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Brain mechanisms supporting flexible cognition and behavior in adolescents with autism spectrum disorder

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Abstract

Cognitive flexibility enables appropriate responses to a changing environment, and is associated with positive life outcomes. Adolescence, with its increased focus on transitioning to independent living, presents particular challenges for youth with autism spectrum disorder (ASD) who often struggle to behave in a flexible way when faced with challenges. This review focuses on brain mechanisms underlying the development of flexible cognition during adolescence, and how these neural systems are affected in ASD. Neuroimaging studies of task switching and set-shifting provide evidence for atypical lateral frontoparietal and midcingulo-insular network activation during cognitive flexibility task performance in individuals with ASD. Recent work also examines how intrinsic brain network dynamics support flexible cognition. These dynamic functional connectivity studies provide evidence for alterations in the number of transitions between brain states, as well as hyper-variability of functional connections in adolescents with ASD. Future directions for the field include addressing issues related to measurement of cognitive flexibility using a combination of metrics with ecological and construct validity. Heterogeneity of executive function ability in ASD must also be parsed in order to determine which individuals will benefit most from targeted training to improve flexibility. The influence of pubertal hormones on brain network development and cognitive maturation in adolescents with ASD is another area requiring further exploration. Finally, the intriguing possibility that bilingualism might be associated with preserved cognitive flexibility in ASD should be further examined. Addressing these open questions will be critical for future translational neuroscience investigations of cognitive and behavioral flexibility in adolescents with ASD.

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Keywords

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1. Cognitive flexibility: Assessment and neural mechanisms

The ability to flexibly adapt to novel circumstances is a critical feature of human cognition (1). Cognitive flexibility is the readiness with which one can selectively switch between mental processes to appropriately respond to environmental stimuli (2), and falls under the umbrella of executive function (EF), which refers to the set of abilities required to guide goal-directed behavior (3). Different aspects of EF such as updating, shifting, and inhibition are thought to be correlated, yet separable (4). EF ability and cognitive flexibility can be assessed using informant-report questionnaires, which typically have greater ecological validity, or laboratory-based measures, which can provide greater construct validity(5).

One such measure, the Behavior Rating Inventory of Executive Function (BRIEF), is an informant-report measure developed for parents and teachers to assess EF in 5–18 year-old children (6). Self-report and informant-report versions of the BRIEF (BRIEF-A) are also available for adults (7). Different subscales of the BRIEF are thought to index different EF components. The ‘shift’ and ‘emotional control’ subscales of the BRIEF load onto a factor that has been labeled ‘flexibility’ in young children (8). Similarly, the ‘shift’ scale of the BRIEF-A assesses the ability to move with ease from one situation to another as circumstances demand. Items on the ‘shift’ scale assess the ability to make transitions, tolerate change, problem-solve flexibly, switch attention, and change focus from one topic to another, thus providing an ecologically valid index of cognitive flexibility (9).

Several neuropsychological measures and test batteries have been developed to measure EF and cognitive flexibility. The Wisconsin Card Sort Task (WCST) measures the ability to infer the categories that should guide behavior, create an attentional set based on abstract categories, and switch attention and flexibly adjust behavior as task demands change (3). The Adolescent Brain and Cognitive Development (ABCD) consortium includes the Dimensional Change Card Sort (DCCS) task from the NIH Toolbox Cognition Battery to index cognitive flexibility (10). The DCCS asks participants to sort an object by either color or shape to match one of two other objects. After blocks of trials sorting solely on one dimension then another, participants alternate pseudo-randomly between sorting based on shape versus color (11). The Delis-Kaplan Executive Function System (D-KEFS) is a standardized set of tests for 8–89 year olds (12), and includes several subtests that load onto a factor labelled ‘conceptual flexibility’ (13). The NEPSY-II, specifically designed for use in 3–16 year olds, also assesses flexibility as part of its EF and attention battery (14).

It is important to note that informant and self-report measures of real-world EF and laboratory performance-based neuropsychological measures do not always converge. The BRIEF correlates with other questionnaire measures, but *not* with laboratory-based measures of EF, suggesting that subjective and objective measures may not assess the same underlying constructs (15). More generally, self-report and behavioral measures of the same construct

are only weakly correlated, possibly due to the fact that behavioral measures tap responses during highly structured situations and typically index maximal performance, whereas self-report assesses how individuals behave across unstructured real-life situations (5). It has been suggested that measures derived from experimental cognitive psychology may provide greater insights into impaired cognition in clinical conditions than neuropsychological measures (16).

