Title

Functional connectome-based predictive modelling in autism

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Short Title

Predictive modelling in autism

Keywords

Machine learning; individual differences; clinical translation; development; resting-state fMRI; fingerprinting.

Abstract

Autism is a heterogeneous neurodevelopmental condition, and fMRI-based studies have helped advance our understanding of its effects on brain network activity. We review how predictive modelling, employing 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 employed 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 modelling in autism.

Introduction

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 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 modelling 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 - 65 years). After detailing autism-specific study design considerations, we discuss three predictive modelling 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 modelling

Predictive models offer biological insight and potential clinical utility

For the purposes of this review, *predictive modelling* encompasses approaches using statistics to relate MRI functional connectivity measures to phenotypic measures (diagnostic status/symptoms) (4). (See Supplemental Materials for background about predictive modelling/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 modelling 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 modelling studies in 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 = an algorithm's ability to correctly classify individuals with autism who actually have the condition; specificity = 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 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 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 the consequences for predictive modelling

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 (GSR) decreases motion artifact (26) and strengthens brain-behavior relationships in those with autism (27) and in neurotypical individuals (28). Implementing GSR is not without controversy (29); see (30) for a full discussion, including how GSR 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 modelling 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 modelling 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 (FIRMM) (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). The 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 modelling

Sex effects play a role in predictive modelling 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). The 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 modelling 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 to 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+).

Brain-based features implicated in autism classification differ across the lifespan

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 (SVM) and resting-state data from ABIDE, Kazeminejad and Sotero (58) have shown that the functional features most discriminative of autism status in 5 – 15-year-olds (connections involving parietal and ventrolateral prefrontal cortex) differ from those most discriminative in 15 – 30-year-olds (with more connections involving 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. Interestingly, 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 modelling 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). Encouragingly, 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 SVM 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 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 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 Supplemental Materials for a discussion of the ethics of such a scenario and the ethics of predictive modelling 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 three 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 modelling (CPM), Lake et al. (27) generated network models predictive of social responsiveness scores (SRS), as well as separate models predictive of Autism Diagnostic Observation Schedule (ADOS) 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 ADOS 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 CPM model built to predict SRS scores in individuals with autism (generated in ABIDE) to an independent sample of children with ADHD (ADHD-200) and found 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 the 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)). Interestingly, 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 hone 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 CPM, 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 this is possible for individuals with autism, in that changes in overall adaptive function could (remarkably) be predicted three years after imaging. Normative modelling 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 (EEG) (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 2-3 autism subtypes (41, 108-112) (Table 3). Consistent with the distributed brain features identified by dimensional models, subtyping methods indicate there is no focal brain area differentiating subtypes—brain-based features distinguishing subgroups are complex and spatially distributed.

Interestingly, though, the DMN and frontoparietal networks (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 analytical 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 ADOS scores.

Toward subtyping of brain-behavior predictive models

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 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, both in terms of 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 modelling 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 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 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), though hidden confounds may persist (129).

Future Directions and Conclusion

We have reviewed how predictive modelling 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 impacted by the autism-specific modelling considerations discussed here. Encouragingly, 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 (fNIRS) (132) or EEG (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 Supplemental Materials for more about dense scanning in autism).

We do not suggest 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 modelling approaches continuing to aid the quest to understand the complex neurobiology of autism.

Acknowledgements and disclosures

This work was supported by a P50MH115716 grant. CH and ASG are supported by a Medical Scientist Training Program training grant (NIH/NIGMS T32GM007205). ASG is supported by NIH grant TR001864. DLF is supported by funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 101025785. JCM contributions were supported by NIMH R21 MH122202 and U19 MH108206. The authors thank Dr. Andres Martin and Dr. Jennifer B. Dwyer for helpful discussions related to this manuscript. The authors report no biomedical financial interests or potential conflicts of interest.

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Figure Legends

Figure 1. Predictive modelling 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 modelling using

functional connectivity data that we discuss in this review: case-control classification, dimensional prediction, and subtyping.

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, though 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 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 ADHD symptoms in young children. ADHD, attention-deficit/hyperactivity disorder; 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; CON, cingulo-opercular network;

DMN, default mode network; IQ, intelligence quotient; FPN, fronto-parietal 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

Ref.	Data source	*N*	Age range, years[a]	Percent male individuals	Algorithm	Features	Validation	Accuracy (sensitivity, specificity)	Notes
(68)	Lab-specific	40 autism, 40 NT	8-42	100	-	FC from 7266x7266 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 102x102 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 70-96%.
(53)	Lab-specific	29 autism, 29 NT	-	83	LRC	FC from 106x106 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 220x220 ROIs (Power atlas) (140)	Bootstrapping CV (1/3 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 162x162 ROIs (Destrieux atlas); validation: leave-one-out CV.
(49)	ABIDE	312 autism, 328 NT	6-19	84	NN	FC from 90x90 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 142x142 ROIs (Dosenbach atlas) (141); multiple	Internal (leave-one-out, 10-fold CV); leave-one-site-out CV	79.2% (77.8%, 80.5%)	Showing results for leave-one-out.

