

## Neural Correlates of Autistic Traits in the General Population: Insights Into Autism

The traditional approach to studying autism has been to compare a group of affected individuals with a group of nonautistic individuals on a particular measure of interest (e.g., genes, brain, behavior) in order to determine how the groups differ. While this methodological approach is of obvious importance and has revealed almost all of what we know about autism, recent developments in the quantification of autistic traits in the general population are providing novel inroads to studying and understanding autism. One example of such an approach appears in an article by Di Martino and colleagues (1) in this issue of the *Journal*. In a nonautistic sample from the general population (for which the term “neurotypical” is preferred by autism researchers and advocates), the authors find that the degree of autistic traits in an individual is related to a functional relationship between two particular regions of the brain (i.e., the pregenual anterior cingulate and the anterior mid-insula). Before describing these findings in greater detail and their implications for understanding autism, some background on two key aspects of the study should be given.

First, to determine the functional relationship between various regions of the brain, Di Martino and colleagues make use of an interesting feature of the brain at rest. Even in the absence of any explicit task demands (including during sleep and light anesthesia), the brain is highly active and exhibits spontaneous low-frequency fluctuations in the range of 0.01–0.1 Hz, which are measurable with functional magnetic resonance imaging (2). At first glance, these fluctuations might seem like random noise, but it turns out that particular regions of the brain exhibit correlated patterns of such spontaneous fluctuations that are found reliably and consistently within and across individuals (1, 3, 4). Furthermore, this functional connectivity exists between regions that are anatomically connected (5) and functionally related (6), including motor, sensory, and cognitive networks. Although the neural processes underlying these low-frequency fluctuations have yet to be determined, it is thought that they reflect an underlying intrinsic organization of the brain (see reference 6 for discussion). However, examination of resting functional connectivity alone is not the exciting part of the Di Martino study, since many others have previously studied this phenomenon in both healthy populations and clinical populations, including autism (see reference 7 for the first examination of functional correlations at rest in autism).

The second key component of the study conducted by Di Martino and colleagues involves the use of the Social Responsiveness Scale (8). Developed by Constantino and colleagues (8), the Social Responsiveness Scale is a 65-item parent- or teacher-report questionnaire that yields a single continuous measure of autistic traits (and includes items representative of each of the three diagnostic domains of autism: social deficits, communication deficits, and restricted/stereotyped behaviors and interests). Importantly, the Social Responsiveness Scale can be used to quantify such traits not only in individuals with autism but also in the general population (9). As such, this instrument allows researchers to move beyond traditional research designs that simply compare individuals across binary categories (autism versus no autism) and allows for more statistically sensitive designs that take advantage of the variability of autistic traits across

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individuals, regardless of diagnostic category. The utility of this approach has already been demonstrated in genetic linkage studies with multiplex autism families (10).

Di Martino and colleagues examine how autistic traits found in the general population relate to individual differences in resting functional connectivity. Their reasoning is as follows: If neural circuitry that is sensitive to the degree of autistic traits in a nonautistic sample could be identified (as measured using the adult version of the Social Responsiveness Scale), then such circuitry could serve as a candidate in further studies of autism. Their investigation focuses on connectivity between the pregenual anterior cingulate cortex and the rest of the brain. This particular region was chosen for several reasons. First, previous resting functional connectivity studies of autism have identified abnormalities in this region (11, 12). Second, their meta-analysis of functional imaging studies in autism found hypoactivity of the pregenual anterior cingulate cortex during social processing (13). Third, the pregenual anterior cingulate cortex is normally engaged during social and emotional processing—processes impaired in autism.

To briefly summarize their main result, Di Martino and colleagues found that functional connectivity between the pregenual anterior cingulate cortex and anterior mid-insula was sensitive to the level of autistic traits across a sample of nonautistic individuals. Those with higher levels of autistic traits had lower functional connectivity, while those with lower levels of autistic traits had greater functional connectivity. Based on previous research and the pattern of anterior cingulate-insula connectivity they identified in their present study, the authors speculate that the anterior mid-insular region might serve as a transition zone between the anterior insula and posterior insula, regions thought to be involved in social and emotional cognition and somatic representation, respectively.

As the authors point out, the significance of their findings for understanding autism is unknown at present and will only be borne out by additional studies that include an autism sample. However, being able to quantify the degree of autistic traits in the general population along side those with autism might yield important insight into the nature of autism. For instance, it is presently unclear whether autism represents an extreme end of a continuum within the general population or whether the diagnosis represents both a qualitative and quantitative rift from typical development. If the former were true, one might expect to see a continuation of the brain-behavior relationship identified in the Di Martino study that spans across diagnostic category. If the latter were true, however, one might expect to find a distinct brain-behavior relationship within each group (autism versus comparison).

In terms of autism research more generally, examination of resting functional connectivity may prove to be a particularly useful methodology for identifying neural abnormalities in autism. The majority of task-based functional imaging studies of autism are only able to include high-functioning individuals due to practical considerations regarding participant abilities and task compliance. However, such individuals make up a relatively small subset of the larger autism population. Given the minimal task demands involved in acquiring resting functional connectivity data (i.e., remain still), individuals representative of a broader range of ability and age can be included. Furthermore, resting functional data sets, by definition, do not involve complicated task paradigms whose details can differ widely across studies. Thus, such data are well suited for combining across research sites, potentially allowing researchers to achieve much greater statistical power in their analyses. Such a platform for autism data sharing has recently been established (see the National Database for Autism Research [NDAR] website at <http://ndar.nih.gov>) and should prove to be an invaluable resource for future autism research.

In summary, the article by Di Martino and colleagues highlights a sensitive approach to investigating the neural bases of autism. While it has yet to be seen whether or not the particular brain circuitry they identified is altered in individuals with autism, future

studies examining brain-behavior relationships using increasingly sophisticated behavioral measures will surely help to inform biological models of brain organization and brain development in autism.

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