The most commonly used cognitive neuroscience paradigms for studying cognitive flexibility are those that require task switching or set-shifting (17–20). Decades of functional neuroimaging work has delineated brain networks underlying EFs that contribute to cognitive flexibility (21,22), namely the executive control/lateral frontoparietal (L-FPN) and salience/midcingulo-insular networks (M-CIN) (23–25). Cortical regions within these networks most strongly implicated in cognitive flexibility are the inferior frontal junction (IFJ), involved in the updating of task rule representations (18,26), the ventrolateral prefrontal cortex (vlPFC) involved in resolving proactive interference, response set selection, and context monitoring (27,28), and the dorsal anterior insula (dAI), which detects behaviorally-relevant stimuli and coordinates dynamic switches between brain networks (29). These regions work in the context of broader EF networks with nodes in the dorsolateral prefrontal cortex (dlPFC), dorsal anterior cingulate cortex (dACC), and superior parietal lobule (SPL) which contribute to working memory (30), motor control (31,32), and attention (33), respectively (see (25) for review) (Figure 1). Other mechanistic models of flexibility further incorporate subcortical structures like the basal ganglia, implicated in updating reward-related context representations in the prefrontal cortices. According to these models, inflexibility results from dysregulation of dopamine circuits leading to rigid behavior that is not informed by learning (34,35).

Cognitive flexibility is important for promoting optimal outcomes during development, including academic achievement and employment success (36). Flexibility supports the transition to adulthood, which is associated with increased demands including navigation of new social relationships and independent living (37–39). As such, tracking the neural substrates of cognitive flexibility in typical adolescent development provides critical foundational knowledge for understanding atypical trajectories.

2. Brain network maturation underlying the development of cognitive flexibility

Cognitive flexibility emerges in early life, showing sharp increases between 7–9 years of age, then follows a protracted development throughout young adulthood, becoming largely mature by age 20 (40,41). However, this skill continues to improve throughout adolescence and adulthood, peaking between 21–30 years of age before declining in later life (40,42,43). Tasks typically used to study the neural systems supporting cognitive flexibility are summarized in Figure 2 (44–46). Several considerations must be taken into account when testing developmental populations, such as ensuring that working memory demands are not excessively high (25,47). Modifications to cognitive flexibility paradigms that render them

age-appropriate often result in reduced complexity compared with those developed for adults (46).

Reduced frontal lobe contributions are thought to underlie immature control processes in children, who activate posterior but not prefrontal regions during EF tasks (48). On a range of EFs including attentional control, goal setting, and cognitive flexibility, little differentiation was observed between adolescents (age 7–16) with frontal lesions and those with extra-frontal lesions, suggesting that adolescents utilize more distributed brain networks for executive skills than adults (49). Studies of the whole-brain functional connectome demonstrate a trend towards 'segregation' (decrease in correlation strength between anatomically close regions) and 'integration' (increase in correlation strength between anatomically distant regions) across development (50,51). Diffusion imaging studies examining structural connectivity in 8–22 year-olds support the network segregation-with-age story, and further link this neurodevelopmental process with enhanced EF with age (52).

During a probabilistic reversal learning task requiring cognitive flexibility, the right anterior insular cortex (rAI) shows increased task-related responses to negative reward prediction errors in adolescents compared with adults (53). Effective connectivity work demonstrates greater causal outflow from the rAI to the L-FPN in adults compared with children (54). Findings from the task-based fMRI literature demonstrate that brain networks involved in EF are in place in children aged 8–14, with the dACC and rAI showing greater activation across more demanding task periods (55). Recent studies examining executive control networks demonstrate changes in network expression and variability with development, interpreted as increased flexibility of frontoparietal brain regions with age (56,57).

While the development of cognitive flexibility is a topic of considerable interest, links between brain network maturation and flexible behaviors are not yet firmly established. A recent study of over 2000 9–10 year olds from the ABCD dataset found that while individual differences in general cognitive ability could be predicted from functional connectivity patterns, whole brain connectomes could not reliably predict individual differences in flexibility (58). The relative immaturity of the basic science in this area is important to consider as translational research questions are addressed.

3. Cognitive flexibility deficits in autism: The importance of adolescence

Individuals with autism spectrum disorder (ASD) exhibit considerable heterogeneity in EF abilities (59). While a majority of those diagnosed with ASD experience difficulties with EF, a great deal of heterogeneity exists with respect to individual levels of impairment (60–62), and EF deficits can improve with age (63). In a meta-analysis, broad impairments across multiple EF domains were observed in children and adolescents with ASD assessed using neuropsychological measures. Deficits in cognitive flexibility decreased with age, and were observed in those with and without comorbid attention-deficit/hyperactivity disorder (ADHD) (64). Another meta-analysis including psychometric, experimental, and questionnaire-based measures of EF and a wider age range of participants also reported

broad dysfunction in ASD that is relatively stable across development. Here, effect sizes were found to be largest for studies using the BRIEF questionnaire (65).