						frequency bands used			
(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 140x140 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 230x230 ROIs (including nodes from Power atlas) (140)	Internal (leave-one-out CV)	96.6% (81.8%, 100%)	-
(55)	ABIDE	55 autism, 55 NT	8-19	76	NN	FC from 116x116 ROIs (AAL atlas) (139)	Internal (5-fold nested CV)	86.36%	-
(57)	ABIDE	126 autism, 126 NT	7-36	81	RF, CRF	FC from 220x220 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 200x200 ROIs (Craddock atlas) (144)	Internal (5-fold, 10-fold CV); leave-one-site out CV	70 (74%, 63%)	Showing results for 10-fold.
(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 200x200 ROIs (Craddock atlas) (144)	Internal (5 fold, 10-fold CV)	70.3% (68.3%, 72.2%)	Showing results for 10-fold.
(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 200x200 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 392x392 ROIs (Craddock atlas) (144)	Internal (10-fold CV); leave-one-site-out CV	70.2% (77.5%, 61.8%)	Showing results for 10-fold.
(63)	ABIDE	505 autism, 530 NT	-	-	NN	FC from 116x116 ROIs (AAL atlas) (139); voxel-wise x ROI FC	Internal (test set validation)	74%	-
(64)	ABIDE	45 autism, 47 NT	7-15	78	SVM	FC from 116x116 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, which resulted in best performance.
(65)	ABIDE	505 autism, 530 NT	-	-	NN	FC from 200x200 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.
(66)	ABIDE	403 autism, 468 NT	-	-	NN	FC from 264x264 ROIs (Power atlas) (140)	Internal (10-fold CV)	79.2%	-
(67)	ABIDE	306 autism, 350 NT	6-18	Varied by analysis	RF	FC from 237x237 ROIs (Gordon (145) + HO subcortical	Bootstrapping CV (1/3 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 neurotypical participants.

						(146) + cerebellar (147) atlases)			Results from subsample including males and females with no ADOS score cutoffs.

Table 1. Representative autism case-control classification studies. 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.

[a]Mean age and standard deviation are used when age range was not reported.

ABIDE, Autism Brain Imaging Data Exchange; AAL, automated anatomical labelling; 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; SVM, support vector machine; ROIs, regions of interest.

Ref.	Data source	*N*	Age range, years[a]	Percent male individuals	Algorithm / approach	Features	Validation	Symptoms/phenotypes predicted	Highlights
(27)	ABIDE, ADHD-200	ABIDE: 122 autism, 230 NT[b] ADHD-200: 77 ADHD, 35 NT	6-24	71[c]	CPM (Linear regression)	FC from 268x268 ROIs (Shen atlas) (149)	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[d]	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. neurotypical 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[e]	14.8 +/- 6.5	74	CCA	FC from 415x415 ROIs (Schaefer atlas (148) + 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 268x268 ROIs (Shen atlas) (149)	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 227x227 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.

Table 2. Dimensional studies using functional connectivity data.

[a]Mean age and standard deviation are used when age range was not reported.
[b]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 neurotypical 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.
[c]Across the SRS analyses, ~70% of the sample was male; in the ADOS analyses, ~85% of the sample was male. Sex was not reported in the ADHD-200 sample.
[d]We report the sample size used in the ADOS dimensional prediction analyses. Twenty-seven participants with autism were used in the ADI-R dimensional prediction analyses.
[e]125 individuals with autism and 78 controls from the LEAP cohort were used in Short Sensory Profile subscales analyses; demographics roughly similar to the rest of the sample.

ABAS, Adaptive Behavior Assessment System; ABIDE = Autism Brain ABIDE, Autism Brain Imaging Data Exchange; ADHD, attention-deficit/hyperactivity disorder; ADHD-RS, attention-deficit/hyperactivity disorder 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 modelling; CV, cross-validation; dFC, dynamic functional connectivity; DMN, default mode network; FPN, frontoparietal network; FC, functional connections; HO, Harvard-Oxford subcortical atlas; IQ, intelligence quotient; LEAP, EU-AIMS Longitudinal European Autism Project; NT, neurotypical; ROIs, regions of interest; SN, salience network; SRS, Social Responsiveness Scale; SVR, support vector regression.

Table 3

Ref.	Data source	*N*	Age range, years[a]	Percent male individuals	Subtyping approach	Features	Validation[b]	No. of subtypes	Highlights
(41)	ABIDE, GENDAAR	306 autism[c]	15 +/- 8	77	LFA[d]	FC from 418x418 ROIs (Schaefer atlas (148) + 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) and 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 76x76 ROIs (Desikan-Killiany-Tourville atlas) (150)	Diagnostic and behavioral measures	2	Neurotypical and autism participants split across two subtypes; ~80% of ADHD individuals in subtype 1, ~80% of OCD individuals 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 160x160 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[e]	7–21	100	LFA[d]	FC from 21x21 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 200x200 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 3. Subtyping studies using functional connectivity data. Table adapted with permission from (133).

[a]Mean age and standard deviation are used when age range was not reported.
[b]Reporting validation based on domains distinct from the features originally used to identify subtypes.
[c]NT sample (n = 348) from ABIDE II 1 GENDAAR was used to generate FC z-scores in individuals with autism.
[d]LFA used a Bayesian model based on latent Dirichlet allocation.
[e]303 NT from ADHD-200, 349 NT from ABIDE I.

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; IQ, intelligence quotient; LFA, latent factor analysis; NT, neurotypical; OCD, Obsessive-Compulsive Disorder; POND, Province of Ontario Neurodevelopment Disorders dataset; PLS, partial least squares; ROIs, regions of interest; RRB, restricted repetitive behavior; SM, somatomotor SN, salience network; SRS, Social Responsiveness Scale; SVM, support vector machine; VN, visual network.

