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An altered scaffold for information processing: Cognitive control development in adolescents with autism

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Abstract

We investigated how cognitive neuroscientific studies during the last decade have advanced understanding of cognitive control from adolescence to young adulthood in individuals with autism spectrum disorder (ASD). To do so, we conducted a selective review of the larger structural, resting state, and diffusion imaging studies of brain regions and networks related to cognitive control that have been conducted since 2007 in individuals with ASD and typical development (TYP) ages 10 to 30 years that examined how these regions and networks support behavioral and task-based fMRI performance on tasks assessing cognitive control during this period. Longitudinal structural studies reveal overgrowth of the anterior cingulate (ACC) and slower white matter development in the parietal cortex in adolescents with ASD versus TYP. Cross-sectional studies of the salience, executive control and default mode resting state functional connectivity networks, which mediate cognitive control, demonstrate patterns of connectivity that differ from TYP through adolescence. Finally, white matter tracts underlying these control-related brain regions continue to show reduced diffusion properties compared to TYP. It is thus not surprising that cognitive control tasks performance improves less during adolescence in ASD versus TYP. This review illustrates that a cognitive neuroscientific approach produces insights about the mechanisms of persistent cognitive control deficits in individuals with ASD from adolescence into young adulthood not apparent with neuropsychological methods alone, and draws attention to the great need for longitudinal studies of this period in those with ASD. Further investigation of ACC and fronto-parietal neural circuits may help specify pathophysiology and treatment options.

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Keywords

executive functions; cognitive control; autism; neuroimaging; adolescent development; young adulthood

Cognitive control – the maintenance of situational context and inhibition of prepotent responding to permit the goal-directed behavior [1] – is a key component in the NIMH Research Domain Criteria project (RDoC; [2]). As specified by RDoC, cognitive control consists of three broad components: working memory or cue/context maintenance; inhibition of prepotent response tendencies; and set shifting, task switching or cognitive flexibility.

In perhaps the most influential theory of the neural mechanisms governing cognitive control, Miller & Cohen [3] proposed that the prefrontal cortex (PFC) is specialized for the representation and maintenance of situational context that provides top-down biasing to facilitate information flow from relevant neural systems. This model has provided a foundation for the development of testable mechanistic hypotheses using cognitive neuroscientific versus clinical neuropsychological measurements [4]. Hypotheses then can be verified using functional magnetic resonance imaging studies (fMRI). These studies have localized control processes to the dorsolateral prefrontal (DLPFC), ventrolateral prefrontal (VLPFC), anterior PFC (aPFC), anterior cingulate (ACC), and parietal cortices [5, 6], and have generated insights about how control is evoked in response to ACC-generated conflict signals [7] and timing differences in neural circuits recruitment [8]; and basal ganglia/PFC interactions that guide reward-driven learning [9].

In typical development (TYP), adolescence is considered a critical period for the development of mature thought and action [10]. This has not been well-examined in individuals with autism spectrum disorder (ASD). To help fill this gap in understanding, this manuscript selectively reviews structural, resting state, diffusion, and task-based functional magnetic resonance imaging (fMRI) studies of brain regions and networks sub-serving cognitive control in individuals with ASD. Peer-reviewed and published scientific papers written in English from 2007–2017 were identified through a computerized literature search using *Google* Scholar and *PubMed*. Search terms used across all studies included autism, cognitive control, adolescence, young adulthood, and MRI. Other terms including brain structure, default mode network, salience network, executive control network, diffusion, DTI, cue/context maintenance, response inhibition, set shifting, and task switching also were used in their respective sections. To be included, studies also had to have a mean of >10 participants per group (e.g. a two-group study where one group had 9 participants and the other had 11 participants was included). Given the relative lack of longitudinal studies of ASD during the adolescence to young adulthood period, many comparisons are of cross-sectional studies, although greater weight is given to existing longitudinal studies when drawing inferences about findings.

Components of the Scaffold

Structural neuroimaging of cognitive control related brain regions

Cortical gray matter volume, increases during childhood, peaks around puberty and then begins to decline across adolescence and adulthood [9]. Frontal and parietal regions reach peak volume around 12 years of age in males, and about a year earlier in females [11]. Increases and decreases in volume pre and post-adolescents are steeper for parietal lobe than for frontal lobe. In TYP, decreases in volume within the cognitive control network during adolescence and adulthood are associated with increased performance on tasks of executive functioning and emotion identification [12].

Several cross-sectional structural MRI studies have evaluated global cortical gray and white matter differences between adolescents with ASD compared to age matched TYPs (see [13]). Since 2007, there has been one study that utilized whole brain voxel-based morphometry (VBM; a technique involving comparing differences in brain anatomy using volumetric MRI scans across groups) that identified volume increases in both the DLPFC and superior and interior parietal lobule, as well as decreased white matter volume across all cerebral lobes in those with ASD versus TYP [14]. Differences in the folding of the cerebral cortex (gyrification), also have been reported in the frontal lobe and intraparietal sulcus in individuals with ASD versus TYP [15].

