifestations of the disorder, or that LOH events in the brain of patients are present at too low of a frequency to reliably detect.

Extrapolating from the results presented by Ishii, Kubo et al. (2015), circuitry changes arising from the presence of isolated LOH events may profoundly impact distant brain areas, leading to seizure formation and cognitive dysfunction. If only a few distinct cells in the brain develop LOH, it would be nearly impossible to detect by current sequencing techniques, but may still yield broad circuitry changes in remote brain regions and be the cause of the behavioral mani-

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festations and seizures observed in TSC. Results from experiments in mice are consistent with this hypothesis. Electroporation has been used to sporadically knock-out *Tsc1* and achieve LOH of *Tsc1* in isolated cells in the brain (Feliciano et al., 2011). The resulting mice have a small circumscribed lesion that produces a neurological phenotype, i.e., increased seizure susceptibility.

The studies by Feliciano et al. (2011) and Ishii, Kubo et al. (2015) lay the groundwork for understanding the potential of focal abnormalities to cause widespread neuropathology. They point to the need for further study of isolated LOH events in the context of TSC as well as widespread effects found in other neurological disorders characterized by migration abnormalities. In addition, they demonstrate that studying isolated affected brain regions may not be sufficient for understanding neurological disorders. The circuit as a whole must be considered, with the knowledge that discrete brain abnormalities may yield dysfunction in more distant brain regions.

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