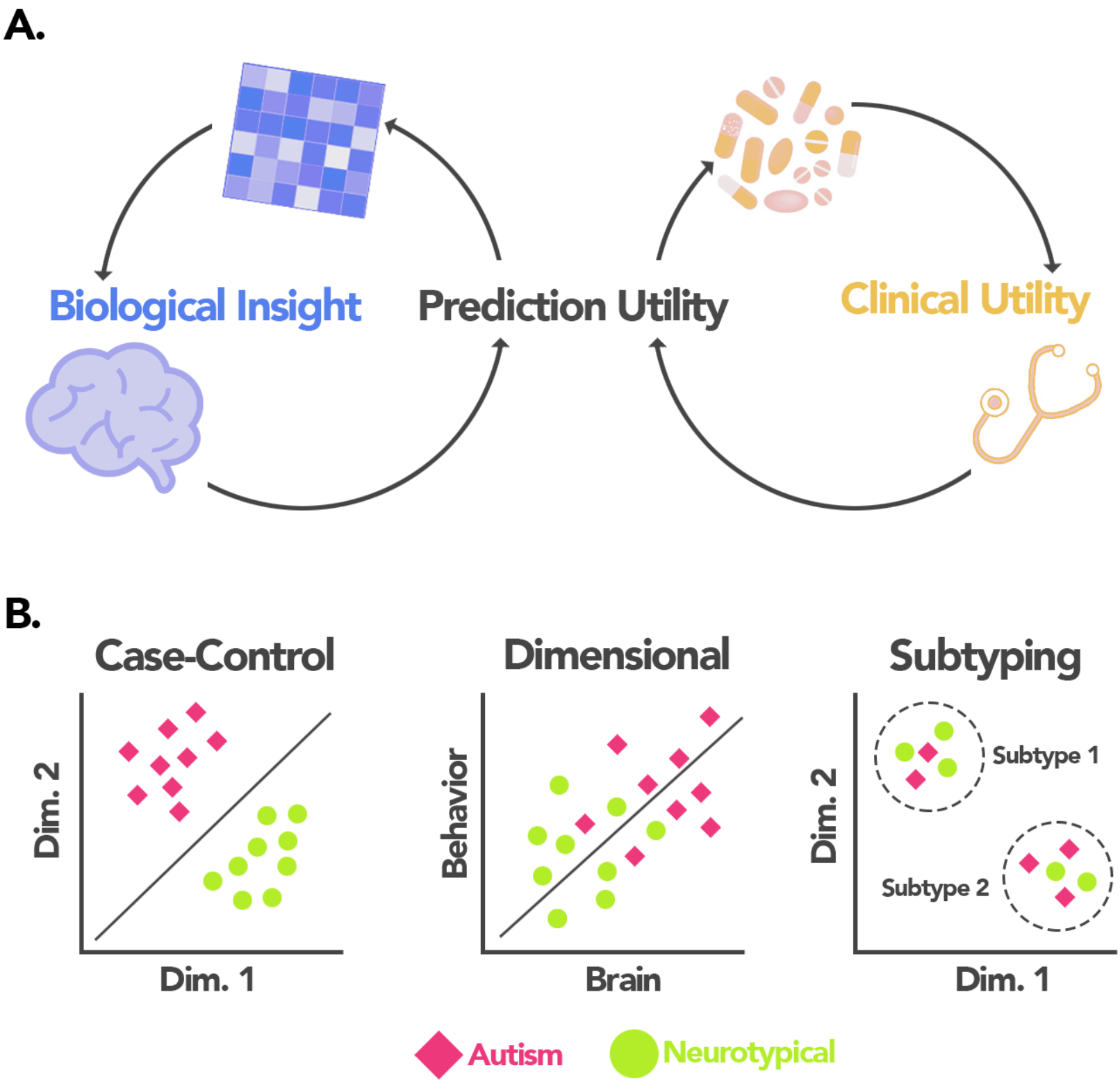
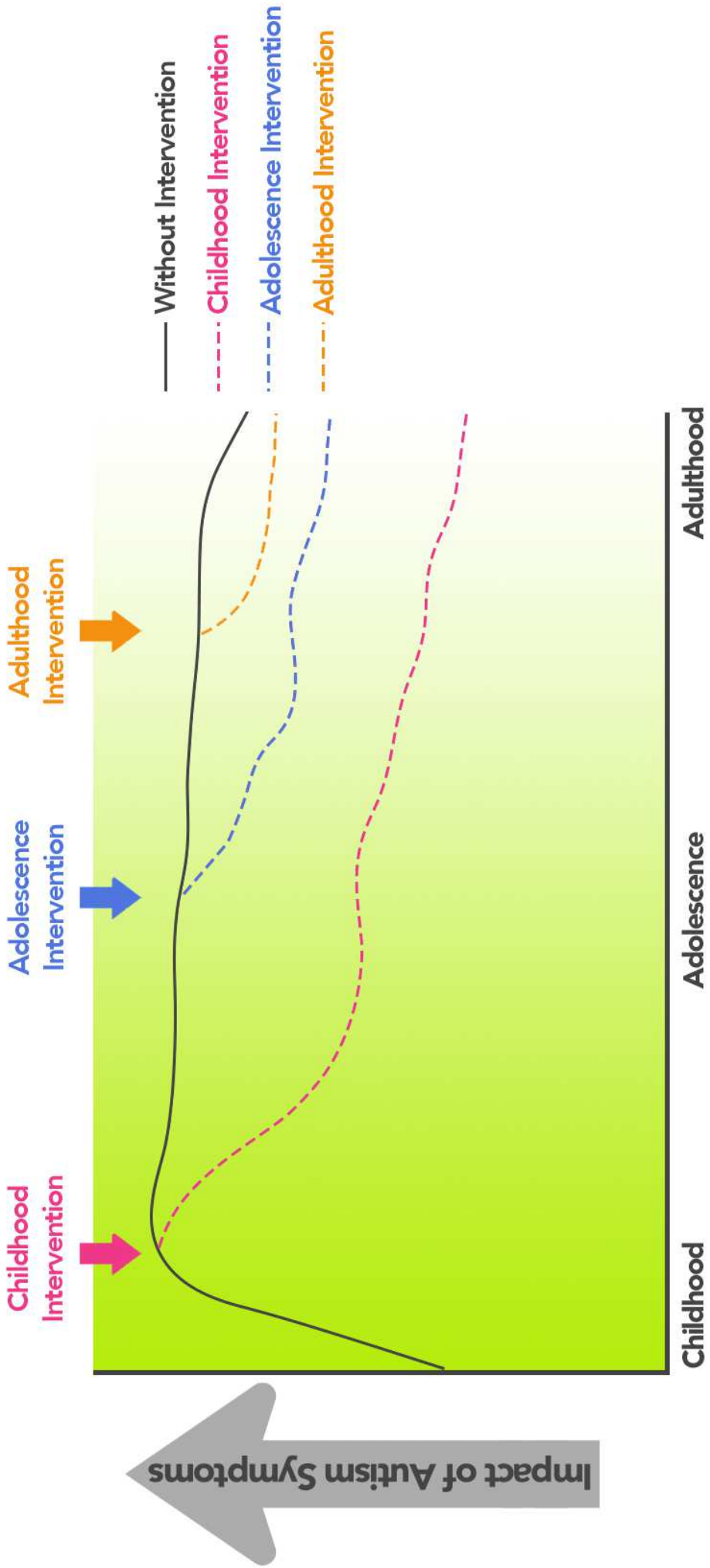
