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Brain network organization in ASD: Evidence from functional and diffusion weighted MRI

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Although the insight that autistic symptomatology reflects neurological disturbances, rather than bad parenting (Bettelheim 1967), is decades old, to the present day neither in vivo imaging techniques nor postmortem cellular analyses permit a diagnostic decision based on brain markers alone. Simply put, we still cannot look at a brain scan and point to a specific anomaly or pattern of anomalies to determine: "This child has autism." Paradoxically, as much as we are convinced that autism is *in the brain*, it appears to be *nowhere* (in particular) in the brain. At the same time, exacerbating the paradox (as we will discuss further down) autism appears to be *everywhere* in the brain.

Many proposals have been put forward. Some of them have been comparatively simple in neuroanatomical terms, focusing on a single brain structure, such as the amygdala (Baron-Cohen, et al. 2000) or the cerebellum (Courchesne, et al. 1988). However, as we shall see, such proposals are incompatible with the extensive evidence implicating numerous other brain loci and systems. Following a general shift of focus in the cognitive and clinical neurosciences, the modern of view of autism spectrum disorders (ASD) refers to atypical brain organization at the level of distributed networks and interconnectivity (Menon 2011). Even within this contemporary paradigm, some relatively simple hypotheses have been proposed, such as a specific underconnectivity between frontal and parietal lobes (Just, et al. 2012) or a dichotomy of increased local but reduced long distance connectivity (Belmonte, et al. 2004, Courchesne and Pierce 2005). While such proposals may be useful in the Popperian sense (Popper 1965) that only falsifiable hypotheses promote scientific advance, they can easily mislead the large lay community (in particular the parents of children with ASD) to believe that we have firm knowledge where in truth the evidence is inconclusive at best.

In this chapter, we first provide an overview of the available literature on functional and anatomical connectivity in ASD, with focus on MRI techniques. Many of the uncountable findings lack replication, and our review will therefore not even attempt completeness. Instead, we will aim to outline patterns in the multitude of findings, before turning to issues and caveats, as well as broader perspectives.

Functional connectivity

Functional connectivity was originally defined as "temporal correlations between spatially remote neurophysiological events" (Friston, Frith and Frackowiak 1993), but a more recent and broader definition refers to any "statistical dependence between remote neural processes" (Honey, et al. 2007). The dominant technique has

been functional connectivity MRI (fcMRI), although a few early studies used positron emission tomography (Castelli, et al. 2002, Horwitz, et al. 1988). However, the temporal resolution of PET is effectively nonexistent, whereas it is typically in the range of 2-3 seconds in functional MRI. The serendipitous observations triggered by the pioneering work in Biswal et al. (1995) showed that low frequency fluctuations in the blood oxygen level dependent (BOLD) signal, which can be detected even at the modest temporal resolution of fMRI, are highly informative of brain network organization. Correlations in very low frequency domains (c. 0.1>f>.01 Hz; Cordes, et al. 2001) probably reflect network-specific fluctuations in local field potentials, i.e. the local summation of neuronal electrical activity (Schölvinck, et al. 2010, Leopold, Murayama and Logothetis 2003). Outside the ASD literature, the dominant fcMRI approach, commonly called *intrinsic fcMRI* (Van Dijk, et al. 2010), has focused on such spontaneous, low-frequency BOLD fluctuations in resting state fMRI data. This approach has been successfully implemented in the study of numerous networks, such as motor (Jiang, et al. 2004, Kim, et al. 2010), visual (Lowe, Mock and Sorenson 1998, Cordes, et al. 2000, Nir, et al. 2006), auditory (Saur, et al. 2010), language (Hampson, et al. 2002), reading (Koyama, et al. 2011), working memory (Lowe, et al. 2000), task control (Dosenbach, et al. 2007, Seeley, et al. 2007), default mode (Greicius, et al. 2003, Wang, et al. 2012), and attention (Fox, et al. 2006) systems.

In the very first fcMRI study of ASD, Just and colleagues (2004) showed that BOLD signal correlations associated with sentence comprehension were reduced between a number of region pairs in adults with ASD and proposed an 'underconnectivity theory' of autism. Consistent with this, evidence of reduced functional connectivity in ASD has been reported in many studies that tested finger movement (Mostofsky, et al. 2009), visuomotor coordination (Villalobos, et al. 2005), face processing (Kleinhans, et al. 2008), sentence comprehension (Kana, et al. 2006), response inhibition (Agam, et al. 2010, Kana, et al. 2007, Lee, et al. 2009), verbal working memory (Koshino, et al. 2005), problem solving (Just, et al. 2007), attention orienting (Fitzgerald, et al. 2014), cognitive control (Solomon, et al. 2009), self-representation (Lombardo, et al. 2010, Mizuno, et al. 2011), and theory of mind tasks (Mason, et al. 2008, Kana, et al. 2009, Kana, et al. 2012). The apparent convergence of these findings led to the tentative conclusion of a "first firm finding" in ASD (Hughes 2007).

A closer look at the long list of studies cited above, however, shows a methodological complication that greatly impacts the interpretation of the findings. In all of the above studies, BOLD signal changes were prompted by domain-specific tasks. As described above, this differs from the intrinsic functional connectivity (iFC) approach. While the iFC paradigm has generally dominated the functional connectivity literature of the past two decades (Biswal, et al. 1995, Fox and Raichle 2007, Van Dijk, et al. 2010, Buckner, Krienen and Yeo 2013, Power, Schlaggar and Petersen 2014), this has not been the case in ASD connectivity research. More recently, however, the early predominance of task-related 'co-activation' fcMRI studies of ASD has been superseded by a growing number of iFC studies. Results from these have been much more complex. A number of studies that statistically regressed out task-related effects in order to isolate intrinsic low-frequency fluctuations reported extensive overconnectivity effects in ASD (Noonan, Haist and Müller 2009, Shen, et al. 2012, Shih, et al. 2010, Shih, et al. 2011, Keehn, et al. 2013, Mizuno, et al. 2006). This suggests that removal of task-related or stimulus-driven effects shifts the distribution of findings from under- to overconnectivity, consistent with a meta-analysis (Müller, et al. 2011) and two empirical comparative method studies (Jones, et al. 2010, Nair, et al. 2014). However, this approach of isolating intrinsic BOLD fluctuations from data acquired during task performance – though legitimate in principle (Fair, et al. 2007) – has been implemented in ASD primarily only by a single group (our own) – warranting caution. A much larger number of studies have instead implemented a resting state fcMRI approach. Findings from this literature are by no means conclusive, ranging from predominant underconnectivity (von dem Hagen, et al. 2012, Gotts, et al. 2012, Abrams, et al. 2013, Anderson, et al. 2011, Di Martino, et al. 2014) to mixed findings (Keown, et al. 2013, Nair, et al. 2015, Washington, et al. 2013, Monk, et al. 2009, Lynch, et al. 2013, Doyle-Thomas, et al. 2015, Abbott, et al. 2015, Fishman, et al. 2014, Fishman, et al. 2015) and even to predominant overconnectivity (Khan, et al. 2015, Delmonte, et al. 2013, Di Martino, et al. 2011, Chien, et al. 2015, Cerliani, et al. 2015, Supekar, et al. 2013, Carper, et al. 2015). While they suggest that a generalized underconnectivity account of ASD is too simple, the question remains what may explain the divergent findings. Aside from effects of task, which as described above demonstrably tend to boost 'underconnectivity' effects in ASD (unless the task taps into an 'island of strength', Keehn, et al. 2013), there must be other factors, which we will now discuss.