More recently, evidence from two longitudinal studies suggest there are between group differences in the structure of cognitive control-related brain regions. Hua et al. [16] evaluated youth with ASD from late childhood into adolescence. They report abnormal overgrowth versus the pruning typically found during adolescence, in the anterior cingulate cortex (ACC) and slower white matter development in the parietal lobe in those with ASD versus TYP. Wallace et al. [17] evaluated cortical thickness (a brain morphometric measure used to assess the combined thickness of the layers of the cerebral cortex) and surface area in slightly older adolescents with ASD beginning at 17 and then again at 19 years. They observed accelerated cortical thinning in superior parietal cortex in ASD relative to TYP. Table 1 presents the two cross-sectional structural, VBM and cortical folding studies and two longitudinal studies of white and gray matter and cortical thickness development since 2017. While older studies are ambiguous, two recent longitudinal studies suggest that the rate of development in key cognitive control regions is implicated in ASD. However, no studies include both males and females with ASD. See Figure 1A for a depiction of brain regions implicated in structural studies.

Resting-state functional neuroimaging studies of cognitive control in ASD

Resting-state fMRI (rsfMRI) examines the correlation in BOLD signal between brain regions during periods of quiet rest. This is referred to as functional connectivity (FC) [18]. A reliable set of rsfMRI networks [19] emerges during adolescence, when there is a strengthening of FC within networks (integration) and decreased FC between networks (segregation). This culminates in the establishment of a mature intrinsic functional brain architecture in young adulthood [20–22]. Atypical connectivity between three specific intrinsic functional networks – the default mode (DMN), salience (SN), and executive

control networks (ECN) [23]–is central to disorders involving cognitive control impairments, and are the focus of this selective review.

Most rsfMRI studies in ASD have examined the default mode network, which includes the posterior cingulate cortex/retrosplenial cortex and medial prefrontal cortex, and which demonstrates robust FC at rest and during self-referential processing [Figure 1B; [24]]. Children with ASD demonstrate aberrant FC within the DMN, and greater FC between the DMN and other intrinsic functional networks [25–27] than those with TYP. During adolescence DMN connectivity does not increase to the same extent in ASD relative to TYP [28, 29], and remains decreased in young adults with ASD [30–33]. Collectively, these data suggest that DMN integration during adolescence may be reduced in individuals with ASD.

The second network implicated in cognitive control impairments is the salience network (SN). The SN is centered around the anterior insula (AI) and the anterior cingulate cortex (ACC; Figure 1B), and plays a role in detecting stimuli of high relevance [34, 35]. FC within the SN is increased in adults relative to children, suggesting this circuit develops during adolescence [36]. Whereas the SN demonstrates *over*connectivity in children with ASD [37, 38], the SN is *under*-connected in adolescents with ASD relative to those with TYP [38–40], suggesting that it demonstrates a flatter developmental trajectory in ASD. This may lead to enduring differences in salience processing within this network in adulthood in those with ASD [41].

One hypothesized role of the SN is to prioritize stimuli for processing by the ECN—the third network implicated in cognitive control. The ECN is anchored in the DLPFC and parietal cortex [23, 34]. Cross-sectional and longitudinal studies of TYP have suggested that ECN FC increases during adolescence and young adulthood, whereas FC between the ECN and other networks decreases [20, 42, 43]. Recently, Elton et al. [26] analyzed ECN connectivity in 90 ASD and 95 TYP youth ages 6.5–18.7 years. Youth with ASD showed underconnectivity within prefrontal sectors of the ECN relative to TYP. In this study there also was a positive association between connectivity of the ECN and the DMN and scores on a dimensional ASD symptom measure [26, 44]. Abbott and colleagues [45] found similar FC anomalies within the ECN and increased connectivity between the ECN and DMN in youth ages 8–17 with ASD relative to TYP. As the DMN and ECN underlie “task-negative” and “task-positive” information processing, respectively, these findings suggest that the typical pattern of segregation between these networks across adolescence may not be present in ASD. See Table 2 for studies of the three networks in ASD since 2007. Notably, there have been no large-scale longitudinal rsfMRI studies in ASD, and hypotheses derived herein are based on cross-sectional comparisons.

Diffusion MRI studies of cognitive control in ASD

Three white matter tracts – the corpus callosum, cingulum bundle, and superior longitudinal fasciculus – underlie brain regions involved in cognitive control. See Figure 1(C). These tracts play a role in processing speed and complex cognition [46], attention and working memory [47], motor behavior, spatial attention, language, and response inhibition [48, 49], respectively. Atypical development of these three tracts in early childhood leads to continued alterations in diffusion properties in adolescents and adults with ASD [50–53].

The corpus callosum is most implicated in ASD. Structural MRI studies have consistently reported reduced size of the corpus callosum, in ASD relative to TYP. The front end or genu of the corpus callosum, and its most anterior portion (the forceps minor), radiates across the lateral and medial sides of the PFC, connecting the PFC and orbitofrontal cortex (OFC) [54].

Alterations in white matter diffusion specific to the genu and forceps minor have been reported cross-sectionally in adolescents and young adults with ASD compared to TYP [55–60], as well as in the white matter tracts connecting to the OFC specifically [61]. In addition, one longitudinal study found that the developmental trajectory of diffusion properties of the genu was altered during childhood in individuals with ASD compared to TYP, leading to persisting atypicalities in the white matter into adolescence and adulthood [50]. The few studies that relate alterations in diffusion with behavioral measurements have found that fractional anisotropy (FA) – a measurement of the directional flow of cerebrospinal fluid thought to reflect fiber density, axonal diameter, and myelination – of the corpus callosum was correlated with performance IQ with a medium effect size and that FA of the genu was associated with processing speed with a large effect size [55].

