Functional Connectome–Based Predictive Modeling in Autism

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Abstract

Autism is a heterogeneous neurodevelopmental condition, and functional magnetic resonance imaging–based studies have helped advance our understanding of its effects on brain network activity. We review how predictive modeling, using measures of functional connectivity and symptoms, has helped reveal key insights into this condition. We discuss how different prediction frameworks can further our understanding of the brain-based features that underlie complex autism symptomatology and consider how predictive models may be used in clinical settings. Throughout, we highlight aspects of study interpretation, such as data decay and sampling biases, that require consideration within the context of this condition. We close by suggesting exciting future directions for predictive modeling in autism.

Autism spectrum disorder (hereafter, autism) is a neurodevelopmental condition characterized by difficulties with social communication and interaction as well as restricted and repetitive behaviors (1) and atypical responses to sensory information. There are limited empirically validated treatments for autistic features, especially with respect to medical interventions. Methods that improve our understanding of the brain-based characteristics underlying this condition could ultimately guide clinical research and practice by identifying targets for individualized interventions.

Functional magnetic resonance imaging (fMRI) connectivity analyses (2) have yielded tools that localize brain circuits supporting specific behaviors. These approaches can be used to infer brain-behavior relationships at the individual level that are validated through predictive models. Prediction-based approaches offer a statistically rigorous framework (by using separate data for model training and testing) to study individual differences (3–5), particularly in neurodevelopmental conditions (6). Here, we assert that models have two broad areas of utility in autism: 1) to deepen our understanding of how functional connections coalesce to give rise to the complex autism symptomatology (hereafter, biological insight) and 2) to potentially assist in diagnosis, prognostication, intervention planning, and monitoring of intervention response (hereafter, clinical utility) (7) (Figure 1A).

With these two areas in mind, we review the autism predictive modeling literature, focusing on studies using MRI functional connectivity data. Consistent with the lifelong nature of autism, we consider studies across a wide range of participant ages (6 months to 65 years). After detailing autism-specific study design considerations, we discuss three predictive modeling frameworks: case-control classification, dimensional prediction, and subtyping applications (Figure 1B). In each section, we emphasize brain-based insights and identify areas in which we expect predictive models to yield clinical utility. Because brain-based insights underlie clinically useful models (and vice versa), we weave their discussion together throughout the text to stress their interdependence. The goal of this review is to highlight key papers of interest and discuss conceptual considerations that can make autism predictive models more useful (8). Our goal is not to perform an exhaustive, systematic review of machine learning approaches/algorithms in autism prediction studies; the reader is referred to (9–11) for comprehensive reviews summarizing recent progress.

AUTISM-SPECIFIC CONSIDERATIONS FOR PREDICTIVE MODELING

Predictive Models Offer Biological Insight and Potential Clinical Utility

For the purposes of this review, predictive modeling encompasses approaches using statistics to relate MRI functional connectivity measures to phenotypic measures (diagnostic status/ symptoms) (4) (see the Supplement for background about predictive modeling/machine learning). These methods separate a dataset into training and testing samples, then apply cross-validation or use external data to test the model. Here, we place emphasis on the functional features (connections and networks) selected through predictive modeling and the potential biological insights/clinical relevance they offer. For example, consider a model implicating connections in frontoparietal areas as important for social attention. Such a model yields biological insight into a complex phenotype by localizing circuits. The model may show clinical utility in the future by predicting which individuals are most likely to respond to behavioral interventions.

Balancing Large Sample Sizes, Concerns About Data Decay, and Site Effects

Predictive modeling studies in participants with autism (12) and neurotypical participants (13) have demonstrated that large samples are needed to obtain reproducible results. In the autism field, using large datasets generally means using data from the Autism Brain Imaging Data Exchange (ABIDE) (14,15) and/or the European Autism Interventions Multicenter Study for Developing New Medications (EU-AIMS) (16). A concern with these samples is data decay (17) and is related to sensitivity and specificity (concepts of relevance for case-control classification studies; sensitivity is an algorithm's ability to correctly classify individuals with autism who actually have the condition; specificity is an algorithm's ability to correctly classify neurotypical individuals who do not have the condition). Data decay means that over time, the capacity of a sample to reveal new, statistically significant relationships (such as sensitivity/specificity) decreases as the number of statistical tests performed in the sample increases (17). Concerns about data decay are not unique to autism research; a similar issue has been noted for those using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset (18).

In addition, ABIDE and EU-AIMS comprise data from multiple sites. Care must be taken to ensure that site effects are not confounding results (4); ComBat is one method investigators have used to minimize site effects (19,20). To help further mitigate concerns about data decay and site effects, other samples could be used to further validate predictive models (21), as has been done with other phenotypes (22). Using multiple datasets to ensure that results hold across samples is one way to increase generalizability of results (23). We describe these issues to increase awareness; we strongly advocate for openly sharing datasets.

Confounds, Tolerability of the Scanning Environment, and Consequences for Predictive Modeling

Confounds, or variables that relate to both the independent and dependent variables in a model, can drive spurious statistical relationships and lead to false conclusions. In-scanner head motion is a notorious confound in measures of functional connectivity (24) and is a concern in the autism field (25). Performing global signal regression decreases motion artifact (26) and strengthens brain-behavior relationships in those with autism (27) and in neurotypical individuals (28). Implementing global signal regression is not without controversy (29); see (30) for a full discussion, including how global signal regression can alter functional correlation structure and affect between-group comparisons.

Barring a consensus approach to remove the effects of head motion, individuals with high-motion data are often excluded in model building (27,31). This practice influences the participants included in predictive modeling studies. Relatedly, individuals with autism who tolerate fMRI scans and produce low-motion data tend to have fewer language/cognitive difficulties and higher IQs. These facts must be kept in mind when considering the feasibility of using predictive modeling in clinical settings. To diversify individuals with autism that meet data quality criteria, the length of the imaging protocol is often minimized by shortening functional scans (<5 minutes) and eliminating task scans. The trade-off is the limited scope of the data obtained. Fewer, shorter scans result in less reliable functional connectomes (32), and resting-state data tends to generate poorer prediction performance (in neurotypical individuals) (31). Exact solutions to confounds depend on analysis goals, but we point the reader to (33) for an examination of confounds in the UK Biobank (and ways to address them). To increase reliability of functional connectomes, we recommend collecting more scanning data (both task and rest data) and/or using methods to increase the quality of scanning data [Framewise Integrated Real-time MRI Monitoring (34), mock scan protocols (35), Inscapes (36)].

Comorbidities and Phenotypic Overlap

Individuals with autism have high rates of co-occurring conditions, including attention-deficit/hyperactivity disorder (ADHD) (37), anxiety disorders (38), and intellectual disabilities (39). Comorbidities can pose challenges for researchers, including how to covary for different diagnoses. Linking analytic approaches (i.e., dimensional and subtyping approaches) is one solution. For example, individuals with and without anxiety symptoms could be grouped into a priori subtypes [as in (40)], and separate dimensional models could be generated to predict autism symptoms in each group. Approaches allowing participants

to express subtype characteristics to varying degrees (multidimensional subtyping) (41) have also shown success in parsing heterogeneity.

