Commentary

COVID-19, Stress, and Brain Morphometry: Opportunities and Challenges for Linking Neuroscience, Translational Psychiatry, and Health Services Research

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The COVID-19 pandemic has been accompanied by an almost unprecedented global health crisis. This health crisis is also a mental health challenge, considering both the direct effects of the disease, such as the emergence of psychopathology or psychiatric disorders in COVID-19–affected patients (1), as well as the indirect effects linked to mandatory or self-imposed isolation (2). Psychiatric disorders, including anxiety, and insomnia have been reported at higher rates in people with a COVID-19 diagnosis (compared with either influenza or other health problems) in large-scale retrospective analyses, while documented psychiatric disorders prior to COVID-19 infection have been shown to carry a higher relative risk of COVID-19 diagnosis (1).

The psychiatric implications of the COVID-19 pandemic, however, reach far beyond the sequelae of infection and associated short- or long-term outcomes in COVID-19 survivors. In fact, the individual-, community-, or government-originated isolation measures, including "lockdowns" and other reductions of social interaction, have been studied for their impact across a range of mental health outcomes across the general population, not limited to COVID-19 survivors: several international studies of multiple general population cohorts have provided evidence for a peak in mental health problems, including depression, anxiety, and (dis)stress (3). Current research in the field is tasked with disentangling potentially complex and interacting effects that differentially impact the mental health of those with prior diagnoses or mental health problems, those being at risk, or those exposed to varying degrees of stress-inducing measures (2,4). Recent meta-analyses on longitudinal data show effects in general population samples to possibly diverge considerably from those reported in psychiatric patients (5), possibly owing to factors such as coping strategies to compensate for individual isolation. Such coping strategies or tools to overcome isolation (e.g., replacing direct social interaction with online conversation) are, however, not equally available for all members of society or across different countries.

Given the extensive biological literature on the effects of stress and isolation, these mental health service challenges also provide a unique opportunity to link neuroscience models of (prolonged) stress with putative brain biomarkers of psychiatric disorders in patients and their impact for mental health service provision.

In the current issue of *Biological Psychiatry: Global Open Science*, Holt-Gosselin *et al.* (6) used structural brain imaging to analyze the interaction of regional brain volumes with psychopathology as well as with coping strategies. The study provides novel evidence that brain structure, in particular insular cortex thickness, prior to the pandemic is a predictor of anxious arousal during the pandemic, while the association of amygdala volume with affective symptoms is related to an interaction with coping strategies such as self-distraction.

The study makes use of well-established robust imaging techniques applied to quantify regional brain volumes as indicators of interindividual variation of brain structure as well as pathology. These regional volumes have been analyzed in large-scale case-control studies of psychiatric disorders, as well as studies in nonclinical populations, where subtle variations have also been associated with subthreshold or subclinical emergence of minor (transient) symptoms (7). Several aspects make this a remarkable and important study that is likely to be followed by similar studies in the near future on established or developing psychiatric cohorts.

Holt-Gosselin *et al.* (6) build on a wealth of data, developed from both basic neuroscience studies and brain imaging in humans, that have delineated particular brain regions and networks that are crucial in the regulation of stress and processing of emotions. In particular, they focus on the amygdala, the hippocampus, and the insula, as well as the caudal and rostral anterior cingulate cortices as brain areas identified both in case-control studies of depression and anxiety disorders, and in imaging studies on emotion processing. These areas are particularly prone to stress in general and possibly also the effects of social isolation in particular. For example, most recent basic neuroscience studies in rodents have shown plastic short-term (as well as enduring) changes in medial parts of the amygdala as a result of isolation (8). Based on these well-established methods, the authors were able to formulate and test specific hypotheses on the relation of pre-pandemic brain volumes versus maladaptive pre-pandemic coping versus their interaction as predictors of symptoms emerging after social isolation and other effects experienced during the COVID-19 pandemic. The findings (linking the insular cortex to anxious arousal and the amygdala to affective symptoms and coping strategies) now connect specific brain volumes to outcomes following the lockdowns and social isolation measures.

