Commentary

Bridging the Gap Between Mouse Behavior and Human Cognition in Neurofibromatosis Type 1

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A new study by Zimerman and colleagues in this issue of EBioMedicine is one of the first to attempt to confirm animal-generated hypotheses in human patients and is of significant interest to NF1 cognitive research (Zimerman et al., 2015). The authors examined the relationship between inhibitory GABAergic neurotransmission and motor skill learning in a highly selected sample of NF1 adults with normal cognitive and functional abilities. Compared to matched controls, the NF1 group demonstrated deficient learning of a fine motor task over a five day period, with impairments driven by poorer initial learning (fast online) and reduced offline consolidation of learned skills between training sessions. This was accompanied by a double-pulse transcranial magnetic stimulation (TMS) experiment assessing short intracortical inhibition (SICI) during performance of a reaction time task as used previously (Heise et al., 2010; Hummel et al., 2009). In control participants, reduced inhibition was reported at the end of the reaction time period (i.e. just before movement onset) compared to levels measured at the beginning of the reaction time period (i.e. beginning of movement preparation). In contrast, this task-related modulation of SICI was not observed in patients with NF1, with trends towards increased inhibitory processes. Interestingly, the authors report significant correlations between behavioral improvements and the degree of SICI modulation, with a relative increase in intracortical inhibition associated with reduced levels of skill acquisition for NF1 patients. Interpreted within the context of the animal literature, these findings provide an important step in bridging the gap between animal models and the human condition, suggesting dysfunctional GABAergic neurotransmission contributes to procedural learning in patients with NF1. Results from a recent magnetic resonance spectroscopy study, however, suggests the relationship between GABA levels and the human phenotype is more complex (Ribeiro et al., 2015). Lower levels of prefrontal GABA were identified in children with NF1, which was significantly associated with poorer IQ, but also with better inhibitory control. These data support the notion that abnormal inhibitory neurotransmission contributes to the cognitive phenotype in NF1, however together with the present data by Zimerman et al., they also indicate a more complex relationship between abnormal GABA-ergic neurotransmission and cognitive functions. There might not be a unitary influence of GABA-ergic dysfunction on all cognitive domains with the same impact, but with differing...
relevance depending on factors, such as age, cognitive function or cortical area. Limitations of the Zimerman et al. study include small sample sizes and a highly selected NF1 group controlled for confounding factors that does not represent the broader NF1 population, limiting conclusions that can be drawn.

While these studies have initiated an evidence base for the pathophysiologic correlates of NF1 in the complex human condition, significant work validating meaningful cognitive biomarkers is still required. Identifying cognitive biomarkers, specifically and directly regulated by neurofibromin, would enable smaller pilot studies to demonstrate proof of principle and dose refinement by testing whether promising preclinical treatments normalize pathophysiologic processes in human patients before expensive randomized controlled trials are conducted. Such an approach would result in better informed clinical research, optimizing trial designs based on findings observed in humans.

Conflict of Interest

The author declares no conflict of interest.

Acknowledgments

Dr. Payne’s research is supported by a Murdoch Childrens Research Institute Career Development Award and awards from the US Army Congressionally Directed Medical Research Programs; Neurofibromatosis Research Program (NF140051; NF140033).

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