Why do findings diverge?

The fcMRI technique had been implemented in ASD for many years before the field grew aware of issues related to head motion. While in conventional activation fMRI, head motion of 2-3mm (quite common in children or clinical populations) may be acceptable, several groups (Power, et al. 2011, Satterthwaite, et al. 2013, Van Dijk, Sabuncu and Buckner 2012) demonstrated that even micromotion in the sub-millimeter range had dramatic effect on fcMRI findings because motion-related signal changes may co-occur in many voxels across the brain, resulting in mostly inflated signal correlations (Power, Schlaggar and Petersen 2015).

The ASD community was not prepared for this. By late 2010, only four out of 32 published fcMRI studies had presented statistical tests of potential group differences in motion (Müller, et al. 2011). The conclusion that underconnectivity in early studies may have been an artifact of group differences in motion was obvious (Deen and Pelphrey 2012), but this account is clearly too simple. First, greater head motion in ASD groups would be overall more likely to inflate (not deflate) signal correlations (Power, et al. 2014), resulting in pseudo-overconnectivity. Secondly, some more recent iFC studies that carefully removed motion effects and matched groups for motion still had predominant underconnectivity findings (Di Martino, et al. 2014, Nair, et al. 2013, Starck, et al. 2013). While scrupulous treatment of head motion is surely crucial in fcMRI (Power, Schlaggar and Petersen 2015), it will not fully resolve apparent inconsistencies in the ASD literature.

Another proposal in this regard relates to global signal regression (GSR), i.e., the use of mean brain signal fluctuations across time points as a nuisance regressor. An initial study (Jones, et al. 2010) suggested that overconnectivity effects were an artifact of GSR. While clearly a powerful tool for noise reduction (Power, et al. 2014), GSR may distort group differences (Saad, et al. 2012, Gotts, et al. 2013), possibly because global signal fluctuations in part reflect true neuronal activity changes (Schölvinck, et al. 2010). An example is provided in Figure 1. However, many studies have reported overconnectivity findings in the absence of GSR (Fishman, et al. 2014, Shih, et al. 2011, Supekar, et al. 2013, Redcay, et al. 2013, Keehn, et al. 2013), contrary to the hypothesis by Jones and colleagues.

Yet another account of fcMRI inconsistencies concerns developmental stage. Uddin et al. (2013) hypothesized that overconnectivity in younger children with ASD may be followed by underconnectivity in adolescents and adults. The proposal rightly points to the importance of maturational schedules, which probably differ between typically developing (TD) children and those with ASD. It also presents an interesting analogy to well-established anomalies in anatomical growth, with early overgrowth in ASD between years 2 and 4 years (Hazlett, et al. 2011, Schumann, et al. 2010, Shen, et al. 2013), and preliminary findings from DTI studies that may suggest precocious white matter development in the first few years in ASD (Solso, et al. 2015, Weinstein, et al. 2011, Wolff, et al. 2012). Using near-infrared spectroscopy Keehn et al. (2013) also reported increased functional connectivity in 3-month old infants with high-risk of ASD (compared to low-risk infants) and a 'cross-over' to underconnectivity in these infants by age 12 months. All these latter findings highlight the need to interpret findings with respect to maturational changes. However, they are not readily consistent with the timeline proposed by Uddin et al. (2013) because they suggest 'cross-over' from early overgrowth and overconnectivity to later flattened growth and underconnectivity in infancy or during the toddler years. In addition, some empirical evidence from fcMRI appears to directly contradict the hypothesis: For example, Dinstein et al. (2011) report interhemispheric underconnectivity in 12-46 month-old toddlers with ASD. Some studies including adolescents and adults have reported overconnectivity in ASD (Monk, et al. 2009, Shen, et al. 2012, Cerliani, et al. 2015, Fishman, et al. 2015, Fishman, et al. 2014, Abbott, et al. 2015, Khan, et al. 2015). Di Martino et al. (2014), in the largest available iFC study incorporating 360 ASD participants (7-56 year old), found that differences from TD controls were mostly stable across different ages. Surveying the entire ASD fcMRI literature, a preponderance of underconnectivity findings in adults can indeed be found. However, it is partly due to the fact that one highly productive group, which applied co-activation methods testing for task-related BOLD correlations, happened to study adolescents and adults (Just, et al. 2004, Just, et al. 2007, Kana, et al. 2006, Kana, et al. 2007, Kana, et al. 2009, Koshino, et al. 2005, Koshino, et al. 2008, Mason, et al. 2008, Damarla, et al. 2010, Mizuno, et al. 2011). The appearance of a 'developmental' pattern in the literature may therefore be in part methodological in nature.

Findings from Nair et al. (2014) suggest that methodological factors (other than GSR) have dramatic impact on group differences detected between ASD and TS samples. This study comparatively analyzed three datasets along competing pipelines. The most striking finding was that for each dataset, effects ranged from robust underconnectivity to robust overconnectivity in ASD, depending on methodological choices. Significant variables were type of analysis (co-activation vs. intrinsic fcMRI, as described above) and field of view (regions of interest vs. whole brain). Co-activation analyses limited to regions of interest tended to detect underconnectivity, whereas intrinsic fcMRI analyses testing for effects across the whole brain yielded mostly overconnectivity (see Figure 2 for an example). Three drastic conclusions could be drawn. (1) *You find what you'd like to find:* Investigators predetermine through methodological choices the probability of detecting under- or overconnectivity in ASD. (2) *If you don't look, you won't find:* Studies limited to regions of expected effects may miss the bigger picture of overconnectivity elsewhere in the brain. (3) *FCMRI doesn't really work:* The fcMRI approach produces such unstable results that it may be unsuitable for investigating abnormalities of the autistic brain.

