VIEWPOINT

Is 'underconnectivity' in autism specific to frontal cortex?

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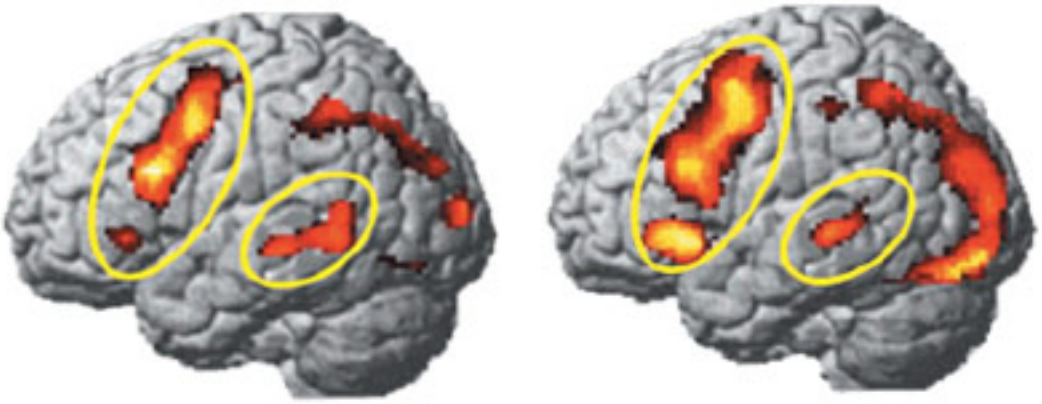

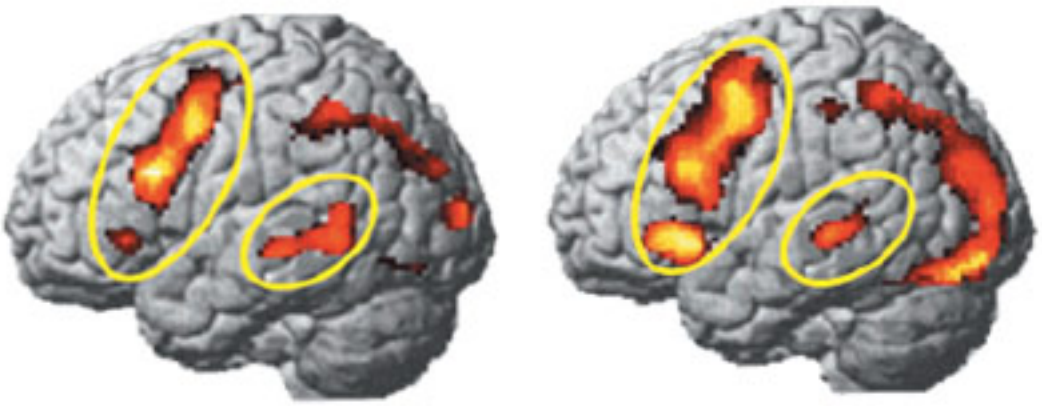

Quiet brain: People with autism (left) have less activation than controls (right) in the left inferior frontal gyrus (left yellow circle), also known as Broca's area, which is important for language production.

Our theory of altered connectivity in autism, which we call 'the underconnectivity theory,' attributes the disorder to reduced anatomical connectivity and functional connectivity between the frontal cortex and more posterior areas of the brain[1, 2]. (Functional connectivity refers to the synchronization of activation between brain regions.)

We propose that this underconnectivity compromises the brain's ability to communicate information between the frontal cortex — the brain area involved in higher-order social, language and executive processes, and abstract thought — and other areas. It therefore affects behavioral performance in any of these types of thinking tasks when substantial participation of the frontal cortex is required.

Our theory attempts to account for a large number of diverse findings — such as the characteristic social, cognitive and language symptoms in autism — and explains them in terms of a single, integrated account that makes predictions about a complex constellation of psychological and biological symptoms of autism.

Here, we first briefly sketch out the evidence for the theory, describe some methodological concerns related to head motion in a magnetic resonance imaging scanner, and describe how the theory is helping to shape the next major phase of autism research.

But first, it is important to recognize that there are different hypotheses about the location of the altered connectivity in autism.

We propose that the underconnected pathways are those between the frontal cortex and other areas. Other hypotheses propose either that the decreased connectivity occurs globally (among all brain areas) or occurs in only the **long-range tracts**, regardless of which areas they connect[3].

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Several recent findings help distinguish between these hypotheses about location, all favoring a frontal involvement in the altered connectivity, with little support for a global or long-range connectivity problem.

For example, a study published in February by **Ralph Adolphs** and his colleagues found that the functional underconnectivity in autism is not global but is involved in frontal and temporal regions[4]. Our own analysisfound evidence for only frontal-posterior underconnectivity in autism and no support for the long-range hypothesis[2].

