Introduction

Autism was first described by Leo Kanner\(^1\) and Hans Asperger\(^2\) in a series of clinical case studies. Both clinicians suggested that the conditions now referred to as autism spectrum disorders (ASDs) may have a neurobiological basis. With the relatively recent advent of modern brain imaging techniques, translational psychiatric research has embraced the systematic study of

This review presents an overview of functional magnetic resonance imaging findings in autism spectrum disorders (ASDs). Although there is considerable heterogeneity with respect to results across studies, common themes have emerged, including: (i) hypoactivation in nodes of the “social brain” during social processing tasks, including regions within the prefrontal cortex, the posterior superior temporal sulcus, the amygdala, and the fusiform gyrus; (ii) aberrant frontostriatal activation during cognitive control tasks relevant to restricted and repetitive behaviors and interests, including regions within the dorsal prefrontal cortex and the basal ganglia; (iii) differential lateralization and activation of language processing and production regions during communication tasks; (iv) anomalous mesolimbic responses to social and nonsocial rewards; (v) task-based long-range functional hypoconnectivity and short-range hyper-connectivity; and (vi) decreased anterior-posterior functional connectivity during resting states. These findings provide mechanistic accounts of ASD pathophysiology and suggest directions for future research aimed at elucidating etiologic models and developing rationally derived and targeted treatments.

Keywords: autism spectrum disorder; functional magnetic resonance imaging; fMRI; social; repetitive behavior; cognitive control; language; reward; connectivity

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ASDs using these measurement tools to gain insight into the pathophysiology and possible etiology of ASDs. The ultimate promise of these approaches is to improve mechanistic accounts of ASDs as well as provide targets for novel intervention approaches.

ASDs emerge early in life and are generally associated with lifelong disability. The defining symptoms of the disorder include social and communicative deficits and restricted and repetitive behaviors and interests. Individuals with milder constellations of symptoms are classified as having an ASD, a term that reflects the highly heterogeneous array of symptom presentations and that will likely be adopted to characterize individuals with a range of intellectual functioning in the next version of the Diagnostic and Statistical Manual of Mental Disorders. Geschwind and Levitt illustrated the complexity inherent to understanding the neurobiology of ASDs by suggesting that there are likely many “autisms,” each with non-overlapping etiologies and presentations. Given the highly heterogeneous nature of ASDs, it is perhaps not surprising that brain imaging studies have yielded a wide array of candidate brain circuits affected by the disorder. This range of brain endophenotypes is consistent with the challenges associated with identifying genes that cause ASDs: although ASDs have a very strong genetic component, with an estimated heritability as high as 90%, the identification of reliable genetic markers remains elusive.

Functional magnetic resonance imaging (fMRI) has proven to be a useful tool to investigate aberrant neurobiological function in ASDs because of its excellent contrast properties, spatial resolution, and temporal resolution. fMRI uses specialized pulse sequences to localize metabolic correlates of neural activity linked to relevant neurocognitive processes. Additionally, unlike positron emission tomography (PET) and single-photon emission computed tomography (SPECT), fMRI does not rely on radiotracers and is noninvasive. The past two decades have witnessed a surge in fMRI research in ASDs, and the goal of this review is to provide an overview of the questions addressed by these studies, to identify consistent patterns across investigations, and to suggest directions for future research.

### Social cognition

Most functional neuroimaging investigations in ASDs have addressed social perception (the automatic and preconscious processing of social information) and social cognition (processing meaning from emotional and social cues). Task-related fMRI studies addressing social functioning in ASDs have focused on nodes of the so-called “social brain,” including the medial prefrontal cortex, implicated in making inferences about others’ intentions, the temporoparietal junction, mediating mentalizing, the posterior superior temporal sulcus, activated by biological motion, the inferior frontal gyrus, involved in emotional judgments, the interparietal sulcus, which guides spatial attention in social contexts, the amygdala, involved in recognizing emotions from facial expressions, the fusiform gyrus, critical for face processing, and the anterior insula, involved in understanding internal states and mimicking social expressions (see ref 9 for a review).