The second white matter tract implicated in cognitive control – the cingulum bundle – stretches from anterior temporal gyrus to orbitofrontal cortex and runs within the cingulate gyrus and over the top of the corpus callosum [54]. Cross-sectional studies have identified consistent alterations in the diffusion properties of the cingulum bundle in both adolescents and young adults with ASD [56, 57, 59, 61–65]. In addition, one study reported a significant negative relationship between FA of the cingulum bundle and scores on a parent-report measure of executive functions, such that lower FA in cingulum predicted greater executive function deficits in participants with ASD with a large effect size [65]. The final tract involved in cognitive control – the superior longitudinal fasciculus (SLF) – extends from the inferior fontal gyrus (IFG) to the superior temporal gyrus (STG) and temporoparietal junction (TPJ), terminating close to Broca's Area, Wernicke's Area, precentral gyrus and the supramarginal gyrus [48, 66–68]. For this tract too, a number of previous cross-sectional studies have found reductions in diffusion properties in those with ASD during both adolescence and young adulthood [56, 59, 62, 64, 69–71]. See Figure 1C, and Table 3 for a review of twenty cross-sectional studies and one accelerated longitudinal study comparing the diffusion properties of these tracts between adolescents and young adults with ASD and TYP. Although we must rely on findings from diffusion MRI studies in ASD that have been almost entirely cross-sectional by design, it appears that alterations of diffusion properties within the three tracts associated with cognitive control are present during adolescence and persist into early adulthood.

Behavioral and neuroimaging studies of cognitive control in ASD

Neuropsychological studies illustrate that executive control deficits are among the most common impairments found in individiuals with ASD [72]. Neuropsychological and cognitive neuroscientific studies find impairments in the three RDoC domains of cognitive/executive control including: working memory or cue/context maintenance [73, 74], inhibition of prepotent response tendencies or response inhibition [75–77] and set shifting or task switching or cognitive flexibility [78]. However, shifting deficits have been questioned

[79], and may only be present if participants must choose to switch tasks [80–82]. Despite the typical maturation of cognitive control from adolescence to young adulthood, studies of those with ASD generally show persisting lag through this period [83] or isolated development of a subset of component processes [75, 84], or limited improvement within the context of persistent delay [85].

Since the advent of fMRI during the decade of the brain (1990–1999), there have been a growing number of task-based fMRI studies of cognitive control in ASD from adolescence to young adulthood. Studies since 2007 are reviewed below.

Cue/context maintenance—Solomon et al. [86] used event-related fMRI to assess holding a cue in mind when preparing to overcome a prepotent response tendency in 12–18 year olds with ASD (n=22) and TYP (n=23). TYP versus ASD recruited significantly more aPFC and parietal (BA 7 and BA 40) regions for correct trials requiring overcoming a prepotent response tendency. ASD also exhibited reduced FC and network integration compared to TYP that was associated, with symptoms of attention deficits (medium effect size). An additional cross-sectional followup study in an overlapping larger sample investigated the development of control through early (ages 12–15) and late (ages 16–18) adolescents [87]. Older ASD and TYP showed reduced activation in sensory and premotor areas relative to younger ones. However, older individuals with ASD showed reduced left parietal recruitment relative to TYP. FC analyses showed that the older ASD group exhibited increased functional connectivity strength between the VLPFC and the ACC, bilaterally. This was interpreted as a signature of cognitive control that was less planful/proactive and more last-minute and reactive. This FC strength was associated with task performance in ASD with a medium effect size, whereas DLPFC and parietal cortex FC was related to task performance in TYP with a large effect size. Vogan et al. [88] examined performance on a simple color matching one-back task. TYP activated regions of the PFC, while ASD activated posterior regions of the brain. TYP recruited more of the PFC and parietal cortex as load increased, while ASD did not. In sum, based on the few studies of context maintenance to date, adolescents with ASD appear to recruit the PFC and parietal cortex less than those with TYP. One study suggested that TYP appear to become more planful (proactive), while those with ASD remain more reactive, and show increasing PFC/ACC FC.

Cognitive control of response inhibition—Response inhibition in ASD has been studied using both go/no-go and saccadic eye movement paradigms which require the participant to look towards a target. Kana, Keller, Minshew, & Just [89] manipulated working memory load in a go/no-go paradigm in young adults with ASD and TYP, and examined recruitment in ROIs in the ACC, PFC, and parietal cortex. The ASD group showed poorer memory performance in greater load conditions than TYP with less recruitment of the PFC, ACC, and insula. In the most difficult condition, the ASD group showed reduced recruitment of the ACC and precuneus, but greater recruitment of premotor regions. A factor analysis of FC showed poorer integration of the inhibitory and control networks in ASD. However, writing about FC in a younger group of adolescents, Lee et al. [90] conducted a left and right IFG seed-based FC study of a similar go/no-go task and found no group FC differences.

Thakkar et al. [91] used rapid even-related fMRI and diffusion imaging of an anti-saccade task in which participants were required to make a saccadic eye movement away from a target, rather than towards it (an anti-saccade), to investigate response inhibition deficits, ACC dysfunction, and restricted interests and repetitive behaviors (RBs) in young adults with ASD versus TYP. The ASD group made more anti-saccade errors; responded more quickly on correct trials; showed reduced discrimination in rostral ACC between error and correct trials and reduced FA in white matter underlying the ACC. Recruitment on correct trials and reduced FA were associated with RBs with a large effect size. Agam et al. [92] then examined ACC regions recruited during anti-saccades versus pro-saccades in the same young adult participants, using an ROI based approach. TYP showed greater bilateral frontal eye field (FEF) and dorsal ACC (dACC) recruitment than ASD. Greater activation in the dACC predicted fewer errors across both groups. In those with ASD, greater recruitment in the dACC during inhibition predicted faster anti-saccades. Activation in both the left and right dACC predicted RBs. Finally, Padmanabhan et al. [93] used fMRI to extend Luna et al.'s [85] behavioral study of cognitive control using an anti-saccade task. The groups did not differ in pro-saccade performance. However, the ASD group showed less BA 7 recruitment during task preparation, but greater activation of this region during anti-saccade performance. Taken together, go/no-go and eye movement studies again suggest that integrated recruitment of the ACC and parietal cortices is critical to cognitive control of response inhibition, although there may be no group differences in FC of these regions with the PFC in adolescents. The presence of RBs may be associated with the functioning of the ACC, but the relation remains complex and difficult to interpret.

