Neuroanatomical Subtyping of Phobias: Implications for Function and Development

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Anxiety disorders are the most common of mental illnesses (Yang et al., 2021), yet their pathophysiology remains poorly understood. Despite over two decades of neuroimaging research which has outlined some of the key brain circuitry underpinning anxiety-relevant processes (Chavanne & Robinson, 2021; Shackman & Fox, 2021), we have yet to find robust brain-based biomarkers of anxiety. This has in part contributed to the cutbacks and discontinuation of drug discovery anxiety research seen in the private sector (Hyman, 2012).

One of the methodological factors contributing to a lack of robust markers derives from issues of statistical power. Some have argued establishing robust brain-behavior relationships demands thousands of participants (Marek et al., 2022). Anxiety research has not traditionally used designs of this magnitude. Smaller scale studies are undoubtedly essential for scientific discovery (Rosenberg & Finn, 2022), but our neuroscientific models of anxiety have faced minimal validation against highly powered samples. Studies which attempt this have not always replicated key findings, such as an association between resting-state derived amygdala connectivity and self-reported trait anxiety (Boeke et al., 2020; Kirk et al., 2022a), emphasizing the necessity of scrutinizing anxiety theory against larger datasets.

From a conceptual standpoint, a further hinderance to the identification of robust biomarkers may be from the very operationalization of anxiety as a unity construct which has carved artificial boundaries with other forms of mental illness. The field has started to move toward a transdiagnostic approach, which acknowledges that anxiety has shared mechanisms with other disorders, such as depression, as well as unique, disorder-specific features (Cuthbert & Insel, 2013). On the other hand, while researchers have started to broaden the lens to encapsulate cross-disorder mechanisms, far less work has focused on idiosyncratic features underlying subtypes of anxiety disorders. Meta-analytic evidence supports the notion of common circuitry shared across anxiety disorders (as well as adaptive anxiety and fear; Chavanne & Robinson, 2021; Shackman & Fox, 2021), but we know far less about how, or indeed if, disorder subtypes differ. In sum, despite an

increased uptake in transdiagnostic approaches, there is a clear need for exploring neuroimaging-based stratification of anxiety subtypes.

In this issue of American Journal of Psychiatry, Hilbert et al. (In Press) conducted the largest study of its kind to investigate brain structure differences in phobias, focusing on two subtypes: 1) animal phobia; and 2) blood injury and injection phobia. Leveraging multi-site data from over 4400 subjects (2991 healthy volunteers and 1452 phobic volunteers), the researcher's preregistered mega-analysis tested for phobia-associated differences in brain structure (i.e., subcortical volume, cortical surface area, and cortical thickness) relative to healthy control samples. They found an overall reduction in subcortical volumes, namely caudate, putamen, and hippocampus for individuals with a phobia (vs healthy controls), except for the pallidum, which was generally larger in patients. These effects appeared primarily driven by participants with animal phobias (n=739). Meanwhile, subjects with a phobia demonstrated predominantly increased grey matter thickness in areas such as medial orbitofrontal cortex and frontal pole, and increased thickness in visual cortices. Orbitofrontal thickening was particularly pronounced in participants with a blood injury and injection phobia (n=182). Many of these effects survived a battery of robustness tests, were of a magnitude higher than those seen in studies of generalized/social anxiety disorders and corroborate their prior findings in smaller samples (Hilbert et al., 2015). Combined with preregistered hypothesis testing and a relatively large sample size, Hilbert et al.'s (In Press) findings give optimism to the idea that identifying robust brain-based measures of pathology is achievable within anxiety research.

Identifying biomarkers is, of course, only the start; to advance our theoretical understanding we need to map markers onto underlying mechanisms (Pine & Leibenluft, 2015). Indeed, in stark contrast with the commonly held view of the amygdala as the 'fear center' (Ledoux, 2020), there were *no differences in amygdala volume* between healthy and phobic individuals. This does not preclude the functional involvement of the amygdala, nor morphology of amygdala sub-nuclei, in anxiety-relevant processes but begs the question of how and when these neuroanatomical differences in phobia impact brain activation. To this end a meta-analysis of activation to emotion tasks amongst phobic patients also published in the American Journal of Psychiatry (Chavanne &

Robinson, 2021) provides an opportunity to compare structural and functional differences region to region across the brain in phobia (figure 1).

