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Idiosyncratic connectivity in autism: Developmental and anatomical considerations

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Abstract

Hahamy and colleagues demonstrate individualized alterations of functional connectivity in the brains of adults with autism, suggesting that previous characterizations of general under- or over-connectivity may be overly simplistic. Adopting a developmental perspective spanning both cortical and subcortical landscapes will further clarify the nature and extent of these atypicalities.

If there is only one point on which autism researchers agree, it is that autism spectrum disorder (ASD) is associated with alterations in brain connectivity. The nature and extent of these atypicalities of brain connectivity however, remain hotly debated. Functional connectivity is a statistical measure of correlation or covariation between functional MRI (fMRI) signals obtained from discrete brain regions [1]. Early investigations reported weaker functional connectivity between brain regions in individuals with ASD, leading to the long-distance cortical “under-connectivity” theory [2]. Recent empirical evidence that functional connectivity between brain regions can be stronger in ASD is beginning to challenge this theory [3, 4]. As a result, the field is grappling with these conflicting findings and calling for more refined models [5–7].

Recent findings from Hahamy and colleagues [8] suggest that these inconsistencies in the literature may be partially explained by examination of the topographical nature of functional connectivity patterns, rather than their overall strength. Using resting state fMRI data, from a large publicly available database [9], the authors found that adults with ASD showed higher inter-subject variability or “idiosyncratic distortions” in intra- and inter-hemispheric connectivity patterns compared with neurotypical participants.

The authors first analyzed regional variation in inter-hemispheric connectivity strength. Typically, the strongest homotopic inter-hemispheric correlations are observed in primary

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sensorimotor cortices, with heteromodal association cortices exhibiting the weakest inter-hemispheric correlations [10]. Hahamy and colleagues found evidence for both under- and over-connectivity of inter-hemispheric connections in participants with ASD compared with neurotypical controls. They next introduced a novel approach for uncovering an underlying principle explaining these group differences. They compared an averaged inter-hemispheric connectivity map (across all ASD and control participants) with the between-group difference maps. This comparison revealed that the direction of group differences in observed inter-hemispheric connectivity depends on the typical magnitude of inter-hemispheric connectivity, such that regions typically exhibiting high inter-hemispheric connectivity tend to show reduced connectivity in ASD (control greater than ASD) whereas regions typically showing low inter-hemispheric connectivity tend to show increased connectivity in ASD (ASD greater than control). They further demonstrated that this "regression to the mean" effect was due to greater individual topographic distortions in inter-hemispheric connectivity patterns in ASD. On average, inter-subject similarities in inter-hemispheric connectivity patterns were higher in the control group than in the ASD groups. Thus, the authors suggest that a more diverse range of inter-hemispheric connectivity patterns across participants with ASD might lead to this observed "regression to the mean". The authors also observed that individuals with ASD with greater symptom severity showed greater deviations from typical inter-hemispheric connectivity patterns. Finally, they found that these idiosyncratic patterns in ASD could be seen in heterotopic and intra-hemisphere connections as well as homotopic inter-hemispheric connections.

Taken together, these findings suggest that the topographic patterns of functional connectivity in adults with ASD are distorted relative to more consistent patterns observed in neurotypical individuals. Further, they elegantly demonstrate how observed group differences (both ASD-related decreases and increases in connectivity) may arise from spatial distortions in connectivity patterns at the individual level. These analyses provide a cautionary tale, with broader implications for future research in this field. In particular, the common practice of comparing group averages of brain connectivity metrics is called into question by the current demonstration.

Whereas the authors suggest that the functional idiosyncrasy as demonstrated by the current analyses may be a "new neural characteristic of ASD", an alternative explanation is that these functional idiosyncrasies develop as a result of the varied treatments and compensatory cognitive strategies that individuals with the disorder engage in over the course of their lives. The high levels of inter-subject variability in connectivity patterns observed in individuals with ASD could be caused by differences in learning strategies or result from differences in therapies experienced throughout the lifespan. As the authors speculate, one might suspect that individuals with ASD have individualized trajectories of interactions with the environment that could contribute to the heterogeneity observed. To test this possibility, it would be necessary to conduct the same study in young children with the disorder to see at what point in development these idiosyncrasies can first be observed. The most stringent test would, of course, require longitudinal rather than cross-sectional investigation.

Autism is a disorder with early life onset and variable developmental trajectory, and there is growing evidence that brain atypicalities observed in adults with the disorder differ from those observed in young children (Figure 1). One recent hypothesis that has been put forth to account for the mixed functional connectivity findings in the literature is that these discrepancies might be reconciled by taking developmental stage of participants into account [11]. For example, independent component analysis comparing within-network connectivity in children with ASD and typically developing children reveals over-connectivity of large-scale brain networks in ASD [12], whereas no group differences are observed in similar analyses comparing adolescents [13] or adults [14]. A limitation of the analyses by Hahamy and colleagues is that they were restricted to adults with ASD. Further studies are indeed needed to address developmental aspects of the findings presented. As there have been no functional neuroimaging studies to date comparing changes in functional connectivity across the lifespan in ASD, compared with typical development, it is unknown whether specific sets of connections mature atypically in the disorder. If, as the current study suggests, individuals with ASD follow unique developmental trajectories resulting in idiosyncratic connectivity patterns in adulthood, this could explain the mixed findings of over- and under-connectivity reported in the literature.

While much of the autism neuroimaging literature has focused on the somewhat arbitrary distinction of long-range vs. local cortical connectivity, much less work has examined connectivity between the cortex and subcortical regions. Thus, another extension of the current work will be to examine whether cortical-subcortical connections are altered in ASD. Studies of typical development have shown that subcortical areas are more strongly connected with primary sensory, association, and paralimbic areas in children, while stronger cortico-cortical connectivity between paralimbic, limbic, and association areas is observed in adults [15]. How these developmental processes unfold in autism remain open questions.

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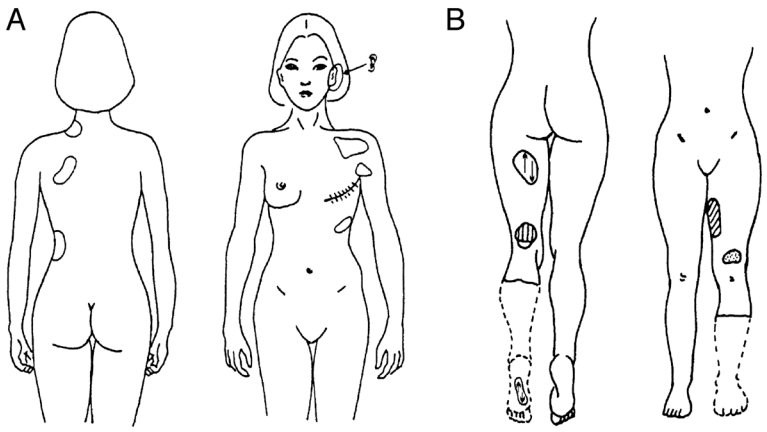

Figure 1. Altered development of functional connections in ASD

Developmental trajectories of functional connections follow relatively consistent patterns in typical development (TD, blue). In individuals with ASD (red), more idiosyncratic patterns of functional connectivity may emerge across the lifespan.