Cognitive control of set shifting/task switching—Shaffritz, Dichter, Baranek, & Belger [94] used an event-related target detection task to examine the association between set shifting and RBs. There were no group differences in the ability to shift versus maintain responding to the target. TYP exhibited greater recruitment of the DLPFC, IPS, and basal ganglia during target, and target shift versus target maintain trials. RBs were negatively associated with ACC activation to targets with a large effect size. Using a different task, Yerys et al. [95] employed event-related fMRI to examine a model of set shifting involving simple versus more complex rules in children and adolescents with ASD and TYP. The ASD group performed more poorly and was slower than TYP. There was no group by trial type interaction for the lowest level dimension shifts. ASD versus TYP recruited more ACC, superior frontal gyrus, frontal pole and right IFG, in the switch versus stay condition. Authors interpreted this as a sign that ASD needed stronger recruitment of task-relevant brain regions to complete the task when task performance was the same for both groups. In conclusion set shifting appears to rely on similar brain regions as other components of cognitive control, and that group differences may emerge with age. Inconsistent study findings may also derive from different levels of task difficulty. As shown in Table 4, during the past decade there have been only 10 task-based fMRI studies (3 of cue/context maintenance, 5 of response inhibition, and 2 of switching) meeting our criteria. Studies were small, and utilized diverse paradigms, study designs, and thresholding. Furthermore, none were longitudinal or examined sex differences.

Discussion

This review of structural, rsfMRI, and diffusion imaging studies converged in suggesting that the scaffold supporting cognitive control in adolescents with ASD transitioning to young adulthood is altered. Longitudinal structural studies suggest there is enlargement of the ACC and excess white matter and gray and white matter pruning in the parietal cortex during this period [16]. This is accompanied by over and under-connectivity within the DMN and other brain networks important for cognitive control (SN, ECN) compared to that found in TYP. Finally, ASD shown early developing, persistent, and widespread diffusion-related differences compared to TYP in the white matter tracts supporting control. Given that a different and compromised neural scaffold restricts the functioning of control processes in adolescents and young adults with ASD, it is not surprising that their performance on executive control and task-based fMRI paradigms across multiple component processes develops less during adolescence than TYP. More specifically, adolescents with ASD appear to recruit the PFC and parietal cortex less than those with TYP when keeping context in mind, inhibiting prepotent responses, and engaging in more difficult forms of set shifting.

This conclusion offers several potential etiological and treatment related leads that could be explored in future studies. First, based on structural findings of its potential increased size [16] and fMRI studies documenting its atypical recruitment and potential relationship to RBs [89, 91, 92, 94], the ACC may represent a node that alters the functioning of the impaired cognitive control network. This assertion is consistent with early theoretical work suggesting that inefficient functioning the dorsal medial PFC system produces social orienting deficits found in young children with ASD [96]. The work of our group, which finds that as adolescence progresses those with ASD show increasing PFC/ACC FC while those with TYP show decreasing FC between these brain regions, also is consistent with the contention that the mechanisms of cognitive control operate differently in those with ASD. Also supportive of the importance of the ACC in ASD, are recent rsMRI FC studies of the SN, which includes the ACC. One such study showed that functioning of this brain region has extremely high and unique power in predicting the development of ASD traits and adaptive functioning from late adolescence to early adulthood [97]. Furthermore, several dimensional psychopathology studies illustrate that the ACC is implicated in ASD-like symptoms across multiple neurodevelopmental disorders such as attention deficits in attention deficit hyperactivity disorder [98], and repetitive behaviors in obsessive compulsive disorder [99].

This review also highlighted the potential role of the parietal cortex and related impairments in the functioning of fronto-parietal neural circuits in both structural neuroimaging and task-based fMRI [86, 87, 89] studies. The parietal cortex has been implicated in the storage of spatial information in working memory [100], rule representation, and attention allocation [101]. Parietal cortex also is thought to help establish and maintain context [102]. Given the ubiquity of executive functions deficits to neurodevelopmental disorders, investigations of atypical fronto-parietal functioning, holds the potential to provide a more trans-diagnostic perspective on neuropsychiatric disorders. The association between fronto-parietal FC deficits and symptoms of attention and hyperactivity in adolescents with ASD constitutes a

promising lead, although it is not likely that RDoC will trully help carve nature at its joints, and there still will likely be multiple mechanisms underlying each symptom domain [103, 104].

It was challenging to complete a comprehensive and integrative review. Although the neuroimaging field has seen the evolution of increasingly rigorous best-practice standards [105], these have not been fully implemented in ASD research. As illustrated by Tables 1, 2, 3, and 4, ASD neuroimaging studies typically are small (< 20 participants/group), which is alarming given the recent suggestion that 50–100 participants/group may be necessary to detect subtle effects in fMRI [106]. Subject motion also can both confound task-based fMRI analyses and alter rsfMRI connectivity metrics [107–109]. While data scrubbing [110] techniques have been developed, they only have been used routinely for the past 5 years. The use of overly liberal thresholds, which still are routinely employed in ASD fMRI research, also has drawn criticism [111]. In addition to methodological challenges related to imaging, studies of cognitive control in ASD often employ heterogeneous neuroimaging tasks with different levels of discriminating power/difficulty, making it virtually impossible to compare and interpret their results. Finally, we can only truly understand development if we complete more longitudinal studies that carefully examine sex differences.