This represents a hypothesis-guided integration of neuroscience models with psychological factors like coping, resulting in findings that will allow us to better understand the neural basis of large-scale effects with actual health care delivery

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needs. As such, it is empirical evidence of the usefulness of established neurobiological models, mostly derived from human brain imaging, to carry out research with direct translational and mental health service delivery implications. A somewhat similar approach was demonstrated in a recent functional magnetic resonance imaging study, in which functional connectome data of patients with anxiety, depression, or schizophrenia versus control subjects were used to analyze associations with pandemic-related anxiety (9): this study, too, found links to insular cortices, although it did not aim at linking imaging data to clinically relevant coping.

Another important aspect of this study is its dimensional and transdiagnostic approach. Holt-Gosselin *et al.* (6) performed their analyses across subjects with prior or current diagnoses of depression or anxiety disorders (while excluding psychosis or mania). As their study originates from a prepandemic cohort rooted in a Research Domain Criteria approach on anxiety and depression, the data are based on a rather naturalistic cohort composition that is more likely to reflect real-life scenarios encountered in mental health care (as opposed to classical case-control studies). This approach has several advantages, as it considers anxiety and depression as dimensions—not restricted to particular diagnostic categories. However, future studies will have to study in more detail whether identified effects are driven by particular subgroups (defined either clinically or by psychometric data). It is not unlikely that results such as the ones seen in this present study emerge as a combination of different effects and effect sizes. Such information might, in the future, be crucial to provide a neuroscientific understanding of diversity in cohorts—and identification of those individuals at particular risk.

This dimensional aspect, however, also extends to the subclinical spectrum, i.e., symptoms not meeting clinical thresholds for a clinical diagnosis yet causing significant subjective distress. It is worth noting that Holt-Gosselin *et al.* (6) also consider this aspect of dimensionality in their approach and interpretation.

Mental health outcomes are not limited to the emergence of clinical diagnoses: both previously healthy individuals as well as those with a mental health history might develop transient or persistent symptoms in a subclinical range. Considering only psychiatric diagnoses as outcomes would thus fall short of providing a fuller picture of mental health sequelae of such a pandemic.

Previous imaging studies have implicated amygdala volumes (among other brain structures) as being associated with such singular depressive symptoms or subclinical depressive states (7). It is therefore conceivable that future studies expanding on these findings will include assessments of symptoms and subjective distress that determine quality of life even in the absence of a categorical clinical diagnosis. While such subclinical expressions of stress might be less distressing than clinical conditions, they are likely to affect a larger proportion of individuals in societies. They serve as a reminder that psychiatry not only is fit to address clinical mental health issues but also has a role in prevention and health promotion in the general population.

Given the complexity of different disease dimensions, predictors of outcomes might also unfold as interactions between risk factors, clinical diagnoses and comorbidities, and psychological factors (e.g., resilience, coping, or social support) (2). This will be associated with the need to better understand the differential contributions of brain areas/networks and risk factors (genetic and environmental) shaping individual outcomes across different continua or spectra of psychiatric disorders. It will certainly necessitate additional study of larger patient and nonpatient samples, considering the heterogeneity of pandemic-related distress (which is different within as well as across different countries and societies). It will also require use of instruments to capture subtle psychopathology and subjective distress. It will also make use of available cohort study data, which might be expanded to include follow-ups, thus allowing for longitudinal magnetic resonance imaging analyses, which consider fluctuations of regional brain volumes.

Holt-Gosselin *et al.* (6) have opened the door to test specific anatomical hypotheses to not only identify brain correlates and mechanisms underlying the response to complex social stress, but also identify vulnerable (sub)groups as well provide an empirical basis for our understand of phenomena related to social isolation and stress. Their work is a foundation for imaging studies to come—and links brain network models of stress and isolation with psychology, human imaging, and mental health delivery research.

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