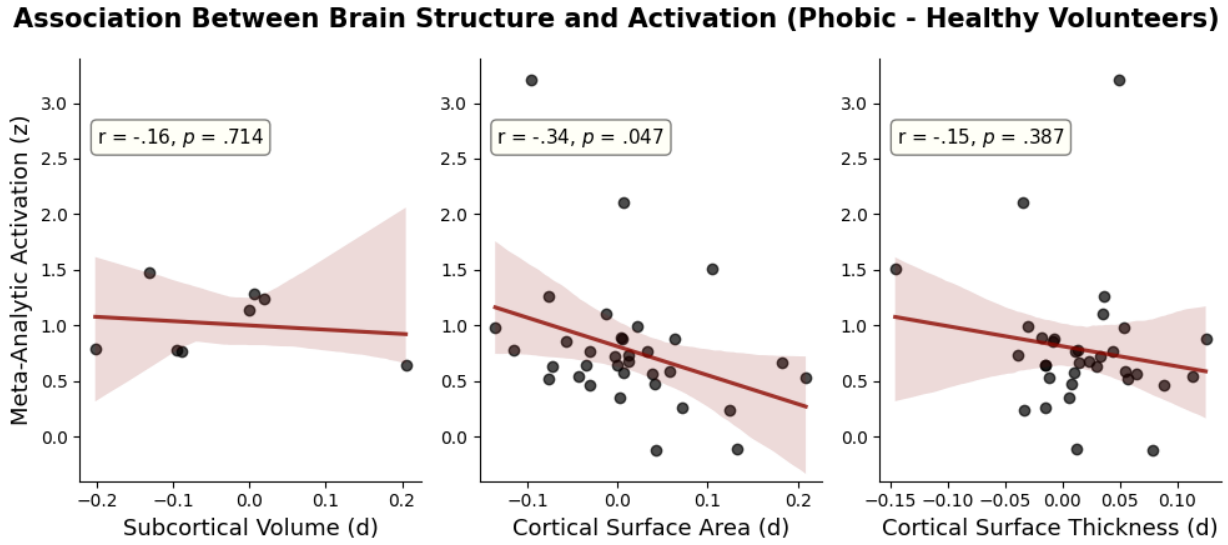

Figure 1. Bivariate correlations between meta-analytic brain activation to emotion tasks (specific phobia vs healthy volunteers, a subset of the full analyses which looked at all anxiety disorders; Chavanne & Robinson, 2021) and mega-analytic measures of: subcortical volumes (8 regions; left); cortical surface area (34 regions; middle); and cortical surface thickness (34 regions; right) for phobic vs healthy volunteers (adults only; Hilbert et al., In Press).

This analysis provides preliminary evidence for an overall negative relationship between function and structure, especially between cortical surface area and functional activation to emotion tasks in relation to phobias (r = -.34, p = .047). Regions for which phobic individuals tend to have a *smaller* surface area is associated with the greatest *increases* in BOLD activation to emotion tasks. Exemplifying this is anterior/mid-cingulate cortex, frequently reported as showing hyper-activation in anxious participants (Robinson et al., 2012, 2014), which appears to show reduced surface area. One interpretation is that a reduced surface area might necessitate greater metabolic and functional activity to achieve the required processing demands of emotional stimuli, which are often biased in patients with phobias (Waters et al., 2014). This relationship is of course tentative given the broad comparisons of summary statistics between datasets (as opposed to subject-

level metrics) and cross-sectional nature of the correlations we present here. We also can't rule out this effect could be driven by differences in how mega-/meta-analytic data points were adjusted for covariates otherwise associated with anxiety symptomatology and cortical morphology. Nonetheless, we must acknowledge there are likely inextricable structure-function relationships shaping cognition and behavior (Johansen-Berg, 2009) which anxiety research has, for the most part, neglected.

It is unclear whether anxiety-relevant brain function changes precede, and potentially drive, structural changes in the brain or vice versa. A fruitful avenue for exploring structure-function relationships in anxiety may come through closer multi-modal examination of developmental trajectories. Hilbert et al. (In Press) report an association between brain structure and phobia existed only in adults. Yet, there is a plethora of evidence demonstrating differential brain activation among children and adolescents with anxiety disorders (Zugman et al., 2021). Speculatively, such activation in the absence of structural differences suggests function might be driving morphological differences during development. However, there is scant longitudinal evidence directly exploring this in pediatric anxiety and is nonetheless likely a bidirectional relationship. Understanding the developmental pathways which give rise to these causal influences between structure and function holds implications for neural malleability in response to treatment, underscoring the importance of age at which treatments for phobia start.

For future studies addressing structure-function hypotheses, we also emphasize strong consideration on the specificity of functional activation. We have previously demonstrated naturalistic neuroimaging paradigms (i.e., suspenseful movies) can elicit differential—and even inverse—brain responses compared to traditional designs such as unpredictable shock and resting-state (see Kirk et al., 2022a, 2022b, 2023, 2024). This negative correlation between surface area and phobia-dependent brain activity to emotion tasks may thus differ dependent on the type of anxiogenic stimuli. Yet, there is a clear lack of naturalistic neuroimaging data collected from those with pathological anxiety. We therefore encourage future investigations into anxiety to consider these paradigms, especially when contextualizing associations between structure and function.

In an age where optimism for neuroimaging-derived biomarkers can seem bleak, Hilbert et al.'s (In Press) work provides robust evidence for neuroanatomical differences

amongst and between phobic individuals. Their evidence points to generally decreased subcortical volumes (except pallidum) and increased cortical thickness/surface area in volunteers with a phobia (vs healthy controls). Moreover, phobia subtypes differed in measures such as frontal pole and medial orbitofrontal cortex thickness. However, contrary to a plethora of functional evidence, there was no indication of phobic individuals having altered whole amygdala volumes. When contrasted with functional imaging data, there is a general negative association between cortical surface area and activation (r = -.34, p = .047), opening an avenue for exploring structure-function associations in anxiety. Going forward, we suggest developmental and naturalistic neuroimaging methods will be crucial for understanding the interplay of brain structure and function in the context of anxiety.

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