Sex Imbalance in Autism and Sex-Specific Effects in Predictive Modeling

Sex effects play a role in predictive modeling in autism. There is an estimated 3:1 male:female imbalance in diagnoses (42), and there are sex differences in the neurobiology of autism (43). Females and males tend to exhibit different symptoms, often leading to missed diagnoses in females (44). Further, models predicting fluid intelligence in neurotypical individuals show higher accuracies when generated separately for each sex, and the functional features underlying the models are sex specific (31). Sex specificity aligns with the high degree of accuracy with which sex can be predicted using connectivity data in neurotypical individuals (45). Therefore, investigators should include equal numbers of males and females in analyses (when feasible) and/or build sex-specific models.

We next highlight how all of these factors can impact the biological and clinical utility of predictive modeling in autism as we review three different approaches: case-control classification, dimensional phenotype prediction, and subtype-specific prediction.

CASE-CONTROL CLASSIFICATION: THE CASE FOR FOCUSING ON DIAGNOSIS

Case-control classification studies (12,46–68) constitute most of the prediction literature in autism (Table 1). A strength of these studies is their unambiguous nature: participants are either correctly classified or not. Another strength is the large number compared with dimensional and subtyping prediction studies, allowing for broad trends to be observed. Below, we highlight the biological and clinical utility of a few of these studies through a developmental lens (69), spanning infancy into older adulthood (65+ years).

Brain-Based Features Implicated in Autism Classification Differ Across the Life Span

Autism is a lifelong condition, with symptoms changing across an individual's lifetime (70). The developmental changes are reflected in the neurobiological correlates differentiating individuals with autism from neurotypical participants. For instance, using a Gaussian kernel support vector machine and resting-state data from ABIDE, Kazeminejad and Sotero (58) have shown that the functional features most discriminative of autism status in 5- to 15-year-olds (connections involving the parietal and ventrolateral prefrontal cortices) differ from those most discriminative in 15- to 30-year-olds (with more connections involving the dorsolateral prefrontal cortex and temporal cortex). Across studies, the general theme of developmental effects holds: the functional network organization discriminating autism cases from neurotypical participants seems to be different at different stages of the lifespan (58,71,72). Differences across the lifespan also hold in case-control studies using T1-weighted structural MRI data (73) and align with the dynamic nature of brain maturation (74,75).

From this evidence, we draw two conclusions. First, predictive models that do not generalize across different age groups should not be viewed as model failures (4). Age-specific models

for autism case-control classification might be necessary to maximize model utility. This observation is in line with longitudinal work conducted in children (11–18 years old), suggesting that functional networks change at different rates among those with autism and those without (76). Second, given the growing evidence, we can make some overarching observations and devise new hypotheses for testing. For instance, maturational trajectories of cortical areas tend to follow a hierarchical sensory-association axis (74). Unimodal sensory areas mature during childhood, and heteromodal association areas mature later in adolescence and young adulthood. Disruptions have been observed in this hierarchy in autism (77,78), making it intriguing to consider this axis in the context of classification. Perhaps developmental deviations along this functional axis could be used to more accurately delineate between individuals with and without autism? In the future, researchers could investigate this hypothesis in large datasets while keeping in mind autism-specific predictive modeling issues (particularly data decay; most recent case-control studies have been conducted in ABIDE) (Table 1).

Clinical Utility: Toward Early Diagnosis

A major push of clinically relevant research is to identify individuals with autism using objective biological markers at early stages of development (Figure 2), when support services can be most effective (79) [see (80) for a review of imaging markers of autism in infants]. Accurate prediction of case-control status using functional connectivity data has been demonstrated in individuals under 5 years of age (81). In a study of even younger ages, Emerson *et al*. (48) used functional connectivity data from 6-month-old infants imaged while sleeping and showed that a support vector machine could be used to predict autism status at 24 months of age (Figure 3A). The network models driving correct classification were complex (Figure 3B), comprising short- and long-range connections distributed across the brain, with many of these clustered in the parietal cortex. The neuroanatomical complexity of successful models is a theme we will note throughout this review.

Evidence that autism diagnoses can be predicted at young ages is promising and sets the stage for imaging even earlier in life. Findings from genetic studies suggest that changes in transcriptional pathways specific to autism may be evident during gestation (82). Given the advent of fetal imaging (83), future predictive models may be generated to gauge autism likelihood prenatally, thus enabling support services to be made available at birth (see the Supplement for a discussion of the ethics of such a scenario and the ethics of predictive modeling in general).

DIMENSIONAL PREDICTION: ACCOUNTING FOR COMPLEX SYMPTOMATOLOGY

Symptoms in a number of psychiatric conditions (84), including autism, exist on a continuum, and the line between what constitutes adaptive versus divergent behavior is often unclear. From a biological perspective, dimensional approaches can be used to characterize function in specific behavioral domains and identify underlying patterns of brain connectivity. The implicated functional circuits can then be monitored clinically following interventions (85). Despite the advantages, there are only a handful of dimensional

prediction studies (27,54,78,86–89) (Table 2). Below, we highlight work of interest in two areas: prediction of symptoms and prediction of cognitive phenotypes important for adaptive function.

Predicting Autism Symptoms

One of the first works demonstrating dimensional symptom prediction was conducted by Plitt *et al.* (87). In a sample of adolescents and young adults, the authors used resting-state connectivity data from a priori networks (default mode [DMN], salience, and frontoparietal) to predict (using ridge regression) changes in social behavior 3 years later. This early report was cause for excitement, in that a prediction approach could be used to interrogate the functional connections associated with a complex symptom.

Work since has used larger samples from ABIDE to search for brain-wide correlates of symptoms. For example, using resting-state data and connectome-based predictive modeling, Lake *et al.* (27) generated network models predictive of Social Responsiveness Scale (SRS) scores, as well as separate models predictive of Autism Diagnostic Observation Schedule scores (Figure 4A, B). While the two models shared some common regions (cerebellum and subcortical areas, regions increasingly recognized as important in cognitive and social processes) (90), they were largely distinct. The fact that different functional circuits were detected is encouraging: despite both instruments measuring social ability, SRS and Autism Diagnostic Observation Schedule scores are only somewhat correlated (27), arguing that potentially subtle relationships between brain and phenotype are detectable using predictive methods.