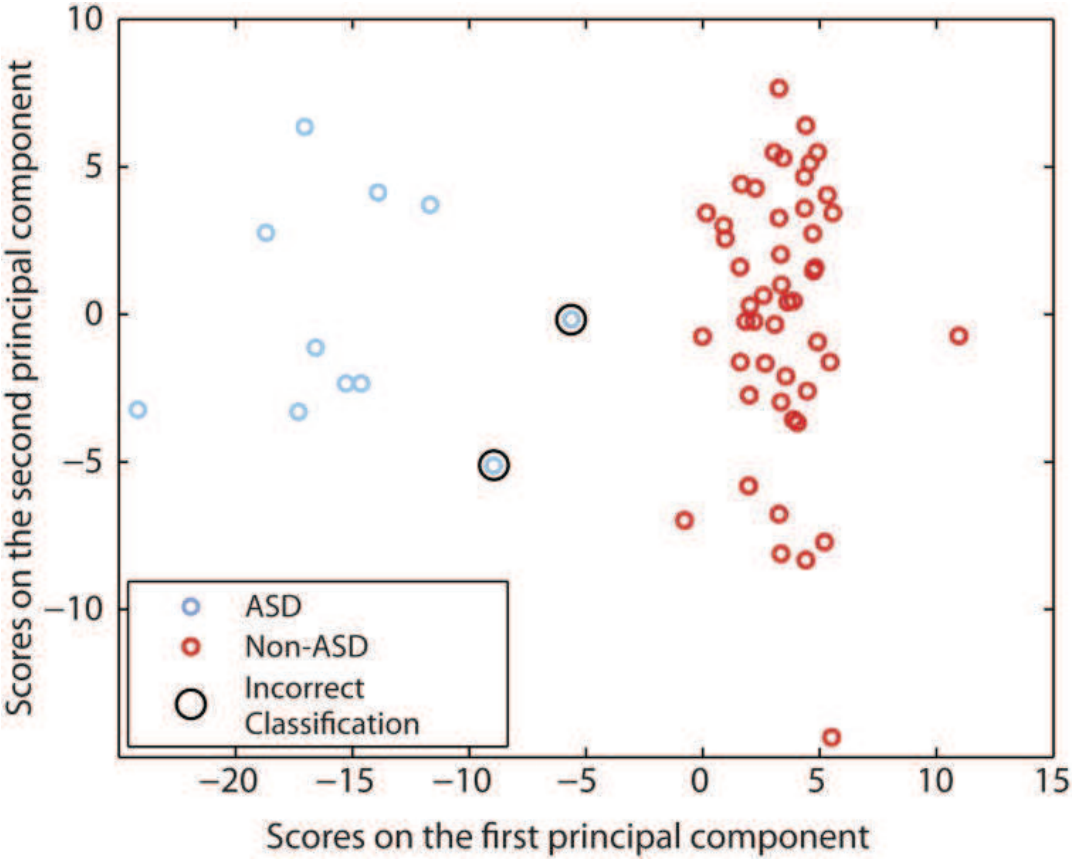