The new paper's findings are notable for two additional reasons. The researchers measured the synchronization of the slow changes in activation to highlight the synchronization of slow biological brain rhythms (say, once every ten seconds).

This approach ignores the informational synchronization involving faster changes (say, twice per second) between frontal and posterior brain areas that occur during the performance of a task such as language comprehension or **theory of mind**.

Despite the fact that the measurement of slow synchronizations underestimates the underconnectivity in autism, the researchers still observed functional underconnectivity in autism.

The second notable point is that the researchers obtained the results in a resting-state condition, during which participants relax with no instructions to think about anything specific. Despite the fact that this condition minimizes the role of organized thought processes, Adolphs and his colleagues still observed the regional functional underconnectivity in autism.

There are now many diverse and interlocking sources of evidence that support our theory of altered frontal-posterior connectivity in autism.

There are tens of studies using functional magnetic resonance imaging to assess functional connectivity, a measure of whether two brain areas are activated in synchrony during thought processes. The vast majority of these studies report lower functional connectivity between frontal and posterior areas in adults with autism during social, language and executive tasks.

And at least 50 studies have used a technique called diffusion tensor imaging to assess the anatomical connectivity in autism, the white matter tracts — bundles of nerve fibers that connect brain areas — that provide the actual connective pathways.

Most diffusion tensor imaging studies report altered white matter in autism[5]. The alterations are generally interpreted as an indication of reduced structural integrity of the white matter, suggesting poorer communication along a tract.

Importantly, the measures of altered functional and anatomical connectivity are interlocked with each other and with behavioral measures. For example, the frontal-posterior functional connectivity in an individual with autism correlates with the size of the individual's corpus callosum (a large white-matter tract).

What's more, the functional underconnectivity in people with autism often correlates with their scores on the Autism Diagnostic Observation Schedule, a gold-standard screening test for autism, and with other behavioral measures.

The theory also includes a computational model that can predict the functional connectivity of individual participants with autism from their white matter measurements. The model demonstrates that a given task can be performed in exactly the way the theory specifies.

Altered brain connectivity in autism is also compatible with what scientists are learning from common genetic variants, such as **CNTNAP2** and **MET**, that are associated with autism risk and have been shown to affect **brain connectivity**[6, 7, 8].

Constellation of effects:

All this together suggests that various components of the theory, such as the altered functional connectivity in autism, are not isolated phenomena but instead are part of a much larger

constellation of interlocking signatures of the disorder.

Some researchers, particularly **Kevin Pelphrey** and **Benjamin Deen** of Yale University, have pointed out that measures of functional underconnectivity may be biased by **head motion effects**, that is, by participants with autism moving more in the scanner than controls do[9]. If there actually were more head motion in participants with autism, that could artificially deflate the estimates of their functional connectivity.

Because head motion is a longstanding concern in brain imaging, we have always equated groups with respect to motion by excluding participants who move too much, and by removing periods of high motion from the remaining participants' data. Last year, **Steven Petersen** and his collaborators described some stringent procedures for equating head motion across groups[10].

To further investigate the concerns about head motion, we applied these stringent procedures to data from some studies we have published over the past few years[11, 12]. We found no differences between the autism and control groups in head motion measured in this rigorous way.

Deen and Pelphrey's concerns regarding a possible bias in estimating functional connectivity find no support whatsoever in our data. Our findings of lower frontal-posterior functional connectivity in autism firmly remain in place.

In coming to understand the true nature of autism, it is important to look beyond methodological issues and focus on the broader picture of autism.

The main challenges to the underconnectivity theory do not consist of eliminating nuisance variables (which remains an important practice) but of further explaining how the altered brain connectivity in autism arises in the first place, how it affects the connective anatomy, how it is affected by early and lifespan developmental processes, and how it may be ameliorated through therapy.

The anatomical connectivity differences in autism are present at 6 months of age[13].We don't yet know how this underconnectivity comes about. It is possible that either during fetal development or shortly thereafter, the white matter tracts undergo some alterations. These alterations are presumably due to combinations of genetic, epigenetic, nutritional, psychological or environmental factors, particularly those that affect the fetal environment.

We also don't know precisely what the alterations consist of: extraneous connections, missing connections, or poor quality of connections (such as poor myelination).

It will also be important to determine whether certain therapies can ameliorate the altered connectivity. For example, in children with severe reading problems, intensive reading therapy has been shown to enhance white-matter connectivity and reading performance[14].

Like other scientific theories, the underconnectivity theory is a tool for understanding and exploring the nature of autism as efficiently as possible. The theory has performed this function quite well, framing some key questions, integrating answers and raising important new questions that are on their way to being answered.

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