Once built, models can be applied to different datasets to test generalizability and to determine if different populations or phenotypes share neurobiological correlates. For example, Lake *et al.* (27) applied a connectome-based predictive modeling network built to predict SRS scores in individuals with autism (generated in ABIDE) to an independent sample of children with ADHD (ADHD-200) and found that the model predicted symptoms of inattention (Figure 4C). This is of note because of the high co-occurrence of autism and ADHD (91) and because of the brain regions (cerebellum, subcortical areas, and DMN) present within the model, which have been implicated as important for mediating aspects of internal and external attention (92). The DMN has also been found to play a significant role in theory of mind and making social inferences, processes commonly atypical in autism [reviewed in (93,94)]. Through a combination of two network models (89) —one for predicting communication, the other for predicting social interaction ability—the DMN also emerged as key for predicting social affect in autism. These results suggest that despite the complexity of symptoms in autism, it is possible to home in on neurobiological commonalities across studies.

Predicting Phenotypes Relevant for Adaptive Functioning

An avenue of clinical interest is generating dimensional predictive models for adaptive functioning. To this end, Rohr *et al.* (88), using resting-state data from ABIDE and connectome-based predictive modeling, generated network models predictive of a component of adaptive functioning—the ability to resist inappropriate behavioral impulses.

Their behavioral inhibition model consisted of distributed, whole-brain functional features, mostly within and between default mode, somatomotor, visual, and cerebellar areas, consistent with other work (92). These findings point to the feasibility of identifying relevant markers that can be tracked to measure improvement after behavioral interventions.

The notion of monitoring adaptive function in response to interventions goes hand in hand with predicting individual outcomes in the future (6,95). The work of Plitt *et al.* (87) suggests that this is possible for individuals with autism, in that changes in overall adaptive function could (remarkably) be predicted 3 years after imaging. Normative modeling approaches (96) have proven useful in disentangling heterogeneity in autism brain-behavior relationships using structural (97,98) and functional (99) MRI data; future work could apply these models to generate longitudinal phenotypic predictions. Future studies could also take a multidimensional approach to predict combinations of different phenotypes (86), as well as incorporating measures of functional connectivity dynamics (100).

SUBTYPING: SIMPLIFYING COMPLEXITY BY FINDING COMMONALITIES

There has been interest in identifying autism subtypes [reviewed in (101)]. This work aims to identify homogeneous clusters to interrogate the biological basis of each subgroup, offering more specific information for potential interventions. The existence of distinct clusters in autism is supported by results in multiple modalities, including structural MRI (102,103), electroencephalography (104), eye-tracking (105,106), and symptom-level measures (70,107).

Initial Efforts at Subtyping Connectomes

Subtyping methods based on clustering functional connectomes suggest at least two or three autism subtypes (41,108–112) (Table 3). Consistent with the distributed brain features identified by dimensional models, subtyping methods indicate that there is no focal brain area differentiating subtypes; brain-based features distinguishing subgroups are complex and spatially distributed. However, the DMN and the frontoparietal network (implicated in dimensional models) (27,78,89) seem to be most consistently involved in discriminating subtypes (101). To date, the majority of studies have been conducted in ABIDE and tend to be male focused. Future work should assess the reliability/generalizability of subtypes in different datasets, include more female participants, and use a combination of rest and task data (31,113). While most studies have focused on identifying nonoverlapping subtypes, sophisticated analytic approaches allowing participants to express different subtypes to varying degrees—dimensional subtyping—are beginning to be reported (41) and are reason for enthusiasm.

After connectome-based subtypes have been identified, they are typically validated by determining if some other measure, usually symptom information, differs between subgroups (114). For example, Easson *et al.* (109) applied *k*-means clustering to resting-state functional connectivity matrices from ABIDE and observed two distinct subtypes (Figure 5). The subtypes were composed of a mixture of individuals with autism and those without. Both subtypes showed wide-scale differences in connectivity. The hallmark feature of the first subtype was stronger connectivity between the DMN and cingulo-opercular,

somatomotor, and visual networks. The second subtype exhibited stronger within-network connectivity. Further, each subtype showed differences in brain-behavior relationships. That is, unique connectivity signatures in each subtype differentially predicted SRS and Autism Diagnostic Observation Schedule scores.

Toward Subtyping of Brain-Behavior Predictive Models

The fact that the subtypes identified by Easson *et al.* exhibited distinct brain-behavior relationships hints at the possibility of subtyping brain-behavioral predictive models. Crucially, these are subtypes based not on brain or phenotype alone, but on the relationship between them (112), setting them apart from work assuming that a single brain-phenotype predictive model is adequate across a sample (115). The groupings revealed by model-based subtyping may help to uncover clusters of individuals crossing diagnostic and demographic boundaries. In addition to data-driven approaches, hypothesis-driven model-based subtypes might also prove useful, whether based on symptom profiles (116,117) or other variables less expensive to measure, such as biological sex. Overall, the brain-based features derived through model-based subtyping will help yield insight into the biological underpinnings of autism (112,116). The phenotypic and demographic features differing across subtypes may help triage individuals for better care management.

LIMITATIONS

Concern has been expressed about the reliability of functional connections (118). There is work suggesting that with enough data per participant (>15 minutes/scan, allowing more reliable estimates of connections) (32), connectomes between individuals with autism and neurotypical individuals become quite similar (119). Most of the studies reported here include only a 5-minute scan. More work could be conducted to determine how increasing the amount of data affects predictive models, in terms of both accuracy and reliability (120). Aside from reliability, the precise biological nature of a functional connection remains elusive, a concern that must be acknowledged in predictive modeling studies.

An issue with case-control studies is the grouping of individuals into a single category. Individuals with autism have unique symptom profiles and complex neurobiological correlates of symptoms. Categorical diagnoses render it difficult to determine how specific aspects of a phenotype are supported by underlying brain circuits (84). Further, predicting a diagnosis is insufficient clinically; more individual-level information is needed to optimize care.

Concerns have been raised about dimensional studies in psychiatry (121,122). For example, severe communication difficulties in a person with autism might be the result of a different neurobiological process than the process supporting communication capacities in a neurotypical individual; it might be incorrect to assume that all individuals can be situated on a single dimension for a given phenotype (121). Certain dimensional indices (SRS) rely on parent/self-report measures; such measures may be weakly related to the symptom or behavioral constructs of interest (123). It is possible that a dimensional approach cannot be used to model all brain-phenotype relationships (124), and computational constraints might limit the practicality of dimensional methods due to the curse of dimensionality (122).

Subtypes in some psychiatric conditions have proved difficult to replicate across datasets (125,126), and a recent study reported an inability to define reliable subgroups in autism (127). It will be crucial to continue to test reproducibility and generalizability of autism subtypes. Additionally, interpretation of subtypes may be complicated by unmeasured, sample-dependent covariates. Collecting precise and inclusive demographic/clinical data can be used to correct for confounds (128), although hidden confounds may persist (129).