Despite revealing an altered scaffold that produces decreased cognitive control development in adolescence, this review is hopeful. The use of minimally invasive neuroimaging methodologies has greatly advanced our capacity for understanding the neural systems underpinning ASD-specific symptoms and strengths. The field should move towards developing adequately powered and standardized cognitive control paradigms that can be used in large longitudinal studies across a wide range of ages and cognitive ability levels, which is important given the dearth of studies in those with intellectual disability who also experience control impairments [112]. Until these studies have been conducted, meta-analyses can help bridge the gap in better understanding the mechanisms of the development of cognitive control in ASD – a goal that is highly consistent with the National Institute of Mental Health (NIMH) view that the best way to advance treatment development is through research that furthers understanding of the function of neural circuits and how to manipulate them.

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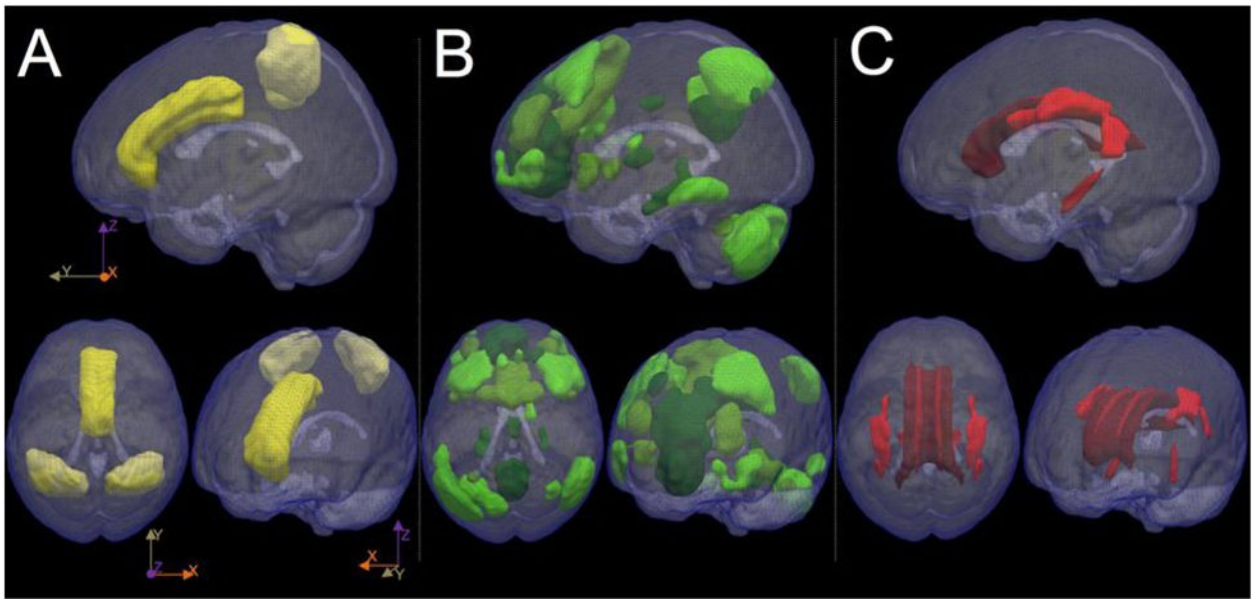

Figure 1.

Glass brain schematic of the neural circuits underlying cognitive control difficulties in ASD. (**A**) Outline of the brain structures that have demonstrated developmental anomalies in individuals with autism spectrum disorders, including the anterior cingulate cortex [yellow; [19]] and superior parietal cortex [yellow/white; [20]]. (**B**) Depiction of the intrinsic functional brain networks that have demonstrated aberrant functional connectivity profiles in ASD [default mode network, dark green; salience network, green; executive control network, bright green; [23]]. (**C**) White matter tracts involved in cognitive control that have demonstrated alterations in ASD [corpus callosum, dark red; cingulum bundle; red; superior longitudinal fasciculus, bright red; [142]].

Table 1

Summary of Structural Neuroimaging Studies in ASD.

STUDY	N	Mean Age (SD)	Method	Finding(s)
Bonilha et al. 2008 [14]	ASD: 12 TYP: 16	ASD: 12.4 ± 4 TYP: 13.2 ± 5	Whole-brain VBM	ASD > TYP: DLPFC and parietal gray matter ASD < TYP: frontal and parietal white matter
Nordahl et al 2007 [15]	ASD[a] : 15 TYP: 29	ASD: 12.3 (3.2) TYP: 11.8 (2.6)	Cortical folding	ASD > TYP: intraparietal sulcal depth
Hua et al 2013 [16]	ASD: 13 TYP: 7	ASD: 12.0 ± 2.3 TYP: 12.3 ± 2.4 Two MRI time points; 2.9 ± 0.9 year interval	Longitudinal brain growth	ASD < TYP: white matter growth in parietal lobe ASD > TYP: gray matter expansion in ACC
Wallace et al 2015 [17]	ASD: 17 TYP: 18	ASD: 17.4 (2.4) TYP: 17.5 (1.5) Two MRI time points; 1.7 (0.8) year interval	Longitudinal cortical thickness and surface area	ASD > TYP: Cortical thinning in superior parietal cortex

[a]These individuals were diagnosed with Asperger's Syndrome per DSM-IV criteria

Abbreviations used: ASD: autism spectrum disorder; TYP: typical development; ACC: anterior cingulate cortex; GI: Gyrification Index.