Symptom severity for restricted and repetitive behaviors (RRBs), which are considered core deficits in the disorder, are associated with measures of cognitive inflexibility in ASD (66–68). Cognitive flexibility deficits in early life can manifest as difficulties in transitioning to independent living and maintaining employment, and may contribute to the grim outcome that less than 20% of adults with ASD live independently and are fully employed (69). Despite reports of cognitive flexibility deficits in ASD (70,71), particularly in younger children (72,73), there are conflicting notions regarding the extent, nature, etiology, and neurobiology of these deficits (74).

Adolescence is a time of dramatic physical, emotional, and social change, and represents a particularly vulnerable developmental period for individuals with ASD. During this period of transition to adulthood, youth with ASD often desire independent living, employment, and social relationships, all of which can be challenging for them to achieve when dealing with persistent social, behavioral, and language deficits (75). Some children with ASD even experience deterioration in functioning in the years after the onset of puberty (76). Young adults with ASD are at increased risk for poor health outcomes, social isolation, financial adversity, and institutionalization (77).

The “two-hit” conceptual model of autism posits that early alterations in neurodevelopment lead to a “first hit”, while pubertal hormones, neural reorganization, and increasing social demands function as a “second hit” during adolescence that affects adaptive functioning and transitioning to adult roles (78). Cognitive flexibility deficits can exacerbate this difficult transition period, whereas relative sparing of flexibility may ameliorate some of the challenges typically encountered during adolescence. In youth with ASD (7–17 years), flexibility assessed by parent-report explained 22.2% of the variance in adaptive socialization skills (79), suggesting that the ability to function independently in everyday life is linked to flexibility. Longitudinal studies demonstrate that EF skills in childhood predict variance in autistic individuals’ adaptive behavior later in life (80,81). Taken together, this work highlights the need for more targeted investigation of the brain mechanisms supporting cognitive flexibility in ASD during this critical developmental stage.

4. Neural substrates of cognitive flexibility in autism: Brain activation

Despite the critical role of cognitive flexibility for supporting adaptive functioning in autism, few functional neuroimaging studies of cognitive flexibility in ASD have been conducted (Table 1). Based on the extensive cognitive neuroscience literature examining cognitive flexibility in neurotypical adults, one might expect to see differential responsivity in the L-FPN and M-CIN during such tasks in individuals with ASD (24,25). Schmitz and colleagues reported greater inferior parietal brain activation in adults with ASD as they performed a cognitive flexibility task (82). Shafritz and colleagues found reduced activation in frontal, striatal, and parietal regions during shifting trials in young adults with ASD. They also reported a negative correlation between severity of RRBs and anterior cingulate and posterior parietal activation (83). Using a reversal learning paradigm to assess behavioral

flexibility, D'Cruz and colleagues found reduced activation in frontal cortex and striatum in adults with ASD (84).

Mixed findings have also been reported in younger cohorts. Yerys and colleagues found that 7–14 year old children with ASD engaged frontal brain regions to a greater extent than typically developing (TD) peers during set-shifting (44). Examining extra-dimensional shifts in 7–14 year old children, Taylor and colleagues found an age by group interaction such that the right insula exhibited increasing activation with age in typical development, but decreasing activation with age in ASD (85). The rAI has been posited to be a locus of dysfunction in ASD (86), and functional and effective connectivity of this region and the broader M-CIN is associated with symptom severity in the domain of RRBs (87,88).

The task-based fMRI literature has not yet converged on the neural circuitry underlying cognitive flexibility in ASD (89), though atypical L-FPN and M-CIN activation is generally observed. This is not entirely surprising, as these tasks may require different forms of flexibility, placing differential demands on various components of shifting (eg. response sets vs. context monitoring). These differences could in part drive conflicting results in terms of brain regions implicated across studies. No studies to date have focused specifically on adolescents with ASD, despite the well-characterized maturation of EF circuitry in typical development (90,91). A few studies of adolescents with ASD have noted alterations in frontoparietal activity during paradigms invoking aspects of flexibility including cognitive control (92–94) and verbal fluency (95), yet much remains unknown about this specific developmental period.

5. Neural substrates of cognitive flexibility in autism: Brain dynamics

Complementary to task-based neuroimaging, resting state fMRI paradigms, with their decreased cognitive demands and potential for data reuse, are a promising approach for exploration of typical and atypical brain networks (96,97). Beyond revealing brain regions activated in response to specific task conditions, resting state functional connectivity approaches permit analysis of how cognition emerges from brain network interactions (98). Dynamic functional connectivity approaches further enable the study of moment-to-moment, or time-varying changes in functional coupling between brain regions (99–101), and are increasingly being applied to the study of neurodevelopmental disorders (102).

