Propagation of focal imbalance through neuronal circuits

Ken-ichiro Kubo[1], Kazuhiro Ishii[1, 2], Masaki Kakeyama[3, 4], and Kazunori Nakajima[1]

[1]Department of Anatomy, Keio University School of Medicine, Tokyo, 160-8582, Japan
[2]Present Address: Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287, USA
[3]Laboratory for Systems Neuroscience & Preventive Medicine, Waseda University Faculty of Human Sciences, 2-579-15 Mikajima, Tokorozawa 359-1192, Japan
[4]Laboratory of Environmental Health Sciences, Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, 113-0033, Japan

We thank M. Sare for her insightful comments on our study. We totally agree with her observation that, “the results obtained from their study have the potential to be even more widespread in their applicability”. She points out the tuberous sclerosis complex (TSC) as being an example of cognitive dysfunction caused by mutations in a few neurons. In addition, our results might also be considered as a demonstration of how abnormal positioning of neurons can potentially exert widespread effects on brain functions. One candidate disorder with ectopic neurons is a subpopulation of schizophrenia-related diseases, since an increased density and altered spatial distribution of subcortical white matter neurons have been repeatedly reported in these disorders. Approximately 25% of the overall patient population with these disorders is reported to show robust alterations in the density of white matter neurons (Connor et al., 2011). Another candidate disorder is autism spectrum disorder, in which the presence of supernumerary neurons within the white matter is one of the most commonly observed histological abnormalities (Hutsler and Casanova, 2015). The abnormal distribution of neurons in the white matter might at least partly underlie the cognitive dysfunction in these disorders. As shown in Fig. 2 of our paper (Ishii et al., 2015), ectopic neurons in the white matter, especially when they have the lineage of neurons in the superficial layers, are assumed to profoundly affect the cortico-cortical axonal projections, which might contribute to connectional changes that have been proposed in the above-mentioned disorders (Stephan et al., 2009; Hutsler and Casanova, 2015). We

must admit, however, that the supernumerary neurons observed in the above-mentioned disorders do not generally form cell aggregates and may thus differ in their effect on the functions of remote brain regions. Future studies will be required to address this issue.

While our paper was in press, an important hypothesis relating to excitatory/inhibitory balance in autism spectrum disorder was presented (Nelson and Valakh, 2015). According to this hypothesis, homeostatic mechanisms try to compensate for the perturbed excitatory/inhibitory balance, but become inadequate and/or maladaptive during development. Homeostatic mechanisms may change the excitability of circuits in high-order regions, i.e., the association and limbic regions. In our paper, the ectopic neurons within the heterotopias are thought to have abnormal excitatory/inhibitory balance, at least at some specific times during development, since the proportion of GABA-positive neurons in the heterotopias was lower and the seizure susceptibility was increased, as shown in Fig. 1 (Ishii et al., 2015). The change in the excitatory/inhibitory balance in a focal region (heterotopias) might be propagated via compensatory mechanisms activated to maintain circuit homeostasis that involve multiple regions (e.g., the prefrontal cortex). In addition to the circuit as a whole, the compensation through circuits might also have to be considered, especially in cases of developmental disorders.

References

Connor CM, Crawford BC, Akbarian S (2011) White matter neuron alterations in schizophrenia and related disorders. International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience 29:325-334.

Hutsler JJ, Casanova MF (2015) Review: Cortical construction in autism spectrum disorder: columns, connectivity and the subplate. Neuropathol Appl Neurobiol.

Ishii K, Kubo K, Endo T, Yoshida K, Benner S, Ito Y, Aizawa H, Aramaki M, Yamanaka A, Tanaka K, Takata N, Tanaka KF, Mimura M, Tohyama C, Kakeyama M, Nakajima K (2015) Neuronal Heterotopias Affect the Activities of Distant Brain Areas and Lead to Behavioral Deficits. The Journal of neuroscience : the official journal of the Society for Neuroscience 35:12432-12445.

Nelson SB, Valakh V (2015) Excitatory/Inhibitory Balance and Circuit Homeostasis in Autism Spectrum Disorders. Neuron 87:684-698.

Stephan KE, Friston KJ, Frith CD (2009) Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophrenia bulletin 35:509-527.