FUTURE DIRECTIONS AND CONCLUSIONS

We have reviewed how predictive modeling frameworks can offer insight into neurobiological correlates of autism, as well as potential clinical utility. Presently, case-control classification studies comprise most of the literature, allowing developmental trends to be observed. Due to the heterogeneity of individuals with autism, more dimensional and subtyping prediction studies are needed. All three prediction frameworks can be affected by the autism-specific modeling considerations discussed here. Classification approaches may one day enable early diagnoses (perhaps even in utero) using objective, biological data. Meanwhile, dimensional and subtyping studies may both deepen our understanding of the brain-based features behind autism and discover means of improving management through imaging-based prognostication and monitoring of intervention response.

Consistent with the complexity of autism symptoms, brain-based predictive models are complex and reveal large-scale networks supporting specific behaviors. To aid interpretation and translation, continuing to collect large datasets is essential (21). Ideally, the datasets will be broad (large numbers of diverse individuals with and without autism) (71) and deep (comprising many data modalities) (130). An example of a biological insight gained by a broad and deep approach is determining if specific genetic signatures underlie different connectivity phenotypes (131), and elegant work linking genes to complex brain activity patterns to behavioral phenotypes in autism is beginning to appear (40). A deep, multimodal focus might offer a marker common to fMRI and functional near-infrared spectroscopy (132) or electroencephalography (133), offering complementary information that can be used clinically (and is less expensive and better tolerated by some than fMRI).

Dense scanning approaches—imaging the same participants many times—have proven useful in neurotypical adults (134). Combined with innovative task paradigms, such as movie watching (135), dense scanning could provide large amounts of individual-level data during naturalistic social settings. Such an approach could help autism researchers better parse participant-specific trajectories (95). Ideally, dense scanning initiatives would comprise many individuals to maximize the detection of individual differences (see the Supplement for more about dense scanning in autism).

We do not suggest that the path forward will be easy. While expectations have been high, fMRI has largely failed to benefit individuals with autism to date. Aside from the difficulty in producing reliable fMRI results (136), there are numerous points at which findings can fail to translate (137). Research and clinical priorities do not always align (138), so it will be essential to maintain open channels between researchers, clinicians, individuals with autism,

and their caregivers. Going forward, we envision predictive modeling approaches continuing to aid the quest to understand the complex neurobiology of autism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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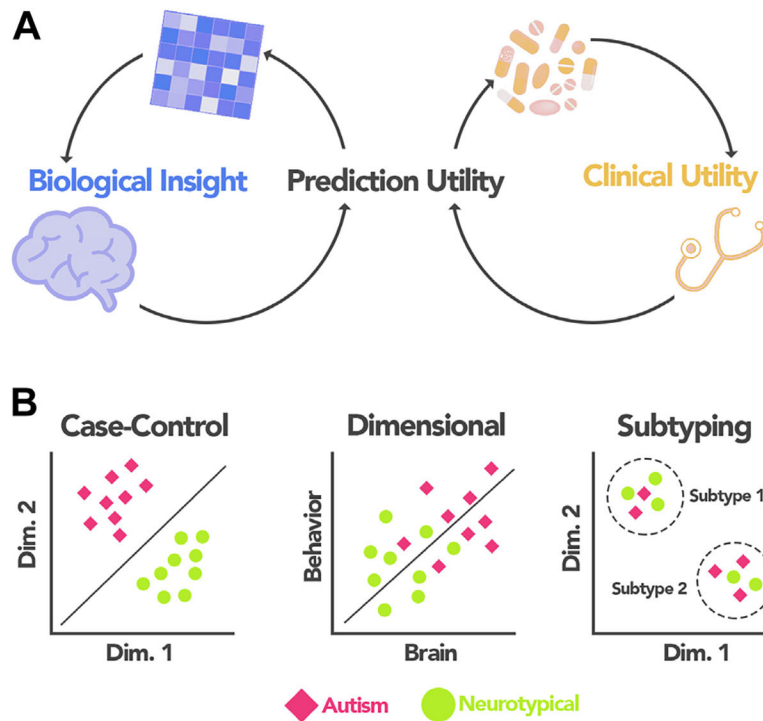
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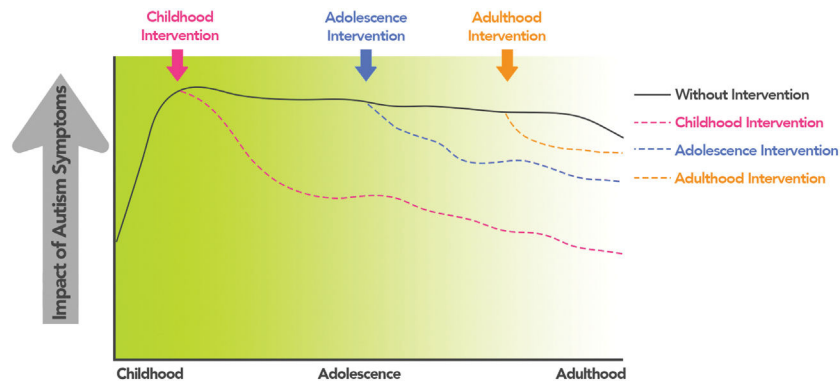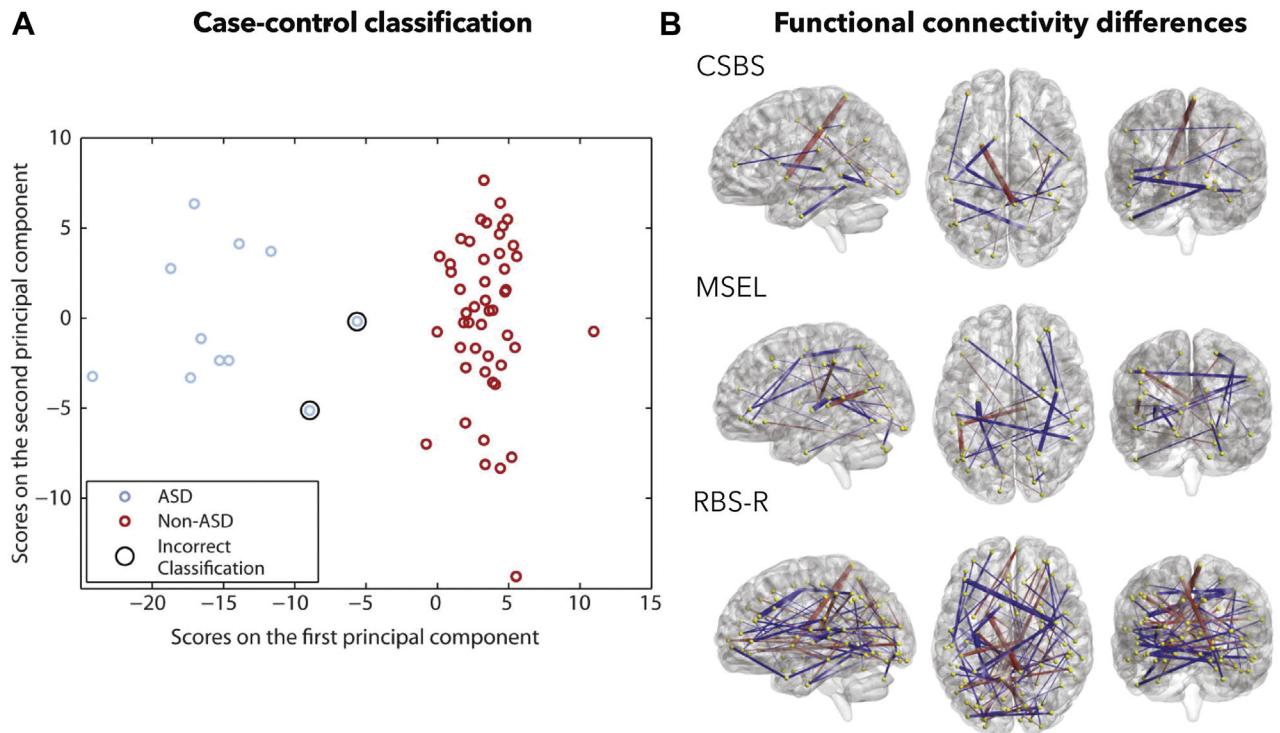
Figure 1.
Predictive modeling applications in autism. (**A**) Prediction-based approaches can serve two needs in autism research: they can help to disentangle the complex brain-based features giving rise to autism symptomatology (biological insight) or be used to potentially inform decisions related to providing care for individuals with autism (clinical utility). Because brain-based insights and clinically useful models are interdependent, their discussion is interwoven throughout the manuscript. (**B**) Three frameworks for prediction-based modeling using functional connectivity data that we discuss in this review: case-control classification, dimensional prediction, and subtyping. Dim., dimension.