One method for computing dynamic functional connectivity is the "sliding-window" approach where functional connectivity strength is computed on the order of seconds rather than minutes (103). Sliding window analyses permit the quantification of metrics including "dwell time" (the amount of time spent in a particular functional connectivity state), "frequency of occurrence" (the number of times a particular functional connectivity state occurs), and "state transitions" (the number of times transitions between functional connectivity states occur). Another method relies on the identification of critical timepoints when the BOLD signal intensity surpasses a certain threshold, giving rise to multiple stable spatial patterns or co-activation patterns (CAPs) that can be obtained by clustering of critical time frames (104). CAP analysis relies on fewer model assumptions than the sliding window approach, and allows for the examination of state alterations closer to the temporal

resolution of individual time frames (105) (Figure 3). A comprehensive review of dynamic functional connectivity approaches is provided in (106).

Specific patterns of brain dynamics are associated with enhanced cognitive flexibility. Individuals who score higher on a card sort task exhibited whole-brain functional connectivity dynamics characterized by greater episodes of more frequently occurring brain states, and fewer episodes of less frequently occurring states associated with low vigilance and arousal (107). Older adults who performed more poorly on a battery of cognitive tests exhibited greater frequency of switching between dynamic brain states, whereas high performers exhibited a tendency to be in a state characterized by global coherence (108). Time-varying (but not static) functional connectivity of the M-CIN (109), as well as dynamics between the default mode/medial frontoparietal network (M-FPN) and L-FPN (110), has been shown to predict individual differences in cognitive flexibility. These works are beginning to reveal the links between brain dynamics and flexible cognition and behavior (111).

While several methodological issues have yet to be resolved (112), dynamic functional connectivity approaches are already revealing interesting patterns of brain dynamics that distinguish youth with ASD (Table 2). The first study of 8–18 year olds focused on the M-FPN, M-CIN, amygdala and thalamus and examined standard deviation of the sliding window correlation, which indicates intra-individual variability over time. For multiple region-of-interest (ROI) pairs, reduced static functional connectivity in adolescents with ASD was related to increased temporal variability of the BOLD signal (113).

A study of 7–18 year old children from the Autism Brain Imaging Data Exchange (ABIDE) (114) found that those with ASD showed weaker whole-brain connectivity for a longer period of time compared with TD children (115). Another study using the entire available ABIDE sample (ages 6–58) found evidence for decreased state transitions in ASD (116). This finding of reduced transitions between brain states has been replicated in adults with autism (117).

Focusing on functional connectivity variance in 6–36 year-olds within ABIDE, greater variance of widespread long-range dynamic functional connections in ASD was reported, and linked with symptom severity indexed by the Autism Diagnostic Observation Schedule (ADOS) (118). Similar findings of hyper-variability of functional connections in ASD have been observed in studies focusing on the adolescent period (119,120). The only study to stratify participants into child, adolescent, and adult groups found evidence for greater hyper-variability of short-range functional connections that distinguished adolescents with ASD (121).

In a very large sample including 774 6–10 year-old children from the Generation R Study (122), higher levels of autistic traits and ASD diagnosis were associated with longer dwell times in a functional connectivity state characterized by global disconnection (123). These findings suggest that atypical brain dynamics in ASD may be present at earlier points in development than adolescence.

Dynamic functional connectivity research has rapidly accelerated (124), in part due to the availability of data made possible through the ABIDE initiative (125–128). The studies reviewed here have utilized different subsets from the larger ABIDE datasets, with minimal sample overlap across studies (Table 2). The data thus far provides evidence for both alterations in the number of transitions between brain states, and hyper-variability of functional connections in adolescents with ASD. Limitations and inconsistencies in this literature could be attributed to variable MRI data acquisition parameters, participant demographics, and data analytic pipelines. Increased sample inhomogeneity due to data pooling across sites can introduce biases that must be considered. Efforts to overcome these limitations include cross-site replication or leave-one-site-out cross validation (118,129).

To date, no studies have explicitly explored the link between atypical brain dynamics and cognitive flexibility in ASD. The hope is that with greater methods development in the field of machine learning (130), these types of neuroimaging markers may eventually be used to parse heterogeneity, monitor treatment response, and predict individual outcomes in ASD (131).

6. Outstanding Issues and Future Directions

Ecological validity and measurement

Measurement issues still complicate the study of cognitive flexibility in ASD. Performance-based measures such as the WCST can hone in on specific cognitive constructs (132), whereas more ecologically-valid measures such as the BRIEF are sensitive indices of real-world behaviors (6) but may be subject to reporter bias. Although individuals with ASD appear behaviorally rigid in daily activities, neuropsychological and laboratory-based measures of cognitive flexibility provide mixed results with respect to patterns of EF deficits (74). Poor convergence between these two types of measures might influence findings of cognitive flexibility impairments in ASD and relationships with outcomes such as symptom severity and adaptive functioning. Measures with high reliability such as informant- or self-report may better predict individual differences in real-life outcomes, whereas behavioral measures that are sensitive to within-person experimental manipulations may be important for studying processes that underlie task performance (5). A clearer neuroimaging story might emerge if cognitive neuroscientifically-derived measures are used alongside informant reports of cognitive flexibility in future studies.