However, such conclusions would be overly pessimistic and unwarranted. While lack of replication is a serious problem in ASD (as discussed below), the same problem applies to ASD studies using other techniques and approaches (Yerys and Herrington 2014, Fletcher and Grafton 2013). Given evidence of the general reliability of fcMRI (Birn, et al. 2013, Buckner, Krienen and Yeo 2013, Shehzad, et al. 2009, Van Dijk, et al. 2010), it is more likely that inconsistencies actually reflect the sensitivity of the technique to subtle variability in study cohorts or methods. Such sensitivity can be a strength, if critical variables are controlled. The methodological literature has made some first steps towards such control, as described above, but deeper issues remain, as will be discussed below. Differential results from co-activation and intrinsic fcMRI approaches should not be contrasted as 'right' or 'wrong'. The challenge is to understand why task-induced BOLD correlations may tell an often completely different story from intrinsic low frequency fluctuations observed during the 'resting' state.

The advantages of co-activation (task-induced) fcMRI are relatively good control over cognitive state and its changes (which may be largely determined by response to the known sequence of task trials) and specificity of the functional domain under study (with a task designed to tap into a domain of interest, e.g., face processing). However, skeptics may point out that stimulus-induced BOLD changes can be correlated between two regions even if these are not connected to each other, simply because they receive concurrent input from a third region (Jones, et al. 2010). In addition, co-activation fcMRI primarily reflects online processing, rather than underlying functional architecture. This latter issue points to the potential main strength of intrinsic fcMRI, which may provide insight into the nature of network organization because of its sensitivity to activity- and experience-driven Hebbian mechanisms of plasticity (Jolles, et al. 2013, Lewis, et al. 2009, Luo, et al. 2012, Schultz, Balderston and Helmstetter 2012, Vidyasagar, Folger and Parkes 2014). While task-induced FC measures may thus be limited to a relatively 'shallow' and transient measure of online cooperation between brain regions, iFC may provide 'deeper' insight into the brain's functional architecture and its plasticity. However, the focus on spontaneous BOLD fluctuations comes at a cost, related to the condition under which data are acquired.

Challenge No.1: 'Resting' state

The study of iFC is often equated with the use of data acquired in a 'resting' state. However, when instructing participants to relax, think of nothing in particular, and keep their eyes closed (without falling asleep) or open and fixated on a cross on a screen, one actually gives them a task (to abide by the instructions, while at the same time keeping very still, not falling asleep etc.). There is awareness of the problem in the field (Buckner, Krienen and Yeo 2013), but there are only partial solutions (e.g., video-recording participants to monitor awake state). This is so because the resting state fundamentally discards principles of experimental cognitive psychology that have dominated functional neuroimaging for decades (e.g., Petersen, et al. 1989). These principles demand the tightest possible control of cognitive state during an experiment. In other words, an experiment needs to be designed in a way to transparently drive the brain to perform certain well-defined operations, usually in a subtraction design, in which task conditions differ by only a single added cognitive component (Price and Friston 1997). None of these iron rules apply to the resting state. Instead, resting state fcMRI emerged from a haphazard observation that error residuals in conventional fMRI data analyses, usually considered noise, actually had surprising spatial specificity (Biswal, et al. 1995, Hyde and Biswal 1999). The exponential growth of iFC in the past 20 years was not founded on

incremental hypothesis-driven advances, but on a serendipitous discovery. There was never a plan, but the technique proved to be miraculously powerful. Given its success in the study of the healthy adult brain, it was soon applied to clinical populations, including ASD. Ten years after the first resting state fcMRI study of ASD (Cherkassky, et al. 2006), the field now has to go back and do the groundwork because a crucial question remains unanswered: Although resting state iFC works so well in the healthy adult brain, could it work *differently* in a disorder such as ASD, which is known for its atypical response to environmental setting and stimulation?

The question has many facets. Some belong to basic science. The iFC methods field is still working to uncover the basic neurophysiological mechanisms at the root of synchronized low-frequency BOLD fluctuations (Schölvinck, et al. 2010, Schmithorst, et al. 2014). Even if these were completely understood, we could not assume that they work exactly the same way in the autistic brain. Functional MRI has been used in ASD for almost 20 years (Ring, et al. 1999, Baron-Cohen, et al. 1999). However, to the present day little research has been done to test whether neurovascular mechanisms generating the BOLD effect may be different in ASD. Given changes in these mechanisms during typical development (Schmithorst, et al. 2014) and the frequent observation that children with ASD appear neurofunctionally immature (Shih, et al. 2011, Fishman, et al. 2014, Nair, et al. 2013, Ben-Ari 2015), an atypical BOLD effect in ASD is not at all unlikely. A recent study using arterial spin labeling, an MRI technique for quantitative measurements of regional perfusion, tantalizingly reported that robust correlations between local perfusion and local iFC detected in TD children were absent in children with ASD, suggesting an atypical relation between baseline blood flow and BOLD correlations (Jann, et al. 2015).

Other facets of the question are more practical. For example, does the uncomfortable, constricted, and noisy environment inside the MRI bore affect people with ASD differently from neurotypical people? Eilam-Stock and colleagues (2014) recently reported reduced skin-conductance responses (SCRs) during resting state fMRI in adults with ASD. Furthermore, SCRs were correlated with FC of visual and medial temporal regions in people with ASD, whereas in neurotypical adults they correlated with regions of default mode and salience networks (including posterior cingulate gyrus and anterior insula). This suggests that autonomic states and links between these states and observed FC patterns may be atypical in ASD. A related question is whether participants with ASD may experience more (or less) anxiety or stress than control counterparts during scanning. Any such differences would be expected to affect the BOLD signal and its low frequency fluctuations (McMenamin and Pessoa 2015, Bijsterbosch, Smith and Bishop 2015).

Yet another aspect of the question has to do with the low sampling rate in fMRI (typically around 2 sec) and the common, indeed almost ubiquitous, practice of analyzing datasets for activation or connectivity effects across the prolonged period of one (or even several) acquisition runs (i.e., ≥5 minutes). However, the brain does not work statically, but constantly undergoes dynamic change.