A.
Biological Insight
Prediction Utility
Clinical Utility
B.
Case-Control
Dim. 2
Dim. 1
Dimensional
Behavior
Brain
Subtyping
Dim. 2
Subtype 1
Subtype 2
Dim. 1
Autism
Neurotypical

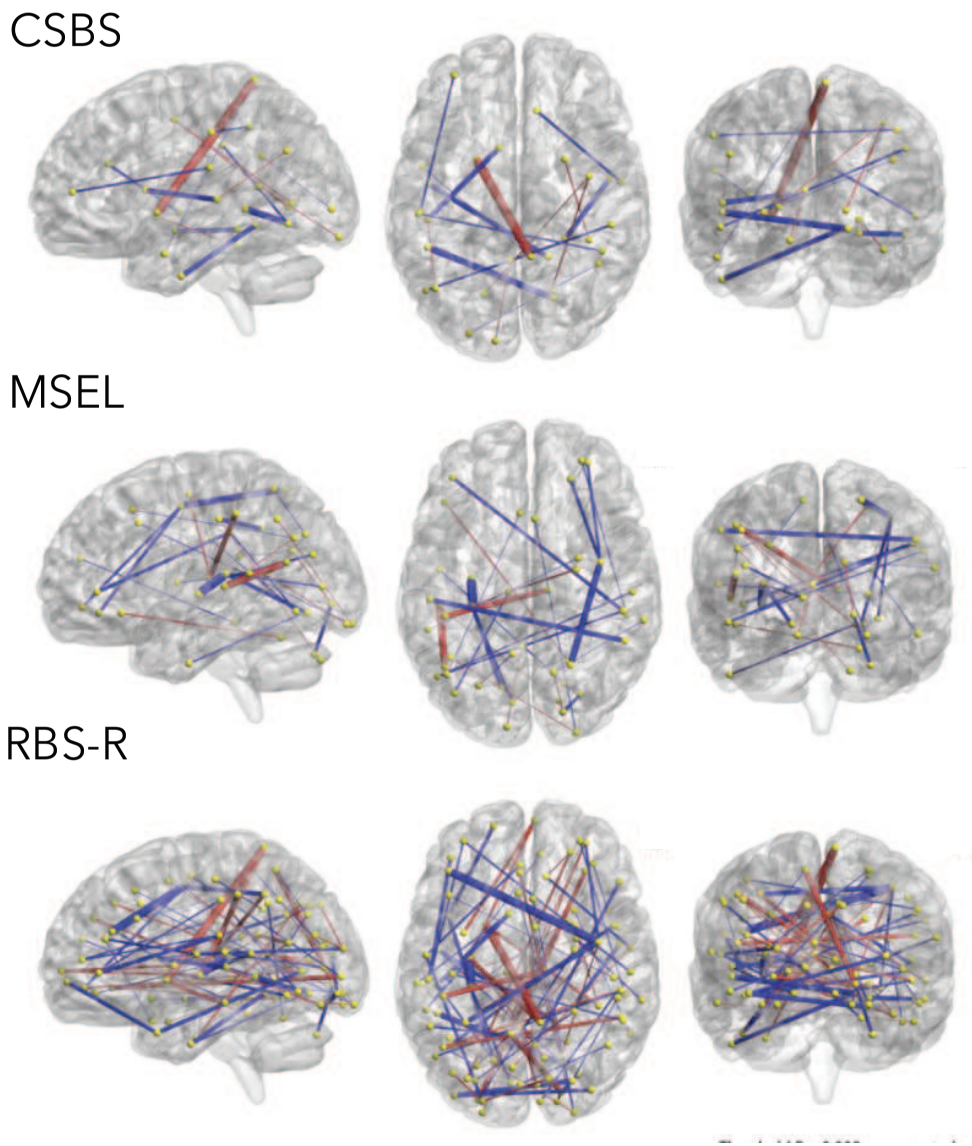
Figure 2


Without Intervention
Childhood Intervention
Adolescence Intervention
Adulthood Intervention
Childhood Intervention
Adolescence Intervention
Adulthood Intervention
Childhood
Adolescence
Adulthood
Impact of Autism Symptoms