In parallel to the identification of neural circuits involved in cognitive flexibility, standardized assessments of flexible behaviors in daily life that potentially have greater ecological validity must be developed and validated. The Flexibility Scale, based on data collected from 300 6–17 year olds, is an informant report that densely samples cognitive aspects of flexibility in everyday settings and has been shown to discriminate participants with ASD and controls. Exploratory factor analysis revealed evidence for five factors related to Routines/Rituals, Transitions/Change, Special Interests, Social Flexibility, and Generativity, and the scale demonstrated convergent and divergent validity with comparative domains in other measures including the ‘shift’ subscale of the BRIEF and D-KEFS performance (133). Once further validated, specific measures of cognitive flexibility such as

the Flexibility Scale could be used in future research to promote standardization and replicability in the field.

Neuroimaging of individual differences and heterogeneity

Children and adolescents with ASD may have difficulties with flexibility that can persist into adulthood (134). Understanding the neural basis of individual differences in cognitive flexibility in ASD will pave the way for development of more targeted early interventions to improve the lives of those affected. Specifically, young children exhibiting impaired EF abilities who are identified early in life may benefit from targeted training in this area. Unstuck and On Target (UOT) is an EF intervention designed for children with ASD that can be implemented in school and at home. UOT targets insistence on sameness, flexibility, goal-setting and planning through a cognitive-behavioral program involving self-regulatory scripts, guided practice, and cueing, and has been shown to be effective for improving classroom behavior, flexibility and problem-solving in children with ASD (135). The neural mechanisms associated with successful implementation of this intervention are yet unknown.

Importantly, not all children with ASD exhibit the same level and profile of EF deficits. While some studies provide evidence of uniform patterns of abilities across EF domains (60,61), others suggest that distinct EF subtypes exist (136). This heterogeneity of EF ability and underlying brain network organization makes accurate characterization of EF in ASD all the more challenging. Neuroimaging can provide a means for understanding neurobiological mechanisms underlying heterogeneous symptom presentation in ASD. Future directions include further attempts at stratifying youth with ASD based on EF profiles and individual connectomes (136–138).

Future studies must work to overcome the limited generalizability afforded by small sample sizes (139) and further consider females with ASD and individuals of varied socioeconomic status, who are largely under-represented in neuroimaging research. Co-occurring conditions that are associated with cognitive inflexibility have also not been adequately considered, despite initial evidence that EF impairment is more severe in children with comorbid ASD and ADHD (60).

Consideration of adolescence and puberty

As Table 1 and Table 2 demonstrate, very few neuroimaging studies have focused on the adolescent period specifically in ASD. Additionally, it is completely unknown how puberty, which marks the beginning of adolescence, influences the development of brain systems underlying cognitive flexibility in autism. Dissociable effects of pubertal hormones and age on the adolescent brain have been documented, suggesting that pubertal stage may be a better predictor of cognitive and behavioral maturity than chronological age (140). Hormonal effects on brain, behavior, and cognition constitute an active area of research (141) that must be incorporated into future cognitive neuroscience work on adolescent ASD.

Alternative approaches for bolstering cognitive flexibility in ASD

The bilingual advantage refers to the phenomenon that individuals who speak two languages fluently often perform better on tasks of EF than monolingual individuals (142, but see 143). Despite the potential advantages that bilingualism may confer for EF, clinical practitioners commonly advise *against* providing children with developmental disabilities a bilingual environment (144), believing that concentrating on one language will better support language development (145). Yet, a growing body of work suggests there are no negative effects of being raised in a bilingual environment (146,147). A study of 6–16 year olds with average IQ levels suggests that second language exposure in children with ASD is associated with reduced clinical impact in the domains of functional communication and EF (148). Bilingualism may even mitigate set-shifting difficulties in children with ASD of average IQ (149). If bilingualism is indeed found to confer an EF advantage in ASD, then encouraging parents to speak two languages in the home may be one “natural intervention” strategy for bolstering cognitive flexibility in high-functioning autism.

Conclusion

Cognitive flexibility may facilitate optimal functioning in ASD during the volatile period of adolescence. Studies of the neural mechanisms underlying the development of flexible cognition and behavior in ASD provide initial evidence for altered brain activation and dynamics in diagnosed individuals. Moving forward, issues of measurement and sample heterogeneity must be adequately addressed in order to maximize ecological and construct validity in studies of cognitive flexibility in ASD. Development of interventions to enhance flexibility, and neuroimaging studies exploring the mechanisms underlying training effects, will be important future directions.