Challenge No.2: Dynamic connectivity

FCMRI studies of ASD have almost exclusively reported BOLD correlations (or some other measure of signal synchronization) for time series of five or more minutes duration. In the methods literature at large, the limitation of this *static fcMRI* approach has been recognized (Hutchison, et al. 2013). An alternative *dynamic fcMRI* approach uses a sliding window technique that detects BOLD correlations for each time window (e.g., 40 sec), successively shifted forward. This yields a higher-order time series of correlations that reflects dynamic changes (Chang and Glover 2010). Using this approach in healthy adults, FC within the default mode network (DMN) was found to be variable across time (Chang and Glover 2010, Handwerker, et al. 2012), possibly reflecting mind-wandering (Christoff, et al. 2009). Allen et al. (2014) expanded these findings identifying large 'zones of instability' (changes across time), not only in the DMN, but also in lateral parietal, extrastriate, and prefrontal regions bilaterally, which they attribute to changes in vigilance (cf. Stamatakis, et al. 2010). Given these spatially extensive findings, it is possible that most static fcMRI findings of ASD may have been affected by undetected differences in temporal variability. An obvious example concerns FC between posterior cingulate/precuneus and medial prefrontal nodes of the DMN, which is extremely robust in the TD brain, but has been found reduced in ASD (Monk, et al. 2009, Assaf, et al. 2010, Murdaugh, et al. 2012, Starck, et al. 2013, von dem Hagen, et al. 2012, Washington, et al. 2013, Abbott, et al. 2015, Doyle-Thomas, et al. 2015). This represents one of the most replicated fcMRI findings in ASD; yet does such a finding from static fcMRI truly imply 'underconnectivity'? Since it reflects reduced correlation across a long

time series, an alternative explanation of greater variability across time could equally apply. This latter account would not imply any architectural impairment of the DMN in ASD, but could be related to more frequent changes in default mode-related cognitive states (e.g., in mind wandering) in people with ASD.

Dynamic fcMRI will surely play a role in the exploration of iFC changes across time, which promises to enrich our understanding of network abnormalities in ASD. However, given limits in temporal sampling rate and sluggishness of the BOLD response, even advanced multiband fMRI protocols cannot rival the temporal resolution of electrophysiological techniques. A review of the EEG and magnetoencephalography (MEG) literature on connectivity in ASD is beyond the scope of this chapter. We will therefore solely mention a few studies that serve as examples of how MEG data can enrich our understanding of functional connectivity in ASD, in at least four respects. First, MEG can identify not only regions in a functional circuit that may activate at atypical levels (detectable also in fMRI), but also those activating at normal levels but with atypical latency (beyond the temporal resolution of fMRI). For example, Pang et al. (2016) showed atypical activation in left cuneus during production of meaningless syllables in children with ASD, accompanied by normal-level activation in right inferior frontal gyrus that occurred at atypically short latency. Second, MEG permits the investigation of signal coherence or synchronization in high frequency domains that are thought to be crucial for online cognitive processing, in particular the γ range (>30Hz) (Canolty, et al. 2007). The finding of reduced γ power in response to simple auditory clicks in children and adolescents with ASD may therefore indicate reduced binding between crucial perceptual brain regions (Wilson, et al. 2007). Another recent finding was reduced fronto-temporal synchronization in the α band during a working memory task in children with ASD (Urbain, et al. 2015). Third, MEG detects signals in several high-frequency bands and patterns of anomaly in ASD may differ across these. For example, Kitzbichler and colleagues (2014) found widespread higher global efficiency (increased connectivity) in α (8-12Hz) and γ (30-70Hz) bands, but reduced efficiency for β (13-30Hz) and δ bands (1-2Hz) in frontal and occipital lobes in participants with ASD during rest. Fourth, divergent patterns in different frequency bands may elucidate organizational principles to which fcMRI is largely blind. For example, Khan et al. (2015) reported differential effects in γ and mu-β bands possibly suggesting increased feedforward, but reduced feedback connectivity in the somatosensory system in ASD. (Khan, et al. 2013)(Keown, et al. 2013, Maximo, et al. 2013)Based on these examples from the as yet small MEG literature, major contributions to an improved understanding of network dynamics and its abnormalities in ASD can be expected.

Anatomical connectivity

As mentioned previously, intrinsic fcMRI examines correlated activity between distal regions as a method of assessing stable networks that have evolved as a result of Hebbian processes. Of course, this correlated activity requires some form of underlying structural connectivity, that is, physical (axonal) connections. Such connections need not be direct, however, which is an important caveat to the interpretation of intrinsic fcMRI studies. Simultaneous input from a third region, or multiple regions, could also drive correlated (or inversely correlated) activity. Diffusion weighted MRI (dMRI) is one method allowing *in vivo* examination of the white matter connections *underlying* functional networks. This may also help to disambiguate typical functional networks from those that reflect *compensatory* networks (i.e. those that show typical correlated activity via atypical physical connections).

Diffusion MRI works by measuring the Brownian motion of water molecules within tissue at the sub-voxel level (Le Bihan, et al. 1986). This random motion is impeded when it encounters structures such as cellular membranes, intracellular filaments, or proteins. When such structures are highly organized, for example when a bundle of axons run parallel to each other, diffusion will be hindered perpendicular to the axons, but comparatively free parallel to the bundle. By applying a series of differentially oriented field gradients during data acquisition, dMRI samples the diffusion at multiple directions (from 6 in early dMRI sequences, to ≥60 in more recent high angular-resolution diffusion imaging (HARDI), to 270 within the Human Connectome Project (Sotiropoulos, et al. 2013)). Microstructural changes such as differences in myelination, organization, or axon caliber are reflected in changes of the quantities derived from dMRI (Beaulieu 2002, and see below for limitations in interpretation). The most commonly reported diffusion-derived measures are derived from the mathematical tensor and referred to as

diffusion tensor imaging (DTI). While axial diffusivity (AD) reflects the direction of greatest diffusion within a voxel and the magnitude of that diffusion, radial diffusivity (RD) quantifies diffusion in the orthogonal plane, and mean diffusivity (MD) measures the overall diffusion, regardless of direction. The most commonly reported tensor measure, fractional anisotropy (FA), varies between 0 and 1 and provides an index of the degree to which water *preferentially* diffuses in the axial rather than the radial direction. Eigen-vectors are also derived from the tensor to describe the predominant direction of diffusion (on average) within each voxel and are often interpreted as indicators of the primary axon orientation. Below we review the current DTI literature on ASD, discuss some of the challenges faced in this methodology, and briefly mention some of the ways these challenges are being addressed.

Findings in children, adolescents and adults

The first dMRI study in ASD (Barnea-Goraly, et al. 2004) reported reduced FA diffusely throughout white matter in adolescents with ASD compared to TD. Reduced FA, as well as increased MD, has been observed in most subsequent diffusion studies of school-age children, adolescents, and adults, including studies using region or tract of interest approaches (Sundaram, et al. 2008, Sahyoun, et al. 2010), voxel-based morphology (VBM, Barnea-Goraly, Lotspeich and Reiss 2010, Keller, Kana and Just 2007), and Tract-Based Spatial Statistics (TBSS, a VBM approach adapted specifically for use in cerebral white matter, Jou, et al. 2011, Shukla, 2011 #1767, see review in Travers, et al. 2012). However, the localization of reported differences has varied across studies, with significant effects reported in uncinate (Poustka, et al. 2012, Cheon, et al. 2011, Jou, et al. 2015), superior and inferior longitudinal fasciculi (Jou, et al. 2011, Shukla, Keehn and Müller 2010, Poustka, et al. 2012), corpus callosum (Alexander, et al. 2007, Keller, Kana and Just 2007, Shukla, Keehn and Müller 2010), cerebellum (Cheung, et al. 2009), and projection tracts (Nair, et al. 2015, Keller, Kana and Just 2007). A meta-analysis of ROI-based studies including data from several hundred participants (Aoki, et al. 2013) found significantly reduced FA or increased MD in corpus callosum, uncinate, and superior longitudinal fasciculus either unilaterally or bilaterally, but not cingulum, inferior longitudinal, or inferior fronto-occipital fasciculus. However, not all tracts were equally represented in the literature and only association tracts were considered in the report. Spatial specificity of the meta-analysis was therefore limited, and age effects were not considered. A handful of studies have reported more mixed effects, including increased FA or decreased MD in some white matter tracts, but even these varied spatially (Cheung, et al. 2009, Sahyoun, Belliveau and Mody 2010, Sivaswamy, et al. 2010). This variability may be due, in part, to methodological limitations such as inter-subject alignment, motion artifacts and biases, and complex fiber crossings (discussed below).