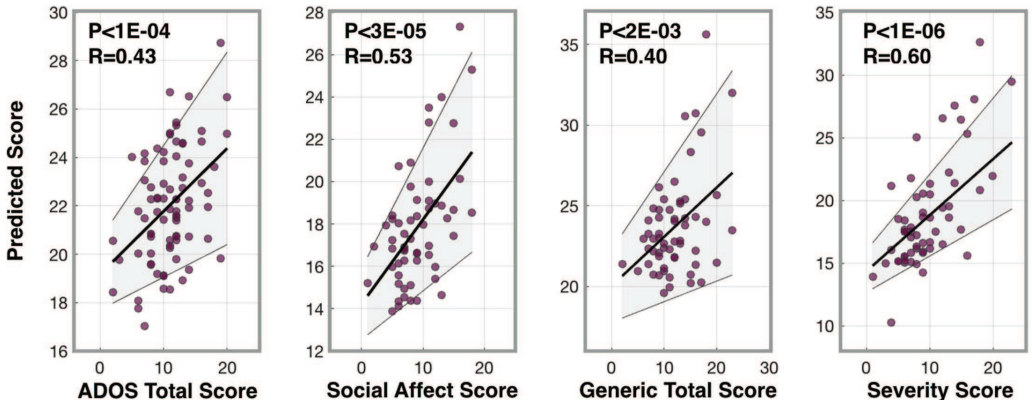
A. **Case-control classification**



B. **Functional connectivity differences**

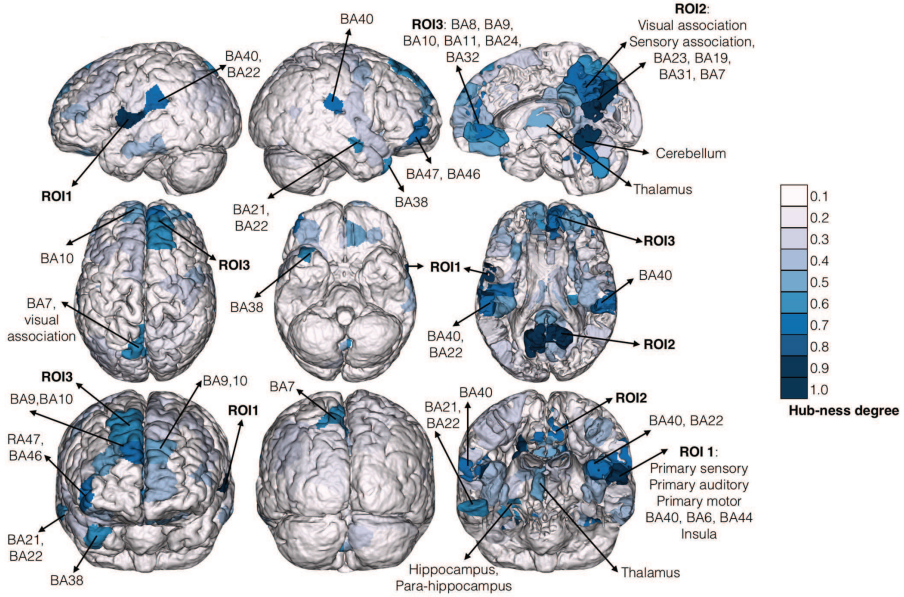


A.



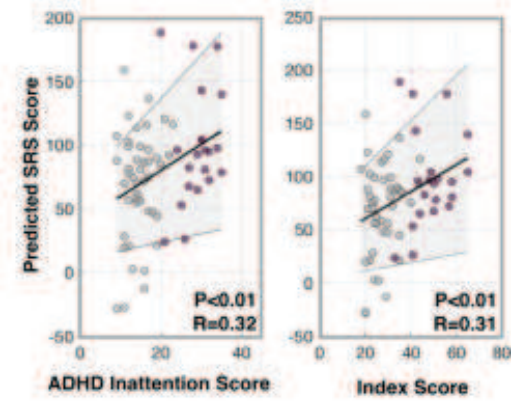
Prediction of autism symptoms

B.



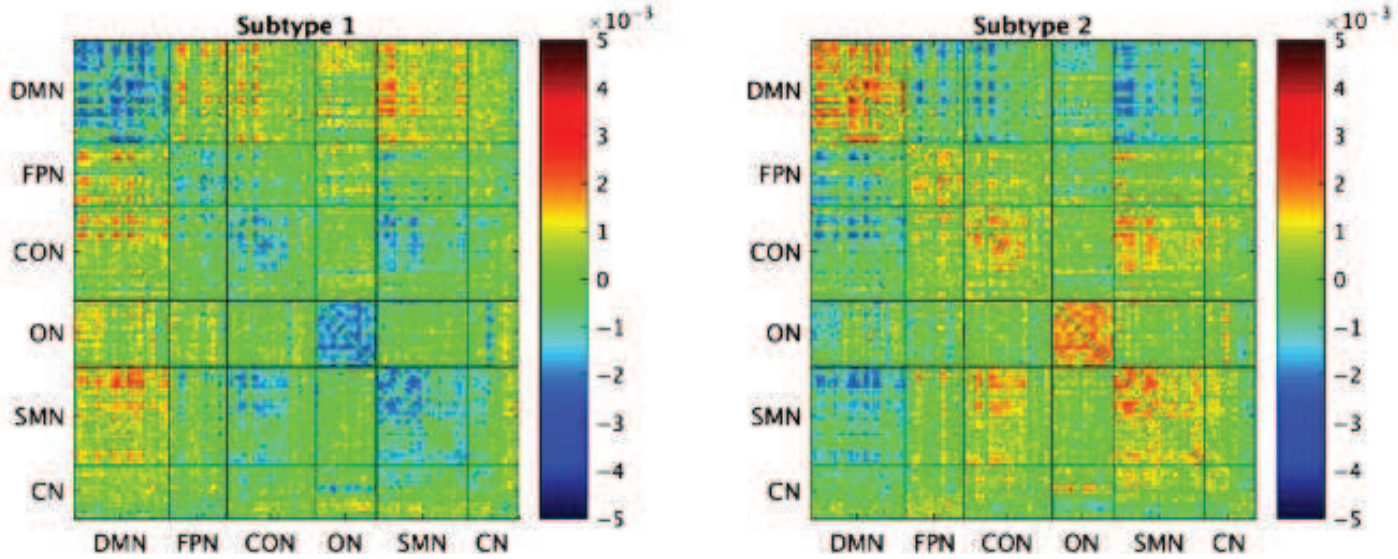
Anatomy of autism symptom models

C.