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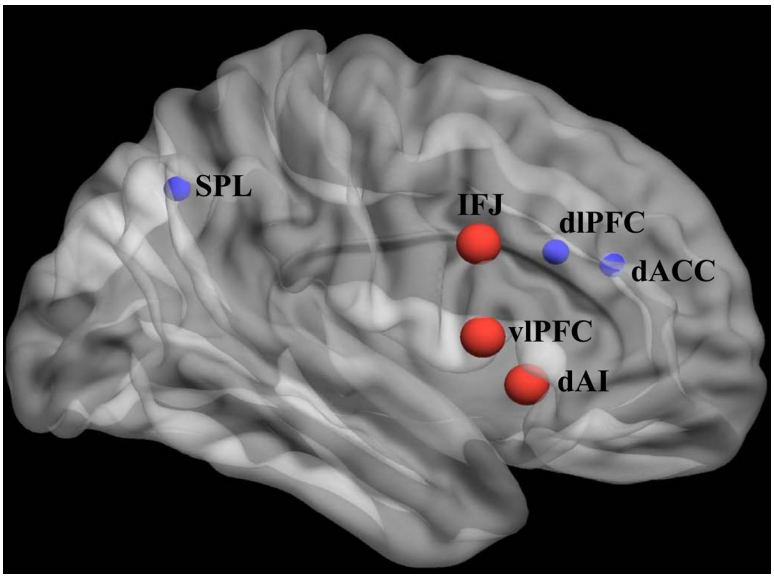

Figure 1. Brain systems underlying cognitive flexibility.

Nodes critical for cognitive flexibility (red) operate within the context of broader lateral frontoparietal (L-FPN) and midcingulo-insular (M-CIN) networks (24) supporting executive functions (blue). The inferior frontal junction (IFJ) is involved in inhibition and response set updating, the ventrolateral prefrontal cortex (vlPFC) in resolving proactive interference, response set selection, and context monitoring, the dorsal anterior insula (dAI) in switching between other large-scale functional brain networks, the dorsolateral prefrontal cortex (dlPFC) in working memory, the dorsal anterior cingulate cortex (dACC) in response selection and motor responses, and the superior parietal lobule (SPL) in visuomotor integration and attention (adapted from (25)).

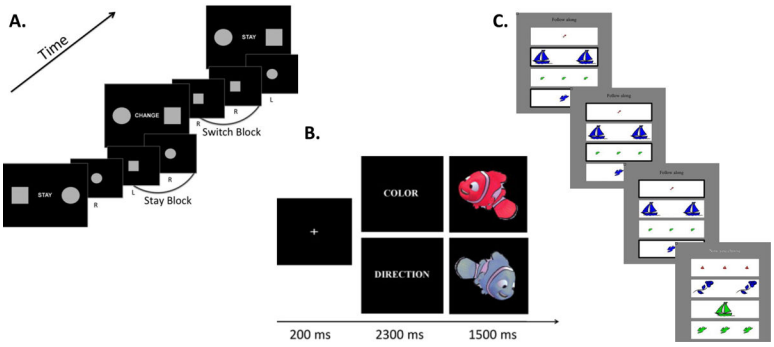

Figure 2. Laboratory tasks for assessing cognitive flexibility in developmental populations.

A. Example set-shifting task. Instruction cues indicate spatial mapping to stimuli to response buttons. When the circle is presented on the right side of the instruction cue, a right-handed button press to circle trials is required (44). B. Example flexible rule switch task. On Color trials, participants are instructed to press one button for red stimuli and another for blue stimuli. On Direction trials, participants are instructed to press a left button for leftward facing stimuli and right button for rightward facing stimuli (45). C. Example flexible item selection task. During Flexibility trials, participants choose three successive pairs of cards that "go together in one way" ("Now you choose"). During Control trials, the correct card pairs are highlighted by a thick black border ("Follow along") (46).

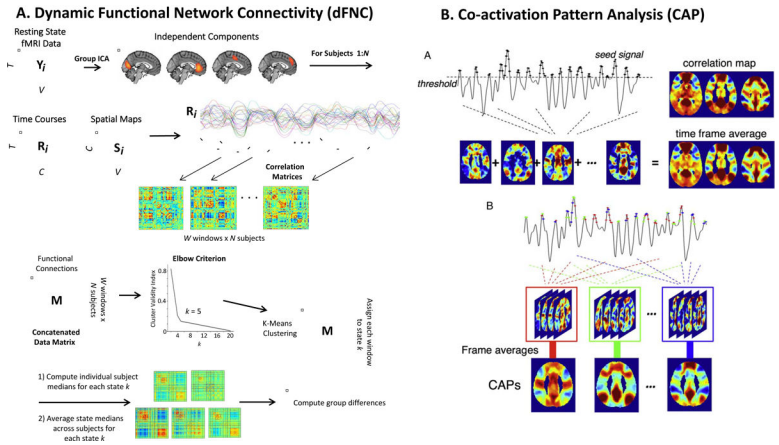

Figure 3. Approaches for characterizing brain dynamics.