Findings in infants and toddlers

Diffusion studies in infants and toddlers with ASD are still limited, but indicate *increased* FA compared to TD children during the earliest years (Ben Bashat, et al. 2007, Weinstein, et al. 2011). These findings appear to mirror the atypical developmental trajectory seen in volumetric studies of early ASD, with accelerated development in the first years of life, but atypically slow growth following (Courchesne, et al. 2001, Hazlett, et al. 2011, Hazlett, et al. 2012, Schumann and Nordahl 2011, Carper and Courchesne 2000, Carper and Courchesne 2005, Zielinski, et al. 2014). In toddlers around 3 years of age, Weinstein (2011) found significantly greater FA in corpus callosum, left superior longitudinal fasciculus, and cingulum. Partially supportive findings come from a longitudinal examination of at-risk infants (younger siblings of children diagnosed with ASD) comparing those who met ASD criteria at 24 months to those who did not (Wolff, et al. 2012). FA tended to be higher for the ASD-positive group at the first (6 month) time point; however, developmental slopes for FA were steeper (increasing more rapidly) for the ASD-negative than the ASD-positive group in both projection and association tracts, resulting in a 'cross-over' of effects during the second postnatal year. A similar difference in developmental trajectories for FA was found in several frontal tracts (but not posterior tracts) in a cohort-sequential study of 1 to 4 year olds (Solso, et al. 2015) and in the corpus callosum in a cohort-sequential study of 3 to 41 year olds (Travers, et al. 2015). This pattern of precocious development followed by a relative slowing, emphasizes the necessity of considering cohort age in all studies of neurodevelopment in ASD. Differences present at one age may appear reversed at a different maturational stage or may simply disappear during the cross-over period or when a wide age range is included.

Challenge No.1: Understanding micro-structural underpinnings

The advent of dMRI was a boon for neuroimaging, providing previously inaccessible insight into the organization and condition of the network of axonal connections that make up white matter from in vivo studies across early development. Our ability to interpret quantitative dMRI findings in microstructural terms is still limited however (see (Beaulieu 2002, Beaulieu 2011) for review). We may wish to draw conclusions about the "strength" of anatomical connections, the number of axons in a fascicle, or the degree of axonal myelination, but dMRI only measures the diffusion of water molecules in tissue, and any interpretation in the neuroanatomical terms of interest remains indirect. Water diffusion is hindered by various cellular and extracellular structures – such as cell membranes, filaments, or proteins – and it is this hindrance that is detected in dMRI. A single $1mm^3$ voxel may contain $3x10^5$ axons of various diameters (e.g., in corpus callosum, Aboitiz, et al. 1992), as well as oligodendrocytes (myelin) and other glial cells, whereas measured quantities (e.g. FA, MD, or RD) reflect average diffusion within a voxel, that is, diffusion within and between all of these cells types. In organized axonal bundles, FA and AD are high compared to gray matter. The proportion of myelin is one important contributor to this difference, but not the only one. Boundaries provided by axonal membranes are also key, as evidenced by animal studies comparing anisotropy in myelinated and unmyelinated nerves (Beaulieu and Allen 1994). Intra-axonal neurofibrils also make a distinct, though quantitatively smaller contribution, and in animal models, selected loss of axonal neurofibrils can lead to an increase in AD without affecting RD (Kinoshita, et al. 1999). Differences in axonal caliber or packing density can alter these dependent measures as well (Takahashi, et al. 2002), as does the overall homogeneity of axonal organization within a given voxel (see below).

Any or all of these microstructural differences can lead to a change in the measureable characteristics of water diffusion. Because it is unknown in an *in vivo* sample which of these sub-voxel factors drives a change or group difference in the voxel average, vague terms like "white matter compromise" are frequently used in DTI studies. Unfortunately, such non-specific descriptions seem to imply neuronal breakdown or poor myelination that simply cannot be concluded from the data available (Jbabdi and Johansen-Berg 2011, Jones, Knösche and Turner 2012). The most commonly reported DTI measures, FA and MD, seem to be most susceptible to this over-interpretation. AD and RD may be slightly less ambiguous and now appear more frequently in DTI reports, but still reflect within-voxel averages. Findings from conventional DTI have improved our understanding of network organization in ASD – but, at present, we cannot conclusively determine what exact microstructural differences the findings reflect. Recent development and implementation of multi-shell diffusion sequences, which rapidly sample at multiple b-values (gradient strengths), will help to improve this. These techniques allow quantification of different water compartments within a single voxel (Sotiropoulos, et al. 2013, White, et al. 2013, Zhang, et al. 2012), with different models estimating intracellular and extracellular water fractions, orientation distribution functions of these compartments, or neurite density within a voxel.

Challenge No.2: Complex fiber orientations

Another challenge of dMRI arises from the presence of multiple fiber orientations within sampled voxels. As with scalar measures (FA, AD, RD) estimates of diffusion *direction* within a voxel reflect the average of the axons contained, which may be in the hundreds of thousands. Axons may not all be in parallel, two or more bundles may cross within a voxel, or 'kiss', fan-out, or bend, any of which can result in nearly identical diffusion measures from traditional tensor-based analytic approaches (Jbabdi and Johansen-Berg 2011, Jones, Knösche and Turner 2012). Tractography can therefore not reliably trace true axonal pathways since generated streamlines (the computational *approximations* of axonal pathways) may fail to extend through areas of crossings or may go off-course and 'jump' from one axonal bundle to another. For this reason it is vital to compare dMRI-derived tracts (streamlines) to gold-standard axonal anatomy (e.g. axonal tracing through autoradiography) to verify anatomical validity. However, even this may be inadequate when studying clinical populations with potential deviations from normal anatomy.