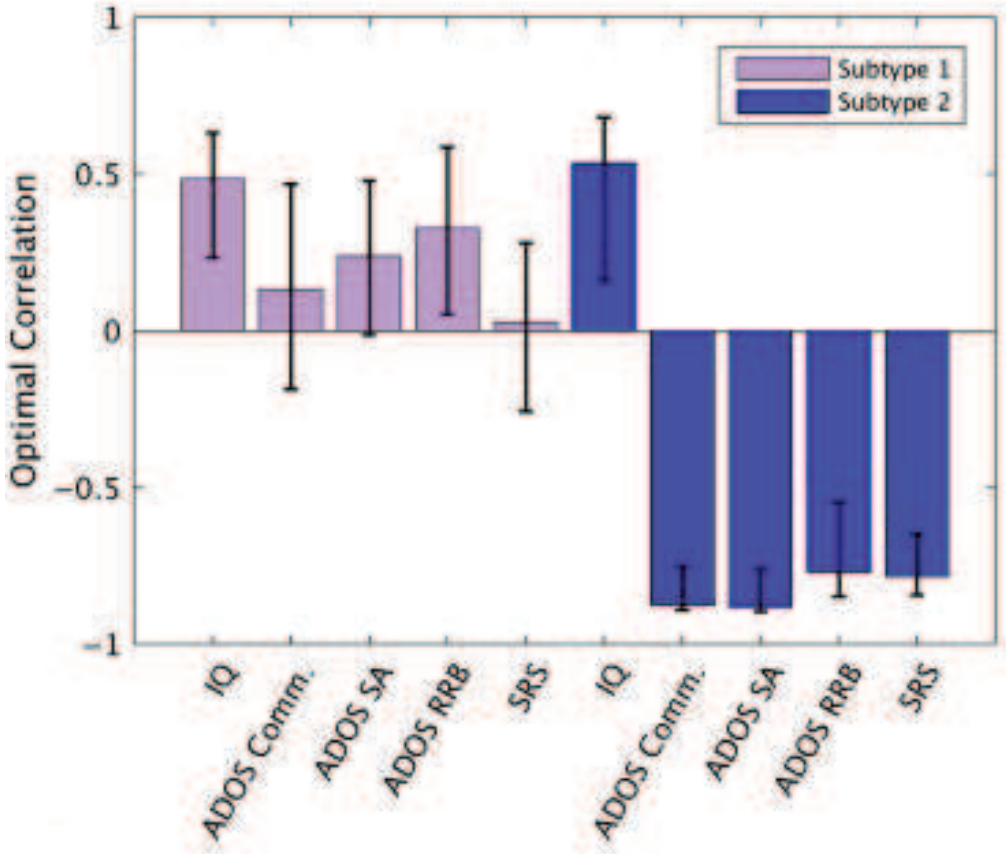
Prediction of ADHD symptoms in external sample

A.



Differences in connectivity

B.



Subtype-dependent brain-behavior relationships

Functional Connectome-Based Predictive Modeling in Autism

Supplemental Information

Predictive modelling and machine learning in psychiatry

Machine learning (ML) is a growing field, commonly referenced in biological psychiatry, where there is an increasing focus on generalizability (1). ML is defined by the use of algorithms to learn patterns in training data, which can be leveraged for automated decision-making on unseen data (2). There are several important decision points in choosing which algorithm suits your needs. Some of these decisions may include whether to use a supervised or unsupervised algorithm, using a regression or classification framework, and how complex a model to use.

These decisions can be influenced by whether you wish to use the algorithm for explanation or prediction. Unsupervised methods (in which patterns are learned from unlabeled data—performing a clustering analysis to determine the number of subtypes in a dataset, for instance) can help to uncover previously unknown relationships in your dataset. However, if one then uses the relationship to automate a decision or predict an outcome, the approach falls within predictive modelling. Broadly speaking, one can be thought of having a predictive approach if you are building a model that can estimate a variable of interest from unseen data, whereas explanatory analyses often focus on deriving causal links, focusing more on interpretation than model performance (3). Many neuroimaging ML applications involve both predictive and explanatory aspects and they can be complementary (4).

This paper has focused on predictive approaches in autism, which rely on supervised algorithms. Supervised approaches (in which data labels are known) can be used to leverage existing data for prediction of categorical variables using a classification approach (autism diagnosis in case-control studies) or prediction of continuous variables using regression (autism-related phenotypes in dimensional studies). One of the benefits of supervised is using priors pre-generated from previous studies. These priors can help ensure that models are less likely to overfit your dataset, due to added (favorable) bias and reduced variance (i.e., bias-variance tradeoff) (5). The downside is that these priors might not fit the dataset well, and you may miss some unique and useful information in the dataset leading to an underfit model which does not perform well enough.

Returning to unsupervised approaches, these methods tend to be more well-suited to explanatory analyses. However, they can still be used as part of a predictive framework. Two prominent types of unsupervised algorithms are clustering and association. Clustering is analogous to classification in that it tends to produce a categorical output (subtyping of autism), while association is analogous to regression (new dimensions of brain variation), as it produces a dimensional output, along which the relationship is continually varying. Unsupervised models can benefit from a lack of bias, as they work with less stringent priors than supervised methods, and can uncover previously unknown relationships in the dataset. However, the lack of bias can also lead to increased variance in the estimated model parameters across different datasets, resulting in overfit models which capture more noise than signal. For a more in-depth discussion of issues associated with supervised and unsupervised learning in fMRI, see Khosla et al. (6).