### Face processing

Perhaps the richest area of inquiry into social cognition deficits in ASDs has been studies of face processing (Table I). Faces are perhaps the quintessential social
stimulus, and infants attend to and recognize faces from very early infancy.10 Studies of face processing in ASDs are theoretically grounded by behavioral evidence of impaired joint attention, eye contact, and face recognition and discrimination in ASDs, as well as impaired social emotional judgments about faces, reduced face emotion recognition and perception, and abnormal eye scanpaths when viewing faces.11,12

In neurotypical participants, the medial-lateral fusiform gyrus (FG) as well as the superior temporal sulcus, amygdala, and orbitofrontal cortex, activate in response to faces.13 The majority of fMRI studies in ASDs indicate FG hypoactivity to faces14-22 and to facial expressions.15,20,23-25 However, other reports suggest no differences in FG activation to familiar faces,26-29 stranger faces in the presence of an attentional cue,30 or when matching upright with inverted faces.31 These apparently inconsistent findings may be reconciled in a number of ways.32,33 The degree of visual attention to faces appears to be a critical factor moderating FG activation to faces in ASDs, with tasks that guide visual attention to faces or analytic approaches that account for point-of-regard resulting in relatively less FG hypoactivation in ASDs.21,30 This conclusion is supported by research indicating that face familiarity moderates FG responses to faces in ASDs39 and that impaired social cognition in ASDs may be mediated, at least in part, by attention to social cues, rather than by deficits in social cue processing per se.44,45 Similarly, lifelong amotivation to interact with faces may result in reduced perceptual skill when processing faces, and, in turn, cause FG hypoactivation to faces in ASDs that is perhaps a downstream consequence of reduced social experience rather than pathognomonic to ASDs.46 Moreover, the FG encodes not only face percepts, but social knowledge as well,47 suggesting that the FG may mediate: (i) the attribution of social meaning to stimuli; (ii) the retrieval of social semantic information; and (iii) self-referential experiences.48 Thus, the disparate results of the face processing literature in ASDs likely reflect the diverse and subtle social processes mediated by the FG and recruited by diverse fMRI tasks.

Amygdala response to faces in ASDs has also been extensively studied, and results in this area are decidedly mixed. There is evidence of no differences in amygdala activation to faces,10 of amygdala hypoactivation during face viewing15,16,26,31,38 and face matching,16 as well as evidence of amygdala hyperactivation to faces30,40 in ASDs, particularly when accounting for gaze time to faces21 (but see ref 41 for an exception). One study reported decreased amygdala habituation to the repeated presentation of faces, suggesting that social deficits in ASDs may be influenced by hyperarousal to faces due to protracted amygdala activation.48

Theory of mind

Theory of mind and mental inferences have been examined in ASDs via fMRI studies that address the ability to infer feeling states and/or intentions (Table II), skills that typically develop during the first 4 or 5 years of life and that are critical for the development of social skills and for successful navigation of the social world.49 Such tasks include images, stories, and animations designed to elicit the attribution of mental states. Results from typically developing individuals indicate with remarkable consistency that theory of mind is mediated by the posterior superior temporal sulcus at the temporoparietal junction, the temporal poles, the amygdala, and dorsal medial and ventrolateral prefrontal cortex.44

The amygdala plays a critical role in multiple aspects of mentalizing, including determining emotional states of others from facial expressions,45 and a number of studies have reported aberrant amygdala activation in ASDs during tasks requiring inferring mental states from pictures of eyes46,47 and judging facial expressions,45 suggesting that the so-called “amygdala theory of autism” may reflect impaired amygdala modulation rather than simply hypoactivation in social contexts. Another brain region that has received scrutiny in fMRI studies of theory of mind in ASDs is the posterior superior temporal sulcus, a region recruited during tasks that involve interpreting other’s mental states from biological motion cues.51 There are reports of posterior superior temporal sulcus hypoactivation while processing incongruent eye gaze shifts,52 while viewing direct and averted gaze,53 during intentional attribution to animated sequences of geometric figures,54 and during speech perception.55 A recent study of children with ASDs and their unaffected siblings found that activation in posterior superior temporal sulcus (as well as the amygdala and ventromedial prefrontal cortex) during biological motion perception differentiated children with ