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Commentary: Splitting and lumping brain and childhood adversity measures – a commentary on Gheorghe, Li, Gallacher, and Bauermeister (2020)

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'Are you a lumper or splitter?', I often asked my fellow psychiatric researchers and then tried to pin them down on this factitious dichotomy. Gheorghe and co-authors conducted a study of the association between childhood adversity and brain structures (Gheorghe et al., 2020). Their choice to split measures on one side of the equation but lump on the other side may not be intuitive to all readers.

The authors use data from 6,751 participants of the UK Biobank with information on retrospective self-reports of adversity experiences in childhood and brain imaging, obtained retrospectively at, on average, 62 years of age. Three single-item questions on emotional abuse ('someone in my family hated me'), emotional neglect ('I felt a loved child', reverse coded) and physical abuse were used to measure different retrospectively recalled childhood adversities 40–50 years later. The analyses of brain structures relied on 139 imaging derived phenotypes (anatomically predefined brain structures in this data set). With a set of principal component analyses, the authors extracted eight latent variables per cerebral lobe and the cerebellum from these volumetric measures, as well as for two diffusion tensor imaging measures. In addition, they studied 13 limbic, paralimbic and basal ganglia structures individually as outcomes. Participants who reported experiences of childhood emotional abuse had smaller cerebellar and ventral striatum volumes. None of the cerebral lobe latent factors was related to childhood adversity. Also, participants reporting emotional neglect or physical abuse did not differ from controls. In an additional cross-sectional analysis, no association of adult partner abuse with any brain imaging measure was detected.

The study of Gheorghe addresses an important topic: about 30% of mental illness is explained by childhood adversity (Green et al., 2010). In some form or other, childhood adversity with such lasting consequences must have a morphological or functional impact on brain development. Indeed, studies have repeatedly shown that severe child maltreatment such as emotional neglect, or physical and sexual abuse are related to enduring alterations in brain structure and function (Teicher & Samson, 2016). Findings from brain imaging studies in children and adults with a history of abuse consistently show that the volume of the hippocampus, the anterior cingulate and the prefrontal grey matter is smaller. Functional MRI and diffusion tensor imaging studies suggest altered fronto-limbic connectivity (Hanson et al., 2010). Yet, Georghe et al. add to this literature in several ways. First, few studies have addressed the long-term consequences of childhood adversity in middle-aged and older adults. Their study suggests that (some) associations of childhood adversity with brain morphology are very long-lasting. Second, they study three different forms of adversity (albeit with single items) and disentangle emotional abuse from emotional neglect and physical abuse. Third, they relate child adversities to imaging data in a population-based study. Previous work mostly included children experiencing very severe abuse; such a design cannot inform about the neurodevelopmental consequences of adversities as they occur frequently in the general population. In the studies of high-risk families, it is often difficult to define a valid control group. Also, adversities co-occur even more than in the general population.

The UK Biobank has become one of the most important resources for imaging studies. In the last 15 years, several large imaging studies like the Framingham or the Rotterdam Study have been conducted, but the UK Biobank is taking imaging studies to another level (although in the study of Gheorghe et al. 'only' 6,751 participants were included). This makes it one of the leading population-based imaging resources and, as the authors repeatedly point out, a large sample providing 'statistical power'. Here, the statistical power is not used for complex or multimodal analyses; instead, the power 'only' allows for careful control for confounding with multivariate approaches, an arguably standard procedure. The large data set enables the authors to detect relatively small effects. Whether it is worthwhile to detect small effects is, of course, in dispute. Some statisticians argue small effects are more likely due to chance; public health experts are convinced that small effects are irrelevant for

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interventions; neuroscientists posit that large data sets rather than be used to detect small effects can better be used to model the functional heterogeneity (such as of the striatum) exploiting inter-individual variation; only geneticists know better than most (they learnt the hard way!) that small effects are the norm (Smith, 2011). Gheorghe et al. detect 'only' a weak association of childhood emotional abuse with differences in the cerebellum and the ventral striatum, and perhaps more importantly, no association of physical abuse or emotional neglect with any brain structure or latent variable was tested. However, it can easily be argued that these small effect sizes are possibly valid and meaningful. Even small effects are impressive against the background of the long follow-up. Not only because the associations provide a proof of principle in the general population, but also because large effects of adversities or any other environmental variable on adult brain structure must be considered unlikely. Most often large environmental effects on the brain in the general population reflect confounding or selection bias (Szucs & Ioannidis, 2017). Brain morphology is not only strongly genetically determined but the product of a myriad of interacting psychological, social and other nongenetic biological factors. Admittedly, small effects of emotional abuse may not be immediately relevant for public health. But the same could be argued for any (even if it were plausible) large effects: we do not need imaging studies to support early interventions preventing childhood abuse. However, this study informs us that in particular the striatum and the cerebellum may differ between older adults with and without a history of abuse. These are not the primary candidate regions typically examined in the neuroscience literature, but provide an interesting lead.

