COMMENTARY

A new vista in psychiatric treatment: Using individualized functional connectivity to track symptoms

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In PNAS, Sylvester et al. (1) assess the functional connectivity of the human amygdala with well-established brain networks using functional magnetic resonance imaging (fMRI). This focus on the amygdala was chosen because this region has been often implicated in psychiatric conditions. Better understanding of its connectivity and functions may therefore be helpful as the field moves in the direction of individualized treatments for psychiatric problems.

Amygdala Structure and Function

The amygdala was first identified in the early 19th century when the German anatomist, Karl Friedrich Burdach, came across an almond-shaped structure in the human brain and named it using a word derived from the Greek word for almond (2). A century later, the term amygdala had come to designate a larger area in which the almond-shaped region was only a component. Today, the amygdala is recognized to have more than 12 anatomical areas, or nuclei, each with several subdivisions and unique patterns of connectivity in the brain (3, 4). These are sometimes grouped into three partitions: basolateral, centromedial, and cortical (5).

Despite the singular designation, the amygdala, like all brain areas, is a twin structure, with one amygdala in each cerebral hemisphere. From a comparative perspective, the amygdala is a common feature of the vertebrate brain, although it is considerably more developed in mammals than in other vertebrates (6).

When discussing brain areas, it is important to recognize that the criteria used in their initial characterization, often in the 19th century, were relatively crude. Consequently, with modern methods the boundaries of areas often shift, and sometimes what seemed like two areas may turn out to be a continuous one, leading to debates about what to call the area. Some, for example, question the existence of the amygdala as an independent region, arguing it is a subregion of the striatum (2).

Resolving what areas of the brain are, and are not, is important. But even more important is the fact that brain areas, however they are defined and labeled, do not on their own perform functions. Functions are products of circuits. And the function any circuit performs depends on its connections with other circuits, both within and outside the area itself (7).

Much work on amygdala functions has involved threat processing, as studied using Pavlovian aversive conditioning (8–11). This research has identified specific circuits and cellular and molecular mechanisms involved in the acquisition, storage, extinction, and behavioral expression of threat memories, making possible appropriate responses to threats in the future based on past experiences. Amygdala circuits have also been implicated in in appetitive behaviors related to feeding, sex, and drug addiction (12).

In general, the lateral nucleus, part of the basolateral complex, is the sensory gateway into the amygdala and the site where much of the work uncovering circuit, cellular, and molecular and genetic mechanisms related to threat processing has been performed in rats (9). This research has also suggested that different subdivisions of the lateral amygdala make distinct functional contributions to learning and memory. More recently, intriguing mechanisms of plasticity have also been found in subareas of the central nucleus (11), which is part of the centromedial subdivision.

Research in humans has confirmed the basic findings about both threat and appetitive processing in the amygdala (13, 14). In addition, as noted by Sylvester et al. (1), the human amygdala has been implicated in

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a variety of clinical problems, including symptoms associated with anxiety disorders, addiction, depression, eating disorders, and other conditions. However, progress in understanding the neural basis of clinical symptoms has been limited by the relatively poor resolution of the methods available to study the human brain. By contrast to the animal studies, research on amygdala function and dysfunction in humans has mostly treated the amygdala as an undifferentiated mass.

Partitioning the Human Amygdala Using Functional Imaging

In recent years, with the emergence of higher-resolution brain-imaging methods, some success has been achieved in assessing functional activity in subregions of the amygdala, typically by applying a common template based on postmortem studies. The template partitions the amygdala into three spatial components called the laterobasal, centromedial, and superficial regions. These are closely related to basolateral, centromedial, and cortical subdivisions of other mammals. Although the same general regions exist, the human amygdala differs somewhat compared to that in other mammals (15).

Sylvester et al. (1) point out several limits of the template approach. First, the template was based on a small number of brains from people who were on average 65 y old when they died. Second, the template required that only 5 of the 10 brains meet the criteria for a given partition. Third, there was considerable individual variation in location and extent of the three partitions. And fourth, brain–behavior relations are stronger in individualized than in averaged network maps. They concluded that variability in the location of amygdala partitions reduces the likelihood of precise identification of amygdala subareas.