Table 2

Summary of resting state fMRI (rsfMRI) of intrinsic functional brain networks in ASD.

STUDY	N	Mean Age (SD)	Motion Correction	Finding(s)
Default-mode network (DMN)				
Kennedy & Courchesne, 2008 [32]	ASD: 12 TYP: 12	ASD: 26.5 (12.8) TYP: 27.5 (10.9)	Scrubbing	Underconnectivity
Monk et al., 2009 [33]	ASD: 12 TYP: 12	ASD: 26 (5.93) TYP: 27 (6.1)	Standard	Mixed (PCC-frontal under-, PCC-temporal overconnectivity)
Weng et al., 2009 [30]	ASD: 16 TYP: 15	ASD: 13–17 TYP: 13–18	Standard	Underconnectivity; Note: no mean/SD age provided
Assaf et al., 2010 [31]	ASD: 15 TYP: 15	ASD: 15.7 (3.0) TYP: 17.1 (3.6)	ICA	Underconnectivity
Wiggins et al., 2011 [29]	ASD: 39 TYP: 41	ASD: 14.0 (2.1) TYP: 15.3 (2.4)	Standard	TYP have greater increases in DMN connectivity with age
Lynch et al., 2013 [27]	ASD: 20 TYP: 19	ASD: 10.0 (1.6) TYP: 9.9 (1.6)	Scrubbing	Overconnectivity
Uddin et al., 2014 [36]	ASD: 17 TYP: 17	ASD: 9.9 (0.4) TYP: 9.8 (0.4)	Standard	Reduced segregation between rest and task in ASD
Washington et al., 2014 [28]	ASD: 24 TYP: 24	ASD: 10.9 (2.3) TYP: 10.1 (3.2)	Scrubbing	TYP have greater increases in DMN connectivity with age
Elton et al., 2016 [26]	ASD: 90 TYP: 95	ASD: 13.1 (3.3) TYP: 13.2 (3.1)	Standard	Overconnectivity
Salience network (SN)				
Ebisch et al., 2010 [40]	ASD: 14 TYP: 15	ASD: 15.8 (1.9) TYP: 16.0 (1.6)	Standard	Mixed (AI under- and overconn. to different seeds)
Uddin et al., 2013 [37]	ASD: 20 TYP: 20	ASD: 10.0 (1.6) TYP: 10.0 (1.6)	Scrubbing	Overconnectivity predictive of restricted and repetitive behavior
Eilam-Stock et al., 2014 [41]	ASD: 14 TYP: 13	ASD: 26.1 (6.5) TYP: 27.1 (8.2)	Standard	Low correlation between arousal and SN activity in ASD
Elton et al., 2016 [26]	ASD: 90 TYP: 95	ASD: 13.1 (3.3) TYP: 13.2 (3.1)	Standard	Mixed (ACC overconnectivity, frontal underconnectivity)
Executive control network (ECN)				
Abbott et al., 2015 [45]	ASD: 37 TYP: 38	ASD: 13.9 (2.6) TYP: 13.0 (2.6)	Scrubbing	Mixed (Right ECN over- and left ECN underconnectivity)
Elton et al., 2016 [26]	ASD: 90 TYP: 95	ASD: 13.1 (3.3) TYP: 13.2 (3.1)	Standard	Underconnectivity

Given its potential to introduce systematic between-group variance in functional connectivity (FC) measures, subject motion is one of the most important methodological considerations in rsfMRI studies in ASD (Power et al., 2012; Van Dijk et al., 2012). “Standard” motion correction refers to some combination of removing subjects with excessive motion and standard image realignment, “scrubbing” refers to the use of temporal masks to censor the influence of high-motion data points within a rsfMRI session, and independent component analysis (ICA) refers to the decomposition of the rsfMRI signal to identify and control for spatial components that represent motion-related artifact. *List of abbreviations*: Anterior insula (AI), autism spectrum disorders (ASD), default-mode network (DMN), executive control network (ECN), functional connectivity (FC), independent component analysis (ICA), posterior cingulate cortex (PCC), salience network (SN), standard deviation (SD), and typical development (TYP).

Table 3

Summary of relevant diffusion-weighted imaging studies in ASD.

