Linking human behaviour to brain structure: further challenges and possible solutions

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In their timely article, Genon and colleagues review recent developments in MRI studies aiming to link human behaviour to brain structure (Genon, S., Eickhoff, S.B. & Kharabian, S. Linking interindividual variability in brain structure to behaviour. *Nat. Rev. Neurosci.* **23**, 307–318 (2022))[1]. Over the past decade, they argue, the field has witnessed low replicability of research findings and decreases in effect sizes. They point to the adoption of multivariate approaches as one promising path forward. We endorse their insightful suggestions and would like to draw attention to two additional points, which in our opinion, represent key challenges and possible solutions going forward.

There exists no simple one-to-one relationship between a structural MRI signal and the underlying 'true' brain structure. MRI signals reflect mixed contributions from various structural components within a voxel, and some of these components affect brain functions in drastically different ways. For example, an increase in a quantitative T1 MRI signal can result from decreased myelination or increased axon diameter[2,3] (FIG.1A), which affect signal conduction speed in opposite directions[4]. The gap between the MRI signal and the underlying brain structure poses a considerable challenge to brain structure–behaviour mapping.

Notably, some promising developments are underway to bridge this gap. We want to highlight two such developments: multidimensional and multimodal MRI[5]. By acquiring multiple structural MRI signals, with each signal reflecting a different weighted sum of structural components, these techniques can disentangle and measure individual structural components such as myelin level[6], axon diameter[7] and cell morphology[8]. The measures represent functionally more relevant units of the brain and provide opportunities for mechanistic insights.

Another challenge to brain structure–behaviour mapping is the many-to-one relationship between brain structure and behaviour. As Genon and colleagues noted[1], the field has long relied on the assumption of a linear structure–behaviour relationship. However, recent studies have raised doubts about this assumption, pointing instead towards a many-to-one structure–behaviour relationship, known as 'multiple realizability'. For example, a U-shaped relationship was observed between visual performance and visual cortical volume, suggesting that the degradation of visual performance can result from increased cortical thickness or decreased cortical surface area[9] (FIG.1B). Likewise, a many-to-one relationship exists between network structure and network behaviour[10].

The lack of a one-to-one relationship between brain structure and behaviour adds an important reason for adopting multivariate and machine learning approaches. These approaches can inspect the entire space of structure–behaviour relationships with minimal pre-assumption. A promising application of these approaches, we suggest, is the search for optimal brain structure. It provides opportunities to address what ratio of myelin to axon is optimal for signal conduction, what ratio of white to grey matter is optimal for different domains of behaviour, and other conceptually important questions.

Taken together, the field is challenged, in our opinion, by a lack of one-to-one mapping from MRI to brain structure and from brain structure to behaviour (FIG.1). Progress, therefore, relies largely on the ability to bridge the gap from MRI to brain structure and examine the multiple realizability of behaviour on brain structure.

Recent developments along these lines, such as advanced MRI techniques and advanced statistical approaches, provide opportunities for a better conceptual understanding of how multifaceted human behaviour emerges from human brain structure.

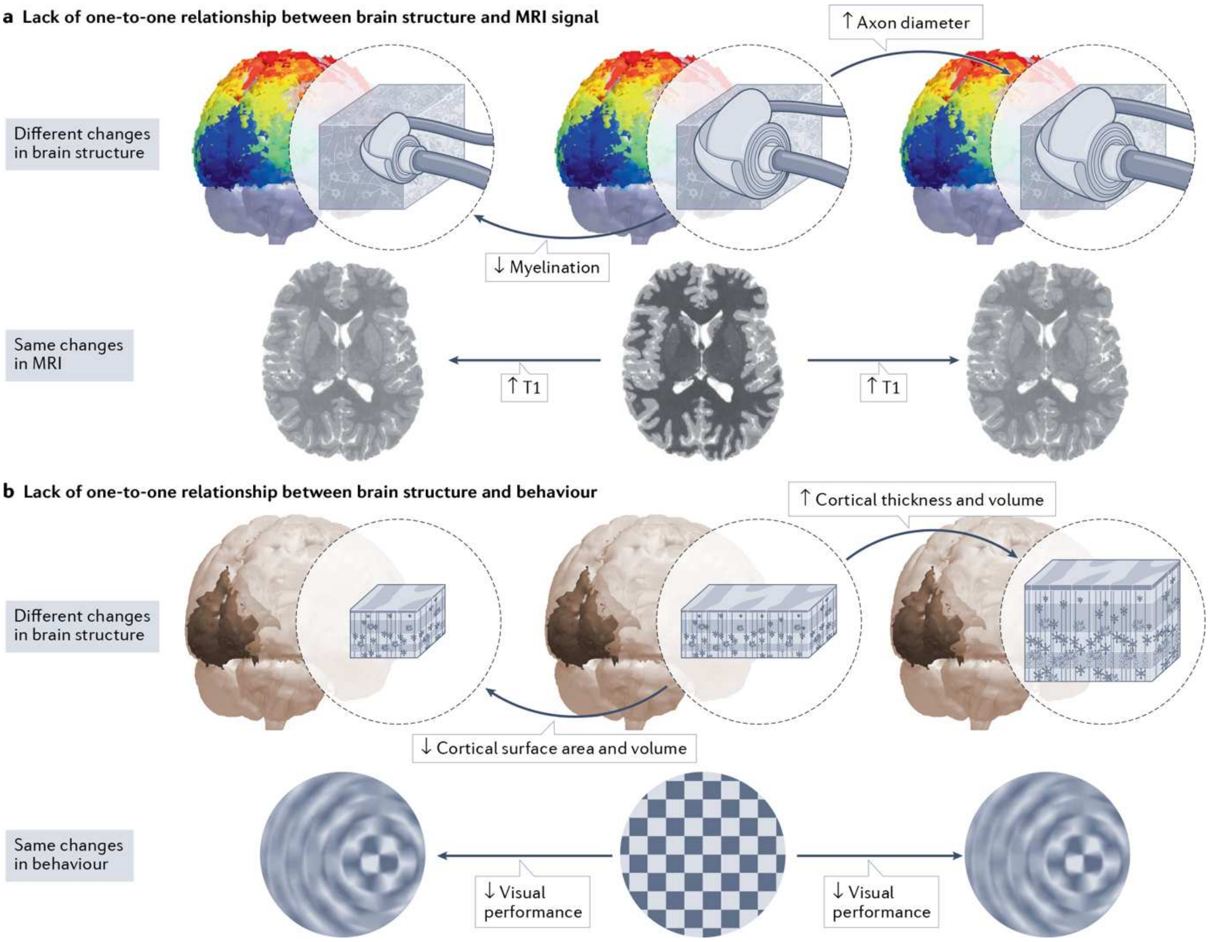

Fig. 1: Lack of one-to-one mapping from MRI to brain structure and from brain structure to behaviour. (a) An increase in a quantitative T1 MRI signal can result from decreased myelination or increased axon diameter, which affect signal conduction speed in opposite directions. (b) A decrease in visual performance can result from increased cortical thickness or decreased cortical surface area, which affect cortical volume in opposite directions.

Acknowledgement: The authors received funding from Wellcome Trust (209192/Z/17/Z to C.S.), H2020 MSCA COFUND (663830-CU119 to C.S.), the Danish Foundation for Research in Neurology (K.S.) and OPUS Grant (2017/27/B/HS6/00937 to K.S. and R.R.). In addition, the contributions of K.S. and R.R. to this article were based upon work from COST Action CA18106, supported by COST (European Cooperation in Science and Technology).

Competing interests

The authors declare no competing interests.

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