Figure 2.

Windows of intervention in autism. The schematic illustrates the clinical utility of correctly identifying a hypothetical individual with autism and then acting on that information to provide appropriate support services. The dark line indicates the individual with autism and the impact of their symptoms (broadly conceived, on the y-axis) over time if no support services are accessed. If autism is diagnosed early (in childhood and adolescence), resources can be allocated to the individual and their caregivers (pink and blue dotted lines, respectively). If correct diagnosis and interventions are delayed, resources can still be leveraged later in life, although they might be less efficacious. The green shading indicates the utility of correct diagnosis and allocation of resources; the darker the green color, the more responsive individuals might be to support services. We stress that this is a hypothetical example; symptoms might not increase from childhood to adolescence, and individuals with late diagnoses might not necessarily have more significant symptoms overall. Indeed, trajectories of symptoms vary across individuals and can vary at different points in the lifespan.

Figure 3.
Case-control prediction is possible using measures of infant brain functional connectivity. (**A**) Classifying 24-month-olds using 6-month-old imaging data. Classification accuracy was 96.6%. (**B**) Post hoc visualization of functional connections and their relationship to different phenotypic scales. A red line indicates a connection that shows more negative connectivity in the autism group, whereas a blue line indicates more positive connectivity. ASD, autism spectrum disorder; CSBS, Communication and Symbolic Behavior Scales; MSEL, Mullen Scales of Early Learning; RBS-R, Repetitive Behaviors Scale-Revised. Adapted with permission from (48).
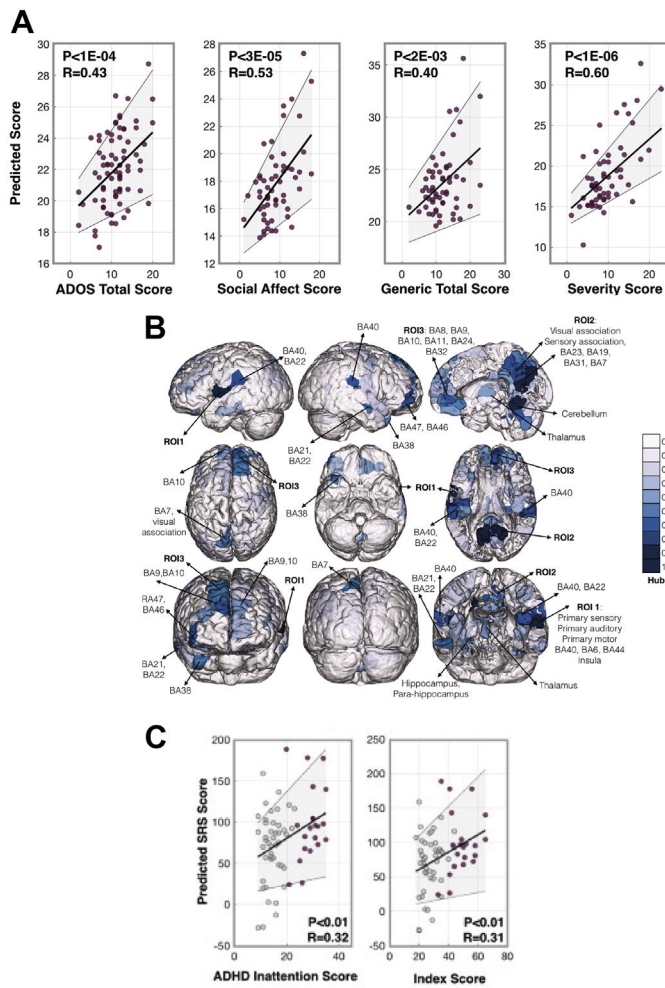
Figure 4.
Dimensional prediction of autism symptoms. (**A**) Models predictive of autism symptoms are built on training data and then validated on left-out testing data within the same dataset. Predicted symptom scores from this process are shown on the y-axis; observed symptom scores are shown on the x-axis. (**B**) Post hoc visualization of predictive functional features (data are summarized at the node level and are shaded according to degree). (**C**) Application of the predictive model derived from autism symptoms to an external dataset to predict attention-deficit/hyperactivity disorder (ADHD) symptoms in young children. ADOS, Autism Diagnostic Observation Schedule; BA, Brodmann area; ROI, region of interest [as defined in (33)]; SRS, Social Responsiveness Scale. Adapted with permission from (27).
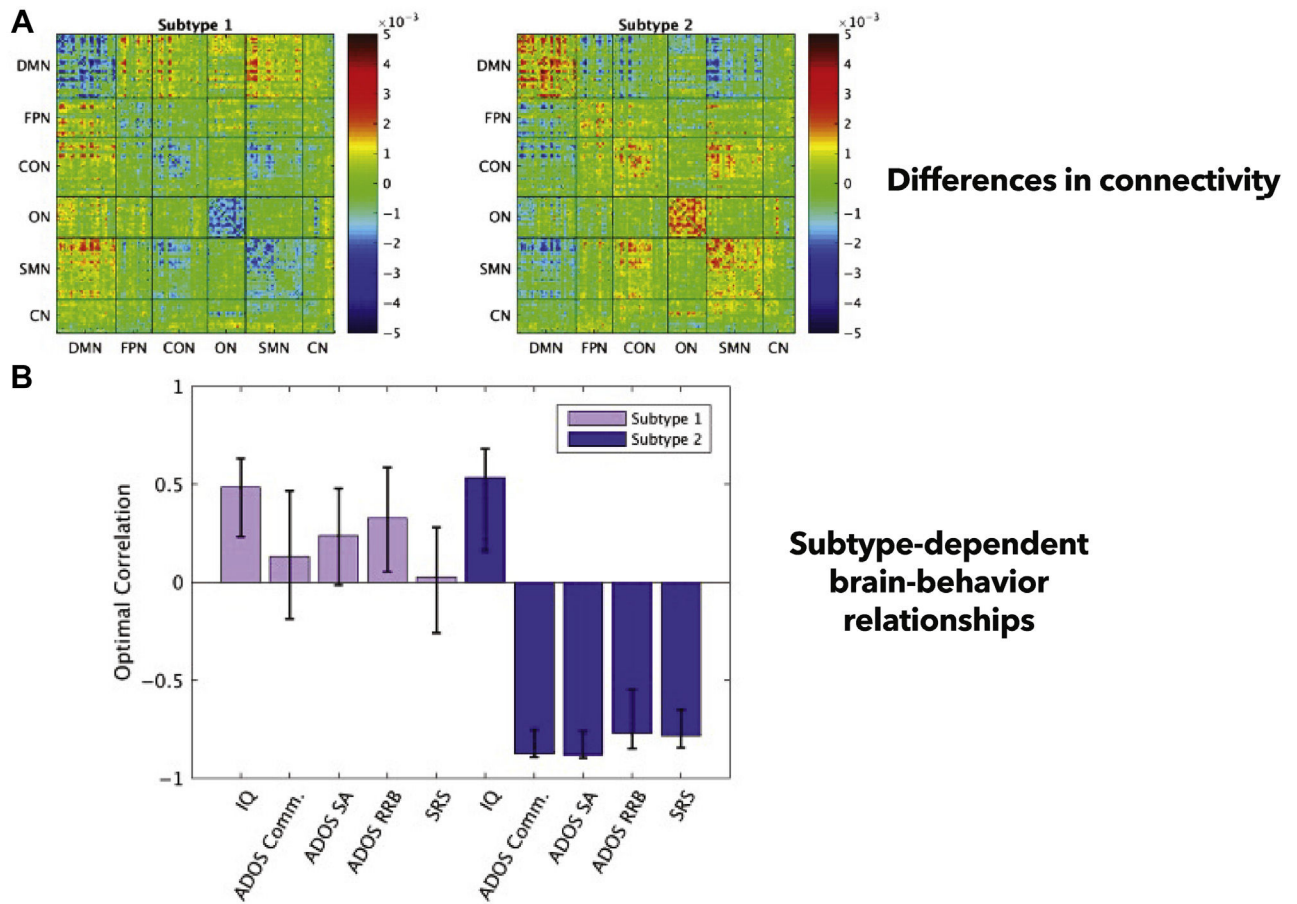
Figure 5.
Subtyping connectomes in autism. (**A**) Easson *et al.* (109) identified two subtypes. Each is composed of individuals with and without autism. These subtypes exhibit differences in functional connectivity patterns; an average matrix for each subtype is shown. (**B**) A multivariate brain-behavior analysis (partial least squares regression) reveals that subtypes exhibit unique brain-behavior relationships among a set of key behavioral measures in autism. ADOS, Autism Diagnostic Observation Schedule; CN, cerebellar network; Comm., communication; CON, cingulo-opercular network; DMN, default mode network; FPN, frontoparietal network; ON, occipital network; RRB, restricted repetitive behaviors; SA, social affect; SMN, sensorimotor network; SRS, Social Responsiveness Scale. Adapted with permission from (109).