STUDY	N	Mean Age	Method	Tract	Findings
Alexander et al., 2007 [55]	ASD: 43 TYP: 34	ASD: 16.23 (6.70) TYP: 16.44 (5.97)	ROI	Corpus Callosum	Reduced FA and AD, increased MD and RD FA correlated with processing speed
Jou et al., 2011 [56]	ASD: 15 TYP: 8	ASD: 10.9 (3.7) TYP: 11.5 (2.6)	TBSS	Corpus Callosum	Reduced FA
				Cingulum	Reduced FA
				SLF	Reduced FA
Brito et al., 2009 [57]	ASD: 8 TYP: 8	ASD: 9.53 (1.83) TYP: 9.57 (1.36)	ROI	Corpus Callosum	Reduced FA
Shukla et al., 2010 [58]	ASD: 26 TYP: 24	ASD: 12.7 (0.6) TYP: 13.0 (0.6)	VBA/ROI	Corpus Callosum	Reduced FA, increased RD
Shukla et al., 2011 [59]	ASD: 26 TYP: 24	ASD: 12.8 (0.6) TYP: 13.0 (0.6)	TBSS	Corpus Callosum	Reduced FA, increased RD
				Cingulum	Reduced FA, increased MD and RD
				SLF	Reduced FA, increased MD and RD
Libero et al., 2015 [60]	ASD :19 TYP: 18	ASD: 27.1 (1.38) TYP: 24.6 (1.22)	Tractography/ROI	Corpus Callosum	Reduced FA, increased RD
Ameis et al., 2011 [69]	ASD: 19 TYP: 16	ASD: 12.4 (3.1) TYP: 12.3 (3.6)	TBSS/ROI	Corpus Callosum	Increased MD and RD
Jou et al. 2011 [62]	ASD: 10 TYP: 10	ASD: 13.06 (3.85) TYP: 13.94 (4.23)	Tractography/VBA	Corpus Callosum	Reduced FA
				Cingulum	Reduced FA
				SLF	Reduced FA
Pardini et al., 2009 [61]	ASD: 10 TYP: 19	ASD: 19.7 (2.83) TYP: 19.9 (2.64)	Tractography/VBA	Cingulum	Reduced FA
				Orbitofrontal cortex network	Reduced FA
Travers et al., 2015 [50]	ASD: 100 TYP: 56	ASD: 18.3 (8.5) TYP: 18.9 (7.8)	ROI	Corpus Callosum	Reduced FA, age effects (under 10 yrs.)
Pugliese et al., 2009 [63]	ASD: 24 TYP: 42	ASD: 23.3 (12.4) TYP: 25.3 (10.3)	Tractography/ROI	Cingulum	Increased MD, greater number of streamlines
Lee et al., 2009 [90]	ASD: 43 TYP: 34	ASD: 16.23 (6.70) TYP: 16.44 (5.97)	VBA/T-SPOON	Corpus Callosum	Reduced FA, increased MD
Noriuchi et al., 2010 [64]	ASD: 7 TYP: 7	ASD: 13.96 (2.68) TYP: 13.36 (2.74)	VBA	Cingulum	Reduced FA and AD

STUDY	N	Mean Age	Method	Tract	Findings
				SLF	Reduced FA and AD
Thakkar et al., 2008 [91]	ASD :12 TYP: 14	ASD: 30 (11) TYP: 27 (8)	VBA	Cingulum	Reduced FA
Ikuta et al., 2014 [65]	ASD: 21 TYP: 21	ASD: 18.1 (2.7) TYP: 18.2 (2.9)	Tractography/ROI	Cingulum	Reduced FA
Ameis et al., 2013 [51]	ASD: 19 TYP: 16	ASD: 12.4 (3.1) TYP: 12.3 (3.6)	ROI	Cingulum	Reduced FA, increased MD, RD, and AD
Poustka et al., 2012 [70]	ASD: 18 TYP: 18	ASD: 9.7 (2.1) TYP: 9.7 (1.9)	ROI	Corpus Callosum	Reduced FA
				SLF	Reduced FA
Libero et al., 2016 [71]	ASD: 42 TYP: 44	ASD: 19.9 (1.27) TYP: 20.1 (1.21)	Tractography/ROI	SLF	Reduced FA, increased RD

Abbreviations used: ASD: autism spectrum disorder; TYP: typical development; ROI: region (or tract) of interest; TBSS: tract-based spatial statistics; VBA: voxel-based analyses; SLF: superior longitudinal fasciculus; FA: fractional anisotropy; RD: radial diffusivity; MD: mean diffusivity; AD: axial diffusivity.

Table 4

Summary of Task-Based fMRI Studies in ASD.