Methodological advances in both acquisition and analysis of dMRI are improving our ability to resolve and interpret complex fiber crossings. Improvements in gradient hardware and sequence programming allow higher angular resolution. At the same time, a diversity of higher-order modeling approaches are moving beyond tensor-based calculations, particularly in conjunction with the multi-shell diffusion acquisitions mentioned above (Figure 3). Whereas tensor-based tractography usually models only one or at best two fiber directions within a voxel, newer

algorithms assess the likelihood of complex fiber architectures and attempt to model them (Farquharson, et al. 2013, Jbabdi, et al. 2012, Tournier, Mori and Leemans 2011, Tournier, et al. 2008). This leads to estimation of more complex orientation distribution functions rather than eigenvectors, and is more successful at tracking through these regions.

Challenge No.3: Motion

Similar to issues in fcMRI described above, diffusion results can also be adversely affected by head motion (Figure 4), which commonly occurs in the study of children and clinical populations. Limited artifacts can be filtered out by removing affected portions of the data, a standard step in data processing, but subtle differences may remain and may bias quantitative findings. In a methodological study, Yendiki et al. (Yendiki, et al. 2013) reported that group-wise differences in small amounts of head motion could lead to spurious between-group findings (such as the commonly reported finding of reduced FA in ASD). Remarkably, this was also observed when a single TD group was split solely on the basis of head motion (i.e., the subsample with greater head motion appeared to have significantly higher RD, but lower FA and AD than the subsample with less motion). This is further supported by a study of healthy adults in which subject motion was found to bias DTI measures, particularly MD (Ling, et al. 2012). These studies raise the possibility that inconsistencies in the ASD literature may be partly explained by insufficient motion matching between groups and some reported differences may be artifactual (Koldewyn, et al. 2014). It remains to be determined whether larger sample sizes or other analytic approaches will be more sensitive to group differences and therefore more robust to motion.

Perspectives

Much of the previous sections on functional and anatomical connectivity in ASD have focused on methodological complexities resulting in non-replications or inconsistencies in the data (Fletcher and Grafton 2013). In the remainder of this chapter, we will first outline a model that may accommodate many (though not all) connectivity findings described above, and will then sketch a roadmap of how neuroimaging findings may ultimately bridge the gap between basic science and treatment of ASD.

A developmental model of neurofunctional organization in ASD

Typical development is characterized by the interplay between constructive processes (e.g., synaptic strengthening, axonal myelination) and regressive events (e.g., synaptic pruning, axonal loss), which are governed by activity and experiential interaction with the environment (Kandel, Jessell and Sanes 2000, Quartz and Sejnowski 1997). These principles determine changes in individual neurons and synapses, but also in larger functional networks, which become progressively more integrated (more strongly connected internally), and also more differentiated from other networks (through pruning of connections whose activity levels do not warrant inclusion within the increasingly specialized network). Much of the fcMRI literature suggests that both constructive and regressive processes are diminished in the functional development of the autistic brain, resulting in a dual impairment of reduced integration and differentiation (or segregation) of networks (Rudie, et al. 2012, Shih, et al. 2011, Fishman, et al. 2015), which may be described as reduced 'network sculpting' (Figure 5). In support, many (though not all) underconnectivity findings have been reported between regions that belong to one network or can be expected to co-activate, whereas overconnectivity findings have been frequently reported for regions outside the bounds of a neurotypical network (Doyle-Thomas, et al. 2015, Nair, et al. 2014). Both underconnectivity (e.g., Abrams, et al. 2013) and overconnectivity (Fishman, et al. 2014) have been found to be associated with symptom severity, suggesting that both aspects of the hypothesized dual impairment have clinical relevance.

Although the network sculpting model may grossly account for neurofunctional patterns detected in children and adults with ASD, it has limited depth of causality because it does not capture *why* constructive and regressive processes may be impaired in ASD. A link with early disturbances of brain growth (Courchesne, et al. 2001), possibly accompanied by precocious development of anatomical substrates of connectivity (Wolff, et al. 2012) at a time when experiential input cannot yet guide the formation of fine-tuned and fully functional networks, is conceivable, but confirmation will have to await long-term longitudinal studies following individuals with ASD

from infancy into adolescence. Given the strong (though by far not absolute) heritability of ASD (Hallmayer, et al. 2011), the ultimate causes surely involve genetic risk.

From genes to treatment: Can neuroimaging bridge the gap?

The number of genes that have been identified to convey some risk of ASD is in the hundreds and growing (Geschwind and State 2015). The task of developing mechanistic models linking these numerous genes with the emergence of idiopathic autism is thus highly complex. On the upside, many of the risk genes appear to converge functionally, as they affect synaptic formation and function (Baudouin 2014, De Rubeis, et al. 2014, Lanz, et al. 2013, Toro, et al. 2010, Sahin and Sur 2015). A similar convergence argument can be made with respect to genetic causes of syndromic forms of ASD (fragile X, tuberous sclerosis, or Angelman syndrome, Ebrahimi-Fakhari and Sahin 2015). While this supports the importance of connectivity science in ASD, the convergence claim requires more than simple counting of the many risk genes that somehow relate to the synapse and circuit formation. The question is whether the number of genes affecting the synapse among all ASD risk genes is actually significantly higher than expected when compared to the proportion of genes with such function within the entire human genome.

Regardless of the answer to this question, genetics alone can at present not fully achieve either of two crucial goals in research on idiopathic ASD: (1) To provide diagnostic markers (sets of risk genes) that would predict ASD before a behavioral diagnosis is possible; (2) to differentiate subtypes of the disorder, which are presumed to exist (Happé, Ronald and Plomin 2006). The problem, in simple terms, is that each susceptibility gene for idiopathic ASD, if affected in isolation, may carry only minimal risk. ASD may emerge when there is polygenic burden (multiple hit scenario), with a critical number of risk genes being affected (Brandler and Sebat 2015), possibly accompanied by environmental risks (Braunschweig, et al. 2013, Kalkbrenner, et al. 2015) and risks involving non-brain bodily systems (such as gut microbiome, Hsiao, et al. 2013).

Neuroimaging may play a pivotal role in linking genetic risk and phenotypic symptomatology. As explained in the previous section, imaging in children or adults cannot have the same 'causal depth' as the study of genetic and epigenetic risk factors. This only partial causal depth, however, may be exactly what is needed to bridge the gap between the depth of the genetic approach and the causal shallowness of behavioral features. Any neuroimaging feature reflects causal disturbances (pre-natal or early postnatal) only indirectly because it is compounded by maturational, environmental, and therapeutic effects. Imaging features thus combine cause and outcome, although in ways that are probably so complex as to limit the success of hypothesis-driven research. An important alternative is therefore to resort to data-driven approaches that can extract complex patterns of interest from highly multivariate data sets.