The childhood adversity measure of the UK Biobank clearly has major limitations. Retrospective assessment after 50 years may tell us more about the present evaluation of the relationship with a parent than about past experiences. In their seminal review, the Danese group noted that more than half of individuals retrospectively reporting childhood maltreatment did not have concordant prospective observations. This likely reflects, to some extent, memory bias. If related to brain characteristics, this memory bias would give rise to spurious associations. Moreover, emotional abuse is a much broader concept not easily captured by one question tapping 'someone hated me'; it encompasses spurning, terrorizing, denying responsiveness and isolating the child – just to name some common forms of emotional abuse. However, the decision of the authors *not* to combine the childhood adversities in one score is interesting. Frequently, different forms of child abuse and neglect co-occur. For this reason, many researchers argue for summing adversities in cumulative ACE scores. This practice also enables researchers to study dose–response effects and yields larger and more robust effect sizes (Bethell et al., 2017). But arguably, this practice of combining emotional abuse with neglect and physical abuse, and even combining exposure to alcohol or drug abuse in the home, witnessing parental violence in the home, or violence in the neighbourhood all in one exposure score has major downsides. The cumulative risk model of ACEs implies that these different exposures have roughly equivalent quantitative associations with a certain outcome although their typical duration and severity might vary wildly. A risk score allows us to study quantitative differences in adversity exposure but not qualitative differences that may be much more important. Why should these different exposures have such homogeneous effects on the brain? Might different adversities such as witnessing violence in the neighbourhood and parental substance abuse not necessitate different interventions on very different levels? It is also problematic from an epidemiological perspective: emotional abuse can be the mediator of the harm caused by other forms of child abuse (Hart, Brassard, & Karlson, 1996). But not only does one adversity likely affect many others downstream, each exposure likely requires a distinct set of confounders. It is not evident that neighbourhood violence and parental substance abuse share the same confounding pattern. Importantly, if researchers combine actual violence and threat, or emotional and physical abuse in one score, we will never fully understand the consequences of the many forms of adversities for brain development. We will only get an idea of the impact of different – often study specific – adversity combinations. It is very likely that the prevalence of specific adversities, such as neighbourhood violence and alcohol abuse, vary across different populations. This would impact the generalizability of results if the associations of individual adversities with brain function or structure differ per brain region. The study of Georghe et al. suggests that emotional abuse impacts the cerebellum and the ventral striatum; it is unlikely they would have found these associations had they combined the exposure with physical abuse. Now we learn that not physical violence or emotional neglect but emotional abuse may have the most detrimental consequences. This is in line with much of the literature on adversity: psychological childhood adversities are often more predictive of adult impairments than physical adversities.

In contrast to the adversity measures, the authors chose to lump the brain measures into a set of latent brain variables using principal component analyses. Not a completely novel approach in neuroimaging, but this decision again is unusual and against the dominant analytical model. Some variance is lost, the results when using a latent variable are less generalizable, and most importantly, the resulting variables do not translate to an anatomical or functional structure anymore (the ventral striatum

measure was not derived using this approach but an a priori candidate morphological structure). Yet, this approach has distinct advantages. From a research perspective, it reduced the number of tests, even with a large data set, the expected small effects of specific adversities may not be detected 50 years later if all the more than 100 variables generated by FreeSurfer had been studied. Arguably, we know too little about the impact of adversity on the brain to frame and examine specific hypothesis. The analytical approach to lump brain measures also makes sense from an epidemiological perspective; it constitutes outcome-wide epidemiology. Had they studied each adversity in relation to hundreds of brain measures individually, we would likely have seen many more associations. Probably, each adversity would have predicted one or another brain outcome. If neuroscientists ever want to make public health recommendations, the region-of-interest approaches will not be helpful. Rather we need to examine different brain outcomes at the same time. There are different options for an outcome-wide approach in studies of the brain: hierarchical testing procedures that examine global brain structures first, latent variables, parallel analyses of all the different outcomes with careful control for multiple testing or the modern machine learning techniques.

In conclusion, Georghe et al. are to be complimented for an analytical approach that splits adversity and lumps brain morphological measures. Their approach goes counter to the dominant ACE model and counter to traditions in region-of-interest-driven neuroimaging models. This is certainly not the only analytical way forward to tackle the important problem of the neurodevelopmental consequences of childhood adversities; it may not even be the best model. Yet, it highlights that in order to move forward we need more epidemiologically inspired analytical strategies, and thus, I compliment the authors for this approach, which I term Population Neuroscience.

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