Rather than using predetermined maps based on averages from postmortem brains, Sylvester et al. (1) identified amygdala partitions in individuals based on functional connectivity of the amygdala with known networks in each person. Specifically, amygdala subdivisions were delineated in each individual by clustering amygdala activity on the basis of functional connectivity patterns with the networks. The empirically discovered individual amygdala subdivisions were named accordingly. One partition was located in the superior (i.e., top) part of the amygdala and overlapped with the traditional centromedial partition. It was defined by connectivity with the default mode cortical network and thus named the default mode amygdala subdivision. Another was located medially (i.e., toward the midline) and overlapped with the traditional laterobasal partition. It was defined by connectivity with the dorsal attention cortical network and was named the dorsal attention amygdala subdivision. The third was located ventrally (i.e., toward the bottom) and was more or less equally connected with a particular external network (in other words, it was connected to several networks). Activity in the three subdivisions was also related to four other cortical networks. All three subdivisions were positively correlated with the ventral attention network and the somato-motor network and negatively correlated with the cingulo-opercular and salience networks.

Of note is that while the empirically defined individual partitions recapitulated the more traditional template partitions in a general sense, there was considerable variability across individuals as to the exact location of their subdivisions. Based on this, Sylvester et al. (1) conclude that applying a common template to all individuals will mislabel the amygdala subdivisions in many individuals. Sylvester et al. (1) suggest that their work may help lay the foundation for creating models of amygdala function and dysfunction in individual patients.

This research comes at a time when the individual approach is being widely touted as a means for improving therapeutic outcomes, not just by imaging functional networks, but also by using information about genes and other biomarkers. It is also gaining traction in approaches that emphasize cognitive and behavioral factors in designing treatments for individuals (16).

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As exciting as the Sylvester et al. (1) study is, we have to remember that our biological understanding of the brain from animal research is much more detailed than is possible in human research. Particularly important is that functional connections seen in fMRI studies in humans are not the same as actual anatomical connections observed in animals. One difference is that functional connections may be direct or indirect. This does not diminish the importance of the human findings, but somewhat limits the extent to which the human findings can be directly related to the research in other mammals. For example, Sylvester et al. (1) find that the centromedial partition is specifically connected with the default mode network. In other mammals, the basolateral, but not the centromedial, subdivision is anatomically connected with the medial prefrontal areas of the default mode network (11). Also somewhat unexpected from animal studies was their finding that the laterobasal amygdala partition is strongly related to the dorsal attention network. In nonhuman primates, the lateral prefrontal cortex, a key component of the dorsal attention network, is only sparsely connected with the basolateral amygdala (3, 17). In both cases indirect pathways exist that could account for the patterns of functional connectivity observed.

Neuroscientific research on animals will continue to be essential for detailed understanding of the brain. But to reap the benefits of animal research we have to be clear about what it can and cannot tell us. And one thing that it cannot do, and may never be able to do, is allow us to understand human subjective experience. Only human research can unequivocally do that.

As the framework of individualized treatment evolves, it is therefore important to keep in mind that individuals often seek treatment because they are suffering subjectively and want to feel better. However, contemporary biological and behavioral/cognitive approaches to treatment arose from traditions that deemphasized subjective experience, often viewing it as a quaint, inaccessible, and scientifically irrelevant factor, something that will be taken care of in the process of changing behavior by administering drugs, extinguishing learned associations, or changing beliefs or other cognitions (18).

Individualized therapy offers an opportunity to change the status quo by making subjective well-being a major outcome target of treatment. If so, exciting findings such as those published by Sylvester et al. (1) may be able to help improve the likelihood that individuals will come to feel better as a result of therapy. But to achieve this, also needed is a better understanding of the cognitive brain network that underlies subjective experience, that is, consciousness, a nascent but growing area of research (19–23).

In light of this, it is particularly interesting to further consider the implications of Sylvester et al.'s (1) finding that the laterobasal amygdala partition is strongly related to the dorsal attention network in humans. The lateral prefrontal cortex, a component of the dorsal attention network, is found only in primates and has been implicated in conscious experience in humans (19, 21–23). Functional interactions between the amygdala and the dorsal attention network, regardless of whether the actual connections involved are direct or indirect, may therefore offer an additional window into the workings of a brain network implicated in conscious experience. Given the role of the amygdala in psychiatric conditions, these findings may also shed light on some aspects of psychiatric afflictions that involve conscious awareness.

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