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Commentary on 'Reproducible brain-wide association studies require thousands of individuals'

Haiku:
Brain and behavior
Individuals differ
They learn and adapt

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A primary assumption of cognitive neurosciences is that brain structure relates to its function and consequently to behavior. Indeed, inquiries assessing genetic relationships between genes and behavior indicate a genetic link, suggesting a shared biological basis (1, 2). At the same time, there are various factors influencing measures of inter- and intra-individual variation in brain structure, function, and behavior. For example, local brain structure and function are not stable features but change across the lifespan (3, 4) and vary as a function of contextual factors, as well as covariates, such as fluid intake (5), time of day (6), blood pressure (7), and sex (8, 9). Moreover, also behavior varies across the lifespan (10) and is modulated, or confounded, by various factors, such as mood (11), social factors (12), and/or time of day (13). In addition, task-based and questionnaire-based markers of the same behavior do not always align (14). Thus, we are left with (i) variable brain metrics, (ii) variable behavioral metrics, mostly measured at a single timepoint in a lot of individuals, and (iii) covariates that may moderate brain–behavior associations.

So, what is the take-home from this? Should any inquiry into the association between covariation of brain and behavior be abolished? We believe not. In our opinion, the work of Marek et al. actually points to an interesting challenge, namely, how to understand individual cognition in the scope of an ever-changing brain structure and function. First, even if brain–behavior associations are not reproducible, it is relevant to understand *why* different subgroups show variable associations between brain and behavior. For example, brain structure has been reported to be differentially linked to fluid intelligence as a function of age (15), and brain function in females may be differentially associated with emotion regulation as a function of the menstrual cycle phase (16). Second, we believe that the question of how brain structure and function relate to behavior needs to go hand in hand with theories on what marker(s) of brain structure and function (area, cortical thickness, volume, in vivo myelin/microstructure, deep white matter, areas, gradients, networks, dynamics) may be relevant for what (kind of) behavioral process and respective functional involvement of which part(s) of the brain. So far, only a little research is done into what dimensions, or substrates, may be relevant for specific types of behavioral variation. Acquiring multimodal brain data, including proxies of microstructure, electroencephalography (EEG), magnetoencephalography (MEG), and high-resolution functional MRI (fMRI), in a small number of individuals using carefully selected behavioral metrics may provide novel mechanistic insights that go beyond associations based on correlating markers of 'cognition' with single indices of local brain structure in large samples.

In sum, we believe not all is lost, but this may be a great opportunity to rethink what we are looking for in the brain and to develop a mechanistic understanding of inter- and intra-individual variation in the brain and behavior. Preregistration of studies, open science, and multimodal acquisitions may help with these endeavors to develop a brain-informed understanding of human cognition in health and disease.

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