Study	N, Mean Age & IQ	Paradigm	Design Features	Thresholding & Methods	Major Findings
Kana et al., 2007 [89]	n=12 (TYP) n=12 (ASD) Age TYP=23 Age ASD=27 IQ ASD=110 IQ TYP=117	Response inhibition under 3 load types.	Blocked design fMRI Time series-based FC of all ROIs from within group maps. Factor analysis of connectivity of these ROIs.	Uncorrected height threshold of p=. 005 cluster size=10	ASD with reduced activation in inhibition and executive control regions. In harder condition, this is greater premotor recruitment in ASD. Factor analysis shows less integration of networks in ASD.
Thakkar et al., 2008 [91]	n=14 (TYP)fMRI n=12 (TYP) DTI n=10 (ASD)fMRI n=10 (ASD)DTI Age TYP=27 Age ASD=30 VIQ ASD=116 VIQ TYP=114	Saccadic paradigm with eye tracking	Event-related fMRI DTI. Correlations of RBs with ACC fMRI activation and FA.	Multiple comparison correction w/ Monte Carlo similation for p<.05 probability that cluster found in masked ACC ROIs.	ASD < ACC recruitment for error and correct trials, driven by ASD group's greater ACC response on correct trials. Less differentiated responding in medial superior frontal gyrus. DTI shows reduced FA in white matter underlying ACC, fronto-polar cortex, parietal cortex, precentral gyrus. RBs associated with correct trials and reduced FA.
Agam, Joseph, Barton, & Manoach, 2010 [92]	n=14 (TYP) fMRI n=11 (ASD)fMRI Age ASD=30 ASD=117 VIQ TYP=114 VIQ	Saccadic paradigm with eye tracking	Event-related fMRI ROIs in FEF dACC	Multiple comparison correction w/ Monte Carlo similation for p<.05 probability that cluster found in masked ACC ROIs.	ASD with reduced inhibition related recruitment of FEF dACC, driven by reduced dfferentiation on anti-saccades in TYP. In ASD&TYP, rACC predicts lower anti-saccade errors. In ASD this region predicts lower RT. Greater FEF activation predicts RBs in ASD. TYP with greater FC. In ASD, lACC activation correlates with RBs.
Shafritz, Dichter, Baranek, & Belger (2008) [94]	n=14 (TYP) n=15 (ASD) Age TYP=24 Age ASD=22 IQ ASD=103 IQ TYP=111	Target detection paradigm involving rule shifts.	Event-related fMRI ROIs correlated with RBs.	Displayed at p<.001, Multiple comparison correct w/Forman method and cluster size of 10.	On targets, TYPs recruit BA9, 46, 6(PFC) BA 24, 32 (ACC) PPC, BG, thalamus, & cerebellum. In ASD there is no significant recrutiment in same regions or equal engagment across target and stay. Between group comparisons for target trials: DLPFC, IPS, BG show > activation in TYPs. ACC and lIPS activation is negatively associated with RBs.
Lee et al. (2009) [90]	n=12 (TYP) n=12 (ASD) Mean TYP=16 Mean ASD=15 ASD=107 TYP=113	Go/No-Go task	Block design fMRI FC of all ROIs from within group maps using method of Kana et al. 2007. Seeds in r and l IFC. Correlations with ADI-R scales.	Whole brain analysis used to generate ROIs with height threshold of t=2.52 and p<.05.	No FC differences for l and r IFC seeds.
Solomon et al. (2009) [86]	n=23 (TYP) n=22 (ASD) Age TYP=11 Age ASD=10 IQ ASD=113 IQ TYP=115	Preparing to Overcome Prepotency (POP) Task. Simple stimulus response incompatibility task.	Event-related fMRI. FC analysis. Factor analysis of network integration. Correlation with ADHD sx & errors.	Voxel-wise FDR corrected for p<.05 t=2.5, cluster size=10 Masked for control related regions.	ASD with reduced recruitment of BA 10, bilaterally, l BA 6, BA 7 bilaterally, lBA 40, driven by red trials. PFC, ACC, parietal FC reduced in ASD. ASD with less network integration. For TYP, BA 9 to BA 7 FC related to red error rates. For ASD, ADHD scores.
Vogan et al. (2014) [88]	n=17 (TYP) n=19 (ASD)	One-back working memory task with	Block design fMRI	Cluster corrected at t=2.3, p<.05 ROIs selected from between group maps.	Within group maps show differences wTYP activating BA 37, 7, 5, 45, 9; ASD BA 19, 37.

Study	N, Mean Age & IQ	Paradigm	Design Features	Thresholding & Methods	Major Findings
	Age TYP=11 Age ASD=11 IQ ASD=109 IQ TYP=115	color matching of different difficulty levels.			Both groups see decreases in BA 23/32 &10 with increased load. No between group differences overall. TYP shows > activation in BA 7, 9, 6 with increasing load.
Padmanabhan et al. (2015) [93]	n=9 TYP adolescents & n=14 TYP adults n=11 ASD adolescents & n= 8 ASD adults TYP Adol.=14yr TYP Adult=23 ASD Adol.=15 ASD Adult=25 TYP/Adol.=110 TYP/Adult=110 ASD/Adol.=106 ASD/Adult=99	Saccadic paradigm with eye tracking.	Examine prep trials; anti-saccade trials; pro-saccade trials. ROIs extracted from within group maps in areas known to be involved in occulomotor control-FEF, SEF, ACC DLPFC, IPS, putamen.	Monte Carlo simul'tn with AlphaSim shows 23 voxel clusters with a single voxel threshold of p<.0001 required for p<.05. 12 mm ROIs from peaks & used as a mask.	Within group maps with no differences. Cortical eye fields (FEF, SEF, and PEF) & putamen, thalamus, & caudate recruited Anti-saccade Trials: Within group maps are similar and include: FEF, SEF, DLPFC, IPL. Both groups show increased SES & lFEF activation with age. ASD with greater left precuneus activation vs. TYP. L putamen w adol with ASD>TYP adol & TYP wASD. TYP > ASD in r IPL activation with age.
Yerys et al. (2015) [95]	Mean TYP=11 Mean ASD=11 ASD=114 TYP=119	Set shifting paradigm Focus on lowest level response reconfiguration.	Event-related fMRI. Correlations with accuracy, RT, switch costs, ADOS scores.	Cluster corrected at t=2.6, p<.05	No group differences in switch + stay trials vs. fixation. ASD with greater activation on switch vs. stay in ACC, l MFG, r IFG. No significant correlations between activation & task performance or ADOS scores.

Abbreviations used: ASD: autism spectrum disorder; TYP: typical development; vs.: versus; FC: functional connectivity; RT: reaction time; ACC: anterior cingulate cortex; DTI: diffusion tensor imaging; FA: fractional anisotropy; w/: with; ROI: region of interest; RB: repetitive behavior; d ACC: dorsal ACC; FEF: frontal eye fields; l:left;r: right; PPC: posterior parietal cortex; BG: basal ganglia; DLPFC: dorsolateral prefrontal cortex; IPS: inferior parietal sulcus; FDR: false discovery rate; MFG: middle frontal gyrus; IPL: inferior parietal lobule; MTG: medial temporal gyrus; IFG: inferior frontal gyrus; adol.:adolescents; ADHD: attention deficit hyperactivity disorder.