Data-driven machine learning approaches have been implemented in a number of ASD studies in the past few years. For example, Ecker and colleagues (2010) reported that distributed patterns of cortical thickness differences predicted diagnostic status (ASD vs. TD) with c. 85% accuracy in small samples of adults. Ingalhalikar et al. (2011) applied a similar approach to DTI data in a larger sample of children (N=75), achieving c. 80% diagnostic prediction accuracy, based on widely distributed white matter differences. However, common leave-one-out validation in these studies may overestimate predictive accuracy through overfitting to the idiosyncrasies of the dataset at hand. Some recent machine learning studies using iFC data have instead used external validation datasets (i.e., strict separation of data used for training and validation). One group first achieved c. 70% prediction accuracy for a large iFC matrix (including >26 million ROI pairings) in a very small validation sample (Anderson, et al. 2011). They followed up with a study implementing the same approach in a much larger sample (N=964) from the Autism Brain Imaging Data Exchange (ABIDE) (Di Martino, et al. 2014), reporting an accuracy of only 60% (Nielsen, et al. 2013). However, this disappointing result does not imply that iFC is inadequate for diagnostic prediction. The modest accuracy in the study by Nielsen et al. (2013) can be primarily attributed to two fundamental problems. The first concerns the use of multisite data, which boosts sample size, but introduces numerous factors of variability beyond those already present in single-site datasets. A second issue concerns the validation process. While use of an external validation dataset is clearly preferable (as it prevents inflated accuracy through overfitting and may thus generate findings for the ASD population at large), it can result in overly conservative estimates of accuracy. If a prediction algorithm is trained on one dataset, validation in a separate dataset will likely be successful only if that dataset is actually comparable, i.e., tightly matched to the training set on all relevant demographic and

clinical variables. Crucially, both sets would need to be matched on their composition with respect to ASD subtypes. Yet although such subtypes are generally expected (Geschwind and Levitt 2007, Happé, Ronald and Plomin 2006), they remain unknown and cannot therefore be matched (cf. Chen, et al. 2015). Ultimately, diagnostic prediction from imaging data may be an elusive goal because of a faulty premise: There can be no unique set of brain features for a disorder that is not unique, but is instead defined by a clinical umbrella term that is derived from behavioral observation and probably encompasses an unknown number of neurobiologically distinct disorders.

Identifying subtypes that are defined by differential neurodevelopmental etiology is therefore of utmost importance. It will help resolve some methodological issues, such as the validation problem described above or the need for more homogeneous ASD samples to be compared to TD samples in hypothesis-driven imaging (or other) studies. A more important implication relates to the baffling complexity of genetic findings mentioned above. Some of this complexity is likely a reflection of the 'umbrella status' of ASD and shallow diagnostic procedures ('shallow' in the same sense as above, because far removed from developmental causation). Why would anyone expect tractable genetic and epigenetic causation for a *set* of disorders that is only loosely held together by a wide range of outcome observations? On the other hand, for any biologically defined *subtype*, causation may be more tractably linked to risk genes and environmental factors. However, the field is facing a vicious circle: In order to optimally analyze data in the pursuit of subtypes, we would first need to know the subtypes. A way out may be the use of large (sample size) and rich data (large number of features for each participant) combining genetic, environmental, neuroimaging, and behavioral variables with multivariate pattern recognition tools.

However, as much of a scientific advance as all of the above would mean, the ultimate question remains: How does this help children with ASD and their parents? Knowledge of subtypes would open up the possibility of fully mechanistic developmental models of each type of disorder on the autism spectrum. Such efforts are already underway for ASD-related syndromes, such as Fragile-X, whose genetic causes are known (Fung and Reiss 2015). However, these syndromes account for only a small fraction of the population under the ASD umbrella. Large and rich imaging data, in particular those capturing brain connectivity – in combination with genetic, epigenetic, and behavioral data – may eventually isolate subtypes of the disorder on the way to a full understanding of causation and the development of optimally tailored treatments.

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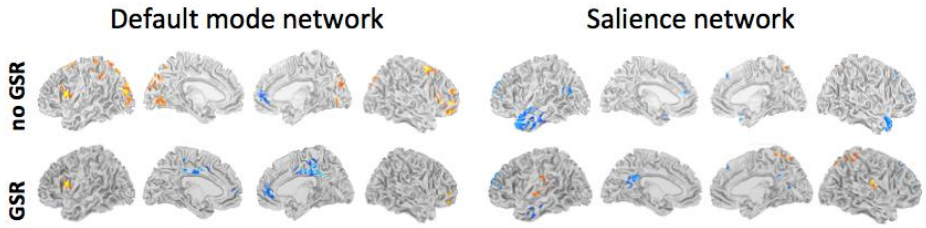

FIGURE 1
Whole brain intrinsic functional connectivity for representative seeds of default mode network (DMN: medial posterior cingulate cortex) and salience network (SN: right anterior insula). While for analyses without global signal regression (GSR; top row), a distinctive pattern of predominant overconnectivity for DMN, but predominant underconnectivity for SN is observed, this pattern is lost with application of GSR. Since findings are from the identical resting fMRI dataset, network-specific findings cannot be accounted for by differences in motion or other noise and therefore likely reflect true activity differences, which are obscured by GSR. Adapted from Abbott et al., *Cerebral Cortex* (2015).

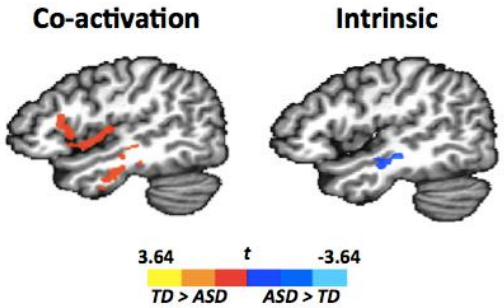

FIGURE 2
Significant BOLD correlations for a seed in left fusiform gyrus. Data are taken from a study by Keehn et al. (*Human Brain Mapping*, 2013), which also provided seed location based on activation peak for a visual search task. While task-driven correlations are greater in the TD group, suggesting greater functional connectivity, the opposite is found in an intrinsic functional connectivity analysis (with low bandpass filtering and after regressing out effects of task paradigm). Adapted from Nair et al. (*Human Brain Mapping*, 2014).