A. Example sliding window approach for computing dynamic functional network connectivity (dFNC). High-model order independent component analysis (ICA) creates functional parcellation of the brain, resulting in several independent components. B) Subject-specific timecourses are used to compute functional connectivity between pairwise components. Dynamic FNC analysis utilizes sliding windows (eg. 45 seconds in duration) to produce multiple correlation matrices for each subject (one per window). A concatenated data matrix is then subjected to *k*-means clustering, and the optimal *k* is identified using the elbow criterion (*k*=5 in this example). Each window is assigned to a dynamic state *k* regardless of subject assignment. Subject-specific medians are then back-reconstructed for each state *k* before they are averaged together to produce the final *k* dynamic states. Finally, group differences in dFNC metrics (eg. dwell time, state transitions) are computed (103). B. Example co-activation pattern (CAP) analysis. In conventional seed-based correlation analysis, functional connectivity patterns associated with a seed region-of-interest is estimated by the linear correlation between the timeseries of each gray matter voxel in the brain and the seed. The CAP method demonstrates that these patterns can be obtained by voxel-wise averaging the spatial maps of time frames when the seed signal intensity surpasses a given threshold. Temporal clustering of the extracted time frames based on their spatial similarity yields multiple spatial patterns reflecting functionally relevant CAPS across the whole brain at each individual time frame. Different colors indicate different CAPs in temporal clustering (adapted from (105)).

Table 1.

fMRI studies of brain activation underlying cognitive flexibility in autism

Study by publication date	Sample Size	Age Range, Years (mean, SD)	Cognitive Paradigm	Behavioral Results	Neuroimaging Results
Schmitz et al., 2005 (82)	ASD: 10 TD: 12	Combined: 18–52 ASD: 38±9 TD:39±6	Set-shifting	No significant group differences	ASD > TD activation in inferior and medial parietal cortex during switch trials
Shafritz et al., 2008 (83)	ASD: 15 TD: 14	ASD: 22.3±8.7 TD: 24.3±6.2	Set-shifting	ASD < TD accuracy, no significant group difference in RT	ASD < TD activation in dlPFC, ACC, IPS, BG during target-shift trials
Taylor et al., 2012 (85)	ASD: 14 TD: 14	Combined: 7–14	Set-shifting	No significant group differences	Age x Group interaction for shift trials: insula increase activation with age in TD, decrease activation with age in ASD; vlPFC increase activation with age in ASD, no change with age in TD
Yerys et al., 2015 (44)	ASD: 20 TD: 19	Combined: 7–14 ASD: 11.32±1.84 TD: 11.36±1.54	Set-shifting	ASD < TD accuracy, no significant group difference in RT	ASD > TD activation in ACC, superior, middle, and inferior frontal gyrus during switch trials
D'Cruz et al., 2016 (84)	ASD: 17 TD: 23	ASD: 9–44; 17.4±8.6 TD: 7–38; 18.6±8.4	Reversal learning	No significant group differences	ASD < TD activation in ventral striatum, ACC, premotor cortex, posterior parietal cortex, and dlPFC during reversal

ASD = autism spectrum disorder; TD = typically developing; dlPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex; IPS = intraparietal sulcus; BG = basal ganglia; vlPFC = ventrolateral prefrontal cortex

Table 2.