Table 1.

Representative Autism Case-Control Classification Studies

Study	Data Source	n	Age, Years, Mean ± SD or Range	Male, %	Algorithm	Features	Validation	Accuracy (Sensitivity, Specificity)	Notes
(68)	Lab-specific	40 autism 40 NT	8–42	100%	–	FC from 7266 × 7266 ROIs	Internal (leave-one-out CV); external validation in independent sample	79% (83%, 75%)	External validation results: 71% accuracy, 75% sensitivity, and 69% specificity
(50)	Lab-specific	13 autism 14 NT	Autism: 21.4 ± 3.9 NT: 22.6 ± 4.2	100%	LRC	FC from 102 × 102 ROIs (AAL atlas) (139); seed-based connectivity	Internal (leave-one-out CV)	77.8% (76.9%, 78.6%)	Whole-brain classification results reported; seed-based accuracies ranged from 70% to 96%
(53)	Lab-specific	29 autism 29 NT	–	83%	LRC	FC from 106 × 106 ROIs (AAL atlas) (139)	Internal (leave-one-out CV)	(82.8%, 82.8%)	–
(52)	Lab-specific	20 autism 20 NT	Autism: 9.96 ± 1.59 NT: 9.95 ± 1.60	80%	LRC	Network FC maps (10 components)	Internal (leave-one-out CV); external validation in independent sample	78% (75%, 80%)	Best performing network (salience network) is shown External validation results: 83% accuracy, 67% sensitivity, 100% specificity
(46)	ABIDE	126 autism 126 NT	6–36	85%	RF	FC from 220 × 220 ROIs (Power atlas) (140)	Bootstrapping CV (one third left out); external validation set	91% (89%, 93%)	Various SVM pipelines also tested, with the highest accuracy obtained = 66%
(51)	Lab-specific	59 autism 59 NT	Autism: 17.66 ± 2.72 NT: 18.3 ± 3.05	100%	Various tested	Various tested	Internal (leave-one-out, stratified 3-fold, stratified 10-fold CV)	76.7% (70%, 83.3%)	Pipeline with the highest accuracy and positive predictive values is shown Classifier: SVM; features: FC from 162 × 162 ROIs (Destrieux atlas); validation: leave-one-out CV
(49)	ABIDE	312 autism 328 NT	6–19	84%	NN	FC from 90 × 90 ROIs (AAL atlas) (139)	Internal (leave-one-out, various k-fold CV strategies tested)	89.4% (92%, 87%)	Showing results for leave-one-out
(47)	ABIDE	112 autism 128 NT	12–18	85%	SVM	FC from 142 × 142 ROIs (Dosenbach atlas) (141); multiple frequency bands used	Internal (leave-one-out, 10-fold CV); leave-one-site-out CV	79.2% (77.8%, 80.5%)	Showing results for leave-one-out
(54)	Lab-specific, ABIDE	Lab-specific: 74 autism, 107 NT ABIDE: 44 autism, 44 NT	Lab-specific: ~30 ± 8 per site ABIDE: site-specific	82%	LRC	FC from 140 × 140 ROIs (extended BrainVisa Sulci atlas) (142)	Internal (leave-one-out CV); external validation	85% (80%, 89%)	Results are reported for leave-one-out; accuracy on external data = 75%
(48)	IBIS	11 autism 48 HR	2	69%	SVM	FC from 230 × 230 ROIs (including nodes from Power atlas) (140)	Internal (leave-one-out CV)	96.6% (81.8%, 100%)	–