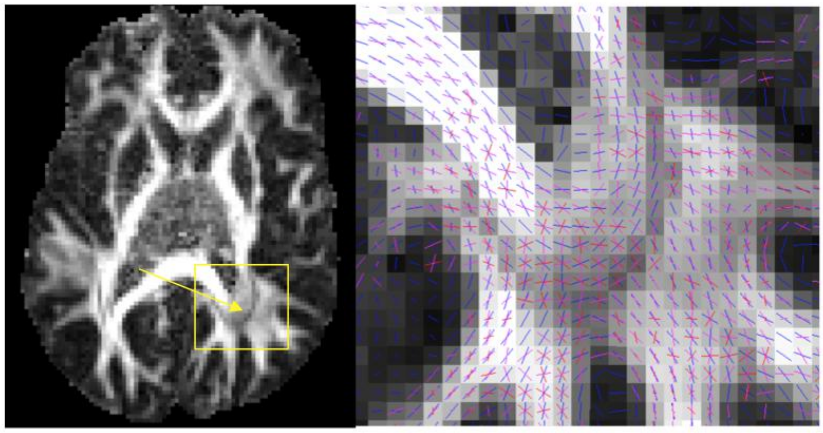

FIGURE 3
Whereas traditional DTI (left: FA image) struggles with areas of crossing fibers (arrow, low FA values), multi-shell diffusion acquisitions and analysis algorithms model multiple fiber directions within a single voxel (right: primary fiber direction in blue, secondary and tertiary in red/fuchsia when present). Acquisition: 2 shells (b=1500, 3000) with 46 diffusion directions each.

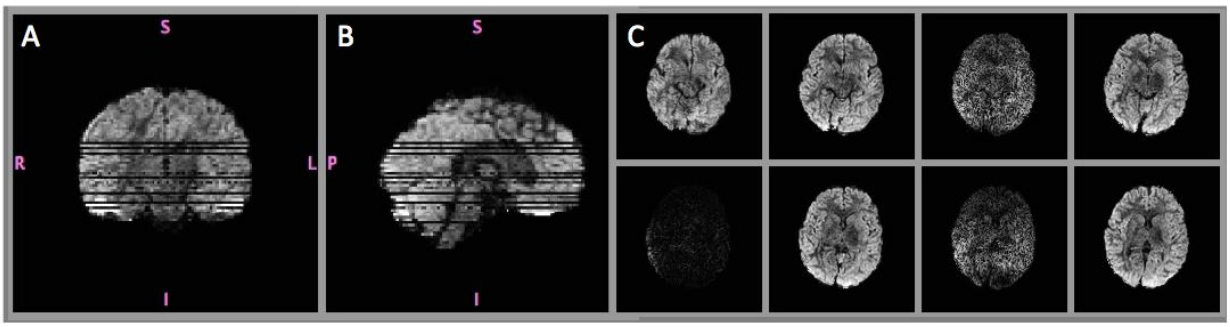

FIGURE 4
Example of motion-induced slice dropout seen in diffusion weighted imaging. Coronal (A) and sagittal (B) views with signal loss evident in several slices. Sequential axial slices from the same scan session shown in (C). Dropout of this type may be seen in one or many diffusion sensitization directions examined in a single EPI examination and may bias the eigenvectors calculated from the tensor.

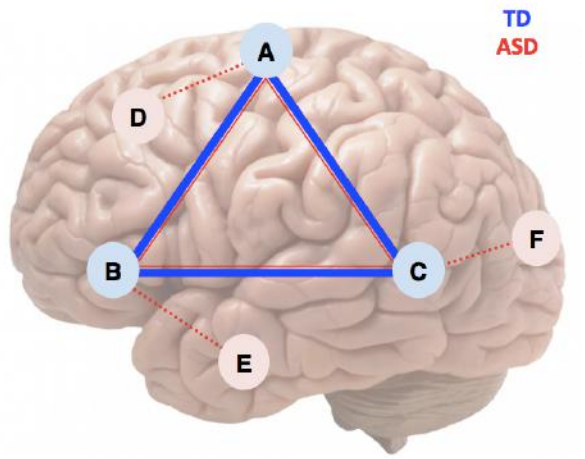

FIGURE 5
Diagrammatic illustration of the reduced network sculpting hypothesis. An exemplary network with 3 nodes (A-C) is shown. Interconnectivity between these nodes (network integration) is robust in the TD brain and reduced in the autistic brain. However, in ASD the brain maintains residual connectivity with extraneous regions (D-F) that do not participate in the network in the mature TD brain (but may have been connected to it at immature stages of development). This residual connectivity reflects impaired network differentiation (or segregation).

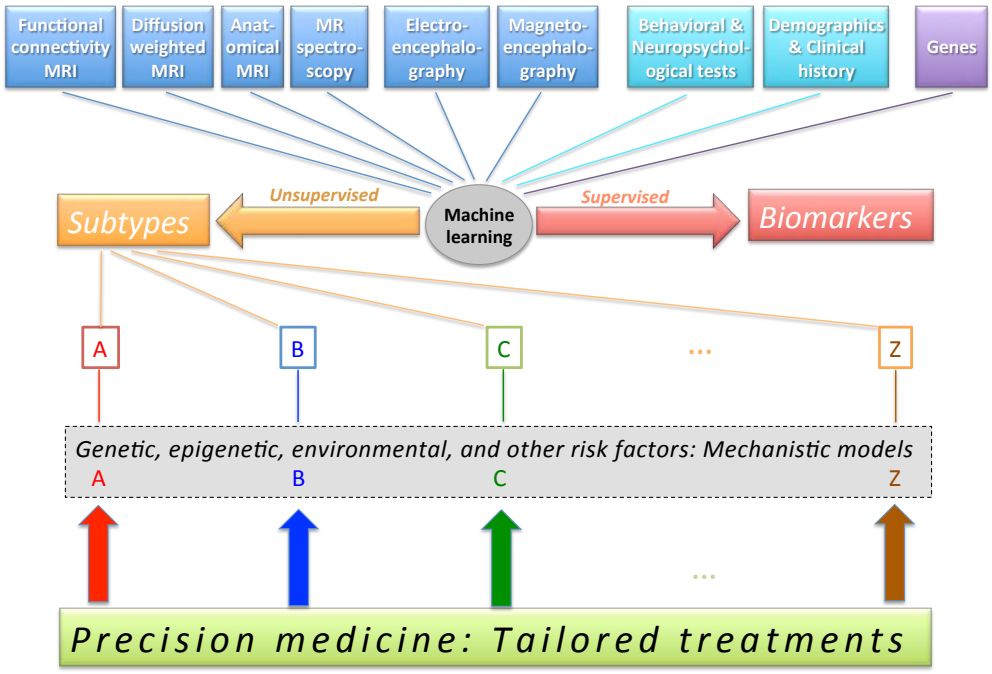

FIGURE 6
Rich data approach to diagnostic prediction (through supervised machine learning, on the right) and subtype identification (through unsupervised machine learning, on the left). Example input data types included in multivariate analyses are shown at the top. For each subtype A to Z detected in unsupervised clustering analyses, a mechanistic model linked to a specific set of causal factors (gray dotted rectangle) may be developed and treatments may be fine-tuned to each subtype and its etiological model.