fMRI studies of brain dynamics in autism

Study by publication date	Sample Size, ABIDE or in house data	Age Range, Years (mean, SD)	Method for ssessing Dynamics	Behavioral Results	Neuroimaging Results
Falahpour et al., 2016 (113)	Study 1 (6 ABIDE sites) ASD: 76 TD: 76 Study 2 (SDSU in house) ASD: 32 TD: 32	Study 1 ASD: 7–29.9; 16.1±4.9 TD: 8–29.9; 15. 8±4.5 Study 2 ASD: 9.5–17.9; 14.3 ±2. 4 TD: 8–17.5; 13.5±2.7	Standard deviation of sliding window correlation between select ROIs (DMN, SN, amygdala, Thal)	N/A	Study 1 ASD > TD SD-iFC several ROI pairs Study 2 ASD > TD SD iFC one ROI pair
Yao et al., 2016 (115)	ASD: 31 TD: 44 (ABIDE NYU site)	Combined: 7–18 ASD: 11.51±2.64 TD: 12.46±3.1	Sliding window correlation across whole- brain ICA-derived ROIs	N/A	ASD > TD mean dwell time in weak FC state
de Lacy et al., 2017 (116)	ASD: 423 TD: 461 (all ABIDE sites)	Combined: 6.5–58; 16.23±7.1	Sliding window correlation across whole- brain ICA-derived ROIS	N/A	ASD < TD transitions between brain states
Watanabe et al., 2017 (117)	ASD: 24 TD: 26 (ABIDE Utah site primary, Indiana and Zurich site replication)	ASD: 18.4–38.9; 25.3±5.5 TD: 18.2–39.3; 25.3±6.3	Energy- landscape analysis across seven functional brain systems	Transition frequency negatively correlated with ADOS	ASD < TD transitions between brain states
Chen et al., 2017 (118)	ASD: 209 TD: 298 (all ABIDE sites)	ASD: 16.5±6.2 TD: 16.8±6.2	Standard deviation of sliding window correlation between whole-brain ROIs	Hyper-variant FC positively correlated with ADOS	ASD > TD SD-iFC for almost all ROI pairs
Rashid et al., 2018 (123)	Combined: 774; 560 with SRS ASD: 22 (Generation R Study)	Combined: 6–10; 7.99±1	Sliding window correlation across whole- brain ICA-derived ROIs	N/A	ASD traits indexed by SRS positively correlate with mean dwell time in globally disconnected state
Mash et al., 2019 (119)	ASD: 62 TD: 57 (SDSU in house)	Combined: 6–18 ASD: 13.7±2.5 TD: 13.1±2.9	Sliding window correlation across whole- brain ICA-derived ROIs	N/A	ASD > TD SD-iFC for almost all ROI pairs
Li et al., 2019 (120)	ASD: 62 TD: 63 (ABIDE SDSU, Trinity, NYU, Stanford sites)	ASD: 7.18–17.93; 11.63±2.84 TD: 7.11–17.6; 11.48±2.59	Sliding window correlation across whole- brain ROIs	SD-iFC between IFGoper positively correlated with SRS	ASD > TD SD-iFC for several ROI pairs; ASD > TD mean dwell time in globally hyper-connected state
Harlalka et al., 2019 (121)	Child ASD: 26 Child TD: 26 Adolescent ASD: 28 Adolescent TD: 28 Adult ASD: 18 Adult TD: 18 (ABIDE NYU site)	Child ASD: 7.15–10.06; 9.51±1.12 Child TD: 6.47–10.86; 9.10±1.32 Adolescent ASD: 11.01–17.88; 13.71±1.79 Adolescent TD: 11.32–16.93; 14.01±1.74 Adult ASD: 18.58–39.1; 24.13±3.92 Adult TD: 18.5931.78; 25.41±5.87	Sliding window correlation across whole- brain ROIs	DMN- Attention network SD- iFC positive correlation with ADOS	ASD > TD SD-iFC for almost all ROI pairs for children, adolescents, and adults ASD > TD SD-iFC for short-range connections in adolescents
Guo et al., 2019 (125)	ASD: 209 TD: 298 (all ABIDE sites)	ASD: 16.5±6.2 TD: 16.8±6.2	Sliding window correlation	Decreased dynamic FC between rAI and vmPFC negative	ASD < TD FC between rAI and vmPFC/PCC in some states

Study by publication date	Sample Size, ABIDE or in house data	Age Range, Years (mean, SD)	Method for ssessing Dynamics	Behavioral Results	Neuroimaging Results
			between rAI and whole brain	correlation with ADOS social	
Fu et al., 2019 (127)	ASD: 170 TD: 195 (all ABIDE sites)	ASD: 15.57±7.35 TD: 16.02±5.9	Sliding window correlation between thalamic ROIs and whole brain	Increased dynamic FC between hypothalamus and sensory region positive correlation with ADOS	ASD > TD FC between hypothalamus and sensory regions in some states ASD < TD meta-state dynamism measures
Guo et al., 2020 (126)	ASD: 105 TD: 102 (all ABIDE sites)	Combined: 7–12 ASD: 10.15±1.26 TD: 10.02±1.38	Sliding window correlation and FCD mapping across whole-brain	Aberrant temporal variability of contralateral dynamic FCD predicted ADOS communication scores	Global alterations in dynamic FCD variability and atypical dynamics of intra- and interhemispheric FCD variability in ASD

ABIDE = Autism Brain Imaging Data Exchange; ADOS = autism diagnostic observation schedule; ASD = autism spectrum disorder; DMN = default mode network; FCD = functional connectivity density; ICA = independent component analysis; NYU = New York University; rAI = right anterior insula; ROI = region of interest; SD-iFC = standard deviation of intrinsic functional connectivity; SN = salience network; SRS = social responsiveness scale; Thal = thalamus; SDSU = San Diego State University; TD = typically developing;