Study	Data Source	n	Age, Years, Mean ± SD or Range	Male, %	Algorithm	Features	Validation	Accuracy (Sensitivity, Specificity)	Notes
(55)	ABIDE	55 autism 55 NT	8–19	76%	NN	FC from 116 × 116 ROIs (AAL atlas) (139)	Internal (5-fold nested CV)	86.36%	–
(57)	ABIDE	126 autism 126 NT	7–36	81%	RF, CRF	FC from 220 × 220 ROIs (Power atlas) (140)	External validation sample	66.7%	Highest accuracy using CRF in validation dataset shown here; highest accuracy using RF in validation data = 71%
(12)	ABIDE	403 autism 468 NT	Site-specific	Site-specific	SVM	Various tested	Internal (10-fold CV); leave-one-site-out CV	66.8%	Highest accuracy obtained in leave-one-site-out analyses using a dictionary learning-based atlas (143)
(56)	ABIDE	505 autism 530 NT	Site-specific	Site-specific	NN	FC from 200 × 200 ROIs (Craddock atlas) (144)	Internal (5-fold, 10-fold CV); leave-one-site-out CV	70 (74%, 63%)	Showing results for 10-fold CV
(58)	ABIDE	816 autism + NT	5–65	–	SVM	GT properties (AAL atlas) (139)	Internal (10-fold CV)	95% (97%, 91%)	Highest accuracy obtained across various pipelines, age groups (obtained in 30+ year olds) using sparse inverse covariance to estimate connectivity GT properties included various measures of integration, segregation, and centrality
(59)	ABIDE	505 autism 530 NT	Site-specific	Site-specific	NN	FC from 200 × 200 ROIs (Craddock atlas) (144)	Internal (5-fold, 10-fold CV)	70.3% (68.3%, 72.2%)	Showing results for 10-fold CV
(60)	ABIDE	408 autism 401 NT	Autism: 16.5 ± 6.7 NT: 16.8 ± 7.8	84%	NN	Various tested	Internal (various k-fold CV strategies tested); leave-one-site-out CV	73.2% (74.5%, 71.7%)	Showing results for 10-fold CV using a combination of features from AAL + HO + Craddock atlases, along with demographic data
(61)	ABIDE	506 autism 548 NT	16.86 ± 7.55	85%	SVM	FC from 200 × 200 ROIs (Craddock atlas) (144)	Internal (10-fold nested CV)	72.2% (68.6%, 75.4%)	–
(62)	ABIDE	505 autism 530 NT	Site-specific	Site-specific	NN	FC from 392 × 392 ROIs (Craddock atlas) (144)	Internal (10-fold CV); leave-one-site-out CV	70.2% (77.5%, 61.8%)	Showing results for 10-fold CV
(63)	ABIDE	505 autism 530 NT	–	–	NN	FC from 116 × 116 ROIs (AAL atlas) (139); voxel-wise × ROI FC	Internal (test set validation)	74%	–
(64)	ABIDE	45 autism 47 NT	7–15	78%	SVM	FC from 116 × 116 ROIs (AAL atlas) (139); various dFC measures	Internal (6-fold nested CV)	83% (82%, 84%)	Showing results from a combination of FC and dFC measures that resulted in best performance
(65)	ABIDE	505 autism 530 NT	–	–	NN	FC from 200 × 200 ROIs (Craddock atlas) (144)	Internal (10-fold nested CV); leave-one-site-out CV	76.4% (77.8%, 75%)	Showing results from 10-fold CV

Study	Data Source	n	Age, Years, Mean ± SD or Range	Male, %	Algorithm	Features	Validation	Accuracy (Sensitivity, Specificity)	Notes
(66)	ABIDE	403 autism 468 NT	–	–	NN	FC from 264 × 264 ROIs (Power atlas) (140)	Internal (10-fold CV)	79.2%	–
(67)	ABIDE	306 autism 350 NT	6–18	Varied by analysis	RF	FC from 237 × 237 ROIs [Gordon (145) + HO subcortical (146) + cerebellar (147) atlases]	Bootstrapping CV (one third left out)	62.5% (60%, 65%)	Main sample size is shown here; different subsamples were tested consisting of n = 200 with autism and n = 200 NT participants Results from subsample including males and females with no ADOS score cutoffs

Table adapted with permission from (9). Note that studies are arranged in chronological order such that more recent studies are at the bottom of the table.

AAL, automated anatomical labeling; ABIDE, Autism Brain Imaging Data Exchange; ADOS, Autism Diagnostic Observation Schedule; CRF, conditional random forest; CV, cross-validation; dFC, dynamic functional connectivity; FC, functional connectivity; GT, graph theory; HO, Harvard-Oxford atlas; HR, high risk; IBIS, Infant Brain Imaging Study; LRC, logistic regression classifier; NN, neural network; NT, neurotypical; RF, random forest; ROI, region of interest; SVM, support vector machine.

Table 2.

Dimensional Studies Using Functional Connectivity Data

Study	Data Source	n	Age, Years, Mean ± SD or Range	Male, %	Algorithm/ Approach	Features	Validation	Symptoms/ Phenotypes Predicted	Highlights
(27)	ABIDE, ADHD-200	ABIDE: 122 autism, 230 NT[a] ADHD-200: 77 ADHD, 35 NT	6–24	71%[b]	CPM (linear regression)	FC from 268 × 268 ROIs (Shen atlas) (148)	Internal (split half, leave-one-out CV; leave-one-site-out CV; external validation in independent sample	SRS, ADOS, ADHD-RS	SRS, ADOS predictive network models were largely distinct; SRS model generalized to predict inattention in a separate ADHD sample
(54)	Lab-specific	58 autism[c]	Not specified for dim. analyses	Not specified for dim. analyses	Linear regression	16 FC	Internal (leave-one-out CV)	ADOS, ADI-R	Functional connections identified as correctly classifying autism vs. NT status generalized to predict the communication domain of ADOS
(78)	ABIDE	103 autism	20.8 ± 8.1	100%	SVR	First score of principal connectivity gradient, stepwise connectivity maps	Internal (5-fold CV); leave-one-site-out CV	ADOS	Prediction of ADOS total and social cognition; DMN and primary visual areas highly represented in predictive models
(86)	ABIDE, LEAP	232 autism[d]	14.8 ± 6.5	74%	CCA	FC from 415 × 415 ROIs [Schaefer atlas (149) 1 subcortical atlas]	Leave-one-site-out CV	Various autism, social abilities scales	Multiple canonical variates predictive of left-out-site; connections within and between somatomotor, DMN, attention, visual networks implicated in models
(87)	Lab-specific	31 autism	17.9 ± 3.4	100%	Ridge regression	FC from DMN, SN, FPN networks (Power atlas) (140)	Internal (leave-one-out CV)	SRS, ABAS	Prediction of change in SRS and ABAS scores and prediction of time 2 SRS scores ~ 3 years after scanning
(88)	ABIDE	85 autism 191 NT	8–13	66%	CPM (linear regression)	FC from 268 × 268 ROIs (Shen atlas) (148)	Internal (leave-one-out, split-half CV); site 1 to site 2 prediction	BRIEF	Complex, brain-wide model with many edges in somatomotor, visual, and cerebellar areas; also edges in DMN and temporal lobe
(89)	ABIDE	82 autism	7–12	100%	Lasso regression	FC from 227 × 227 ROIs (Power atlas) (140)	Internal (leave-one-out CV)	ADOS	Separate predictive brain networks predicting communication and social interaction phenotypes can be merged to predict social affect scores