Another important factor in model selection is model complexity. Simpler models may miss complex relationships in the data but can yield much more interpretable parameters. This may be important in the context of gaining biological insight. On the other hand, if the underlying biological relationships are of less concern, and one wishes to derive a model with the best possible performance (i.e. for accurate diagnosis of autism status), one could opt for a more complex algorithm. Complex algorithms tend to perform better on unseen data due to their capacity to capture complex patterns, but can hinder interpretability, (see Figure 1 of Bzdok et al. (7). The complexity of the model can also impact generalizability, as complex models are more likely to overfit a dataset due to the increased number of parameters that can be optimized. The balance of complexity and interpretability is a key consideration in selecting an algorithm for predictive modelling in functional neuroimaging.

The ethics of predictive modelling in autism

The use and implementation of predictive models to diagnose autism requires careful ethical consideration (8). Recent research has revealed that brain-based changes in autism precede the development of behavioral symptoms (9), which has ushered in the creation of predictive models to forecast diagnosis before the emergence of symptoms. Moreover, it may become possible to identify the likelihood of autism *in utero*. These studies open the possibility for pre-symptomatic intervention, which could potentially alter developmental trajectories sufficiently to prevent the development of autism (9). However, in these scenarios, several ethical matters should be considered.

Autism is an extremely heterogeneous condition with a complex phenotype. Individuals with autism can range from having profound difficulties and disabilities to being highly successful and independent. Autism can manifest with significant intellectual difficulties with no or minimal functional language capabilities or with extremely high intelligence and highly articulate language capacities. However, our current predictive models are not able to identify which infants will develop which phenotype later in life. Further, neurodevelopment in the perinatal period has tremendous plasticity, and it is likely that autism emerges as a sequala of numerous genetic and environmental effects acting in concert (10). Therefore, there is risk for inaccuracy and imprecision in models that could have devastating effects on families.

Additionally, infants who are identified with a high likelihood of developing autism through MRI or other tools incorporated into predictive models will not yet have developed the core features of autism. Thus, existing interventions that focus on addressing autism-associated difficulties would not yet be suitable for this population and new interventions would need to be developed (9). This raises the question: is earlier diagnosis beneficial if it is not possible to provide support services? Current guidelines for newborn screening for other disorders, such as phenylketonuria and hypothyroidism, suggest that a diagnosis should only be made if there is a known and accepted treatment (11). When applying these principles to predictive models for early identification of autism, a key difference arises. While pre-symptomatic interventions do not currently exist for autism and it will initially be unlikely to begin intervention as soon as a diagnosis is made, during this initial period the infants' development can be carefully tracked and existing early intervention services can be provided to optimize developmental outcomes, until new interventions can be developed.

In addition, for many individuals with a diagnosis, autism is a core tenet of their identity and being "atypical" does not equate to impairment. The neurodiversity movement maintains

that autism should be conceptualized as a difference rather than a disability (12). Some have contended that efforts to predict and prevent development of autism are attempts to eliminate neurodiversity (13, 14). Further, rather than focusing on early childhood diagnostic tools, many adults with autism would prefer research funding to be directed towards programs and services for individuals living with autism (15). However, the goal of pre-symptomatic intervention is not to eliminate neurodiversity, but rather to provide opportunities to achieve developmental milestones that are critical for subsequent adaptive functioning and independence (9).

Some issues for consideration with dense scanning and prediction in autism

An approach that has proven useful in neurotypical young adults is dense scanning (16-18), in which the same individuals are scanned many times. Such studies have led to exciting insights, including the fact that participants exhibit remarkable stability of individual-specific networks (16) and such individualized networks exhibit brain state-dependent organization (19). Using a dense scanning paradigm and prediction-based approaches could similarly inform our understanding of autism neurobiology and symptom expression. For example, do models generalize to predict fluctuations in individual patients over time, as has been shown in attention (20)? The large amounts of data from dense-scanning studies have been used to obtain exquisitely detailed areal parcellations within individual participants (e.g., (16)). Would similar participant-specific parcellations help increase the utility of dimensional predictions in autism? Could these large amounts of scanning data be combined with other data types to better subtype individuals with autism and construct more specific clinical models?

A major hurdle that has to be overcome if dense scanning studies are to be conducted is ensuring the data are of high quality, as participants with autism can be difficult to scan (21). Another barrier is determining whom to scan—given the heterogeneity of autism, what type of symptom profile will allow the research community to draw generalizable conclusions? Should we aim for a broad array of individuals (22), or should we instead focus on a single symptom dimension? Based on the work of Byrge and Kennedy (23), more data per participant reduced classification accuracy of autism status to around chance levels. Thus, large numbers of participants are possibly needed in dense scanning studies to achieve discriminative utility. What does this mean for predictive modelling studies--how many participants do we need to densely scan to help us build useful models, and is this feasible?

Furthermore, what sort of scanning data should we collect—simply resting-state scans or a variety of task-based scans covering as many aspects of the Research Domain Criteria (RDoC) matrix as possible? How do we motivate participation? Would an individual with autism be open to weekly scans over the course of a year, if they stand to gain little beyond financial compensation?

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Horien et al. review studies using MRI functional connectivity data to predict autism phenotypes. The authors discuss how autism-specific study/analysis design issues affect the biological and clinical utility of predictive modelling methods. Emphasis is placed on interpreting the neurobiological correlates of predictive models, as well as approaches (dimensional- and subtyping-based applications) that focus on individual patients.