in the current study included the presence of white matter hyperintensities on MRI, the datasets do not include systematic information regarding comorbidities. Particularly in older individuals, further knowledge concerning co-existing conditions such as diabetes and hypertension is likely to throw light on the pathogenesis and development of Alzheimer’s disease. Specifically, knowing whether certain subtypes are more likely to suffer from one or more of these conditions may further inform our understanding of the variable rate of progression across subtypes (Li et al., 2011). The lectures will keep becoming more complicated, and even more interesting.

Magdalena A. Kolanko and Paresh A. Malhotra
Division of Brain Sciences, Imperial College London, UK
Correspondence to: Paresh A. Malhotra
E-mail: p.malhotra@imperial.ac.uk
doi:10.1093/brain/awy282

Competing interests
The authors report no competing interests.

References

Brain connections and social connections in autism spectrum disorders

This scientific commentary refers to ‘Local structural connectivity is associated with social cognition in autism spectrum disorder’, by d’Albis et al. (doi:10.1093/brain/awy275).

Autism spectrum disorder (ASD) has been estimated to affect one in every 160 children worldwide (World Health Organization, 2017). However, the impact of ASD on people’s lives varies greatly, with some individuals having severe and global disability while others have preserved abilities in many domains (Lord et al., 2015). Little is known about why this is so, but social outcomes in adulthood seem to relate most strongly to how severe social and behavioural symptoms were in childhood (Kirby et al., 2016). In order to predict and improve outcomes for those with ASD, it is therefore important to understand differences between individuals in the severity of symptoms, and increase our knowledge about how these differences evolve. The brain is a natural place to look for sources of individual differences in symptoms and outcomes. Thanks to the advent of powerful, non-invasive imaging techniques, we are beginning to understand more and more about the myriad connections among regions of the brain and the way the brain coordinates activity to produce complex behaviours. In this issue of Brain, d’Albis and co-workers illustrate the power of state-of-the-art imaging methods to understand how differences in brain connectivity underlie differences in social cognitive abilities among those with ASD (d’Albis et al., 2018).

A growing body of neuroimaging evidence suggests that communication between regions of the brain is disrupted in ASD. This has been primarily examined in older children, teens, and adults with ASD using functional MRI or diffusion tensor imaging (DTI). Functional connectivity is the synchronization of blood oxygenation level-dependent signals across distant parts of the cortex either while the brain is challenged with a social, emotional, or cognitive task or while it is unengaged in a particular activity. DTI measures the diffusion of water in order to assess microstructural properties of the white matter—the myelinated axonal connections between different parts of the brain. A large number of studies
have observed that long-range structural and functional connectivity is reduced in ASD compared to people without the disorder (Rane et al., 2015). On the other hand, the opposite result has also sometimes been observed—greater coherence of functional signals in ASD, particularly when examining relationships within a local brain area. However, it has been difficult to measure comparable short-range structural connectivity with traditional DTI methods. This has limited our ability to examine the integrity of the superficial white matter, which includes the U-shaped fibres that help adjacent cortical regions communicate with one another and which may play a role in complex behaviours (Fig. 1). Recently, however, an atlas of superficial white matter has been developed (Guevara et al., 2017), which allows examination of fibre connections between 20 and 80 mm in length. d’Albis et al. now use diffusion imaging in combination with this novel atlas to report on short-range structural connectivity in adult males with ASD. They also examine the relationship between brain connectivity and differences in social abilities, adding to the very sparse literature on the clinical implications of altered connectivity.

Males aged between 18 and 55 years who had been diagnosed with ASD according to the criteria of the DSM-V were evaluated with self- and other-rated clinical questionnaires and cognitive testing and each underwent MRI (d’Albis et al., 2018). Those with IQ <70 or who had significant movement during the scan were excluded, yielding a final sample of 27 males with ASD and 31 comparison males without an ASD diagnosis. d’Albis et al. applied the superficial white matter atlas of Guevara et al. (2017) to the diffusion weighted images and calculated generalized fractional anisotropy within 63 short-range fibre bundles. Fractional anisotropy is a commonly used metric that indicates the directionality of water diffusion along a presumed set of axonal fibres, and reflects the degree of fibre coherence, myelination, and/or volume of fibres in the tract. To reduce the number of statistical comparisons between participants with and without ASD, principal components analysis was applied to the 63 fractional anisotropy values, yielding three components, each of which explained some portion of the overall variance. These components were orthogonal, such that there were no correlations between them, and the superficial white matter parcels contributing to each were non-overlapping. The investigators tested the difference in component scores between groups and examined the relationship between clinical features and component scores.

Fractional anisotropy of a component with frontal, temporal and parietal lobe contributors was found to be lower among adult males with ASD compared to those without (Fig. 1 in d’Albis et al.). Scores on this component were lowest among the males with ASD rated as having the most impairment on several sub-scales of the Social Responsiveness Scale and who demonstrated the least empathy. Subsequent analyses showed that reduced anisotropy of connections between insula and parietal cortex and within the temporal lobe were particularly associated with social cognitive deficits. In other words, adult males with ASD who had poorer quality short-range brain connections also had poorer ability to make social connections.

The results of this study thus provide important clues to the underpinnings of differences in social functioning among adults with ASD, and emphasize the role that sensitive neuroimaging techniques play in understanding symptoms of the disorder.

Additional work will be needed, however, to discover how these social cognitive and connectivity differences observed in adulthood develop across time. Since brain changes in ASD are likely to start in the womb (Courchesne et al., 2018), a full understanding of variability in outcomes among individuals will need to consider each person’s developmental trajectory from a very early age. The many imaging investigations demonstrating early brain overgrowth, and post-mortem studies of neural tissue from young children showing an overabundance of cortical neurons, indicate that early hyper-connectivity in ASD is likely (Courchesne and Pierce, 2005). Consistent with this, Solso et al. (2016) showed that long-distance frontal connections measured with DTI had higher fractional anisotropy and volume in very young children later diagnosed with ASD and that age-related changes happened at a slower...
rate than in a typically developing group. These results, and those of similar recent studies showing higher long-range fractional anisotropy among very young children with ASD, emphasize that over-connectivity is present at the earliest clinical stages of the disorder and likely influences the way that children learn and develop social skills. Connectivity of short-range fibres early in the course of ASD remains to be systematically examined, however. As reviewed by d’Albis et al., the methods of the limited number of studies have varied widely and samples have included mostly older children. Creation of an infant and toddler tractography atlas of both short- and long-range fibres across the earliest stages of development would allow study of the complex interplay between local and long-distance structural connectivity and its trajectory across childhood. There is also a pressing need for longitudinal studies that examine structural and functional connectivity changes in the same children and how those changes precede and predict later outcomes in behavioural domains. Through a developmental approach incorporating brain and behavioural measures across the lifespan, we can better understand the varied paths travelled by those with ASD and devise individualized strategies to help each person reach his/her full potential.

Lisa T. Eyler PhD
Department of Psychiatry, University of California San Diego, USA

E-mail: lteyler@ucsd.edu
doi:10.1093/brain/awy293

Competing interests
The author reports no competing interests.

References