ABAS, Adaptive Behavior Assessment System; ABIDE, Autism Brain Imaging Data Exchange; ADHD, attention-deficit/hyperactivity disorder; ADHD-RS, ADHD Rating Scale; ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; BRIEF, Behavior Rating Inventory of Executive Function; CCA, canonical correlation analysis; CPM, connectome-based predictive modeling; CV, cross-validation; dFC, dynamic functional connectivity; dim., dimension; DMN, default mode network; FC, functional connectivity; FPN, frontoparietal network; LEAP, European Autism Interventions Multicenter Study for Developing New Medications Longitudinal European Autism Project; NT, neurotypical; ROI, region of interest; SN, salience network; SRS, Social Responsiveness Scale; SVR, support vector regression.

[a] Here, we report sample size used for most of the SRS analyses (SRS total scores as well as the following subscales: communication, motivation, and mannerisms). The sample size was n = 180 NT and 80 autism for predicting SRS cognition and awareness subscales and n = 79 autism and n = 58 autism for predicting ADOS modules 3 and 4, respectively.

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[b] Across SRS analyses, ~70% of the sample was male; in ADOS analyses, ~85% of the sample was male. Sex was not reported in the ADHD-200 sample.

[c] We report the sample size used in the ADOS dimensional prediction analyses. A total of 27 participants with autism were used in the ADI-R dimensional prediction analyses.

[d] A total of 125 individuals with autism and 78 control subjects from the LEAP cohort were used in Short Sensory Profile subscales analyses; demographics were roughly similar to the rest of the sample.

Table 3.

Subtyping Studies Using FC Data

Study	Data Source	n	Age, Years, Mean ± SD or Range	Male, %	Subtyping Approach	Features	Validation[a]	No. of Subtypes	Highlights
(41)	ABIDE, GENDAAR	306 autism[b]	15 ± 8	77%	LFA[c]	FC from 418 × 418 ROIs [Schaefer atlas (149) + subcortical atlas]	Multiple clinical and demographic measures	3	Subtypes had dissociable whole-brain hypo/hyper-FC and shared atypical FC in DMN. Individuals expressed multiple subtypes to different degrees. Subtype 1 = decreased FC (DAN, SM, SN, VN) and increased FC (including in DMN) in autism and with symptom severity. Subtype 2 = opposite patterns of FC (compared with subtype 1) with comorbid symptoms. Subtype 3 = complex mixture of increased and decreased FC; preferentially expressed in older male individuals.
(108)	POND	175 autism 93 ADHD 55 OCD 84 NT	12 ± ~4 diagnostic group	73%	k-means clustering	FC from 76 × 76 ROIs (Desikan-Killiany-Tourville atlas) (150)	Diagnostic and behavioral measures	2	NT participants and participants with autism split across two subtypes; ~80% of individuals with ADHD in subtype 1, ~80% of individuals with OCD in subtype 2; participants' distance ratio between two subtypes was significantly correlated with general adaptive functioning, social deficits, and inattention symptoms.
(109)	ABIDE	145 autism 121 NT	7–39	100%	k-means clustering	FC from 160 × 160 ROIs (Dosenbach atlas) (141)	SRS, IQ, ADOS	2	Subtype 1 (59% autism, 45% NT), subtype 2 (41% autism, 55% NT). Subtype 2 had decreased FC between networks and increased FC within networks relative to subtype 1. Subtypes did not differ in behavior, demographics, or IQ. PLS brain-behavior analyses showed FC correlations with a combination of symptom scores unique to each subtype.
(110)	Lab-specific	57 autism	9–18	82%	k-means clustering	FC from occipital cortex to frontal pole cortex	IQ, ADI-R, ADOS, comorbidities, medication use, age, sex	2	Post hoc clustering of FC in ROIs identified by group mean. Subtypes had opposite FC patterns and did not differ in clinical and demographic metrics.
(111)	ABIDE, ADHD-200	369 autism 284 ADHD 652 NT[d]	7–21	100%	LFA[c]	FC from 21 × 21 ROIs (in DMN, SN, DAN)	Diagnostic labels, symptom questionnaires (unspecified)	3	Subtype 1 = increased DMN-DAN, medium DMN–SN, decreased intra-DMN and intra-DAN FC, and positive association with ADHD; subtype 2 = decreased DMN-DAN and DMN–SN, positive association with autism diagnosis and total IQ; subtype 3 = decreased DMN-DAN with no behavioral associations.
(112)	ABIDE	210 autism	Most sites ~12 ± 2	85%	Hierarchical clustering	Relationship between FC from 200 × 200 ROIs (Craddock atlas) (144) with clinical symptoms	Multiclass SVM of brain-clinical symptom relationships	3	Subtype 1 = increased within-network connectivity, high IQ and RRB scores; subtype 2 = decreased connectivity including in DMN and cerebellar regions, increased ADI-R and SRS scores; subtype 3 = hypoconnectivity between subcortical and DMN nodes, hyperconnectivity involving the DMN, low IQ; greater social motivation difficulties and verbal difficulties (relative to subtype 1).

Table adapted with permission from (101).

ABIDE, Autism Brain Imaging Data Exchange; ADHD, attention-deficit/hyperactivity disorder; ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; DAN, dorsal attention network; DMN, default mode network; FC, functional connectivity; GENDAAR, Gender Exploration of Neurogenetics and Development to Advance Autism Research; LFA, latent factor analysis; NT, neurotypical; OCD, obsessive-compulsive disorder; PLS, partial least squares; POND, Province of Ontario Neurodevelopment Disorders dataset; ROI, region of interest; RRB, restricted repetitive behavior; SM, somatomotor network; SN, salience network; SRS, Social Responsiveness Scale; SVM, support vector machine; VN, visual network.

[a] Reporting validation based on domains distinct from the features originally used to identify subtypes.

[b] NT sample ($n = 348$) from ABIDE II 1 GENDAAR was used to generate FC z scores in individuals with autism.

[c] LFA used a Bayesian model based on latent Dirichlet allocation.

[d] 303 NT from ADHD-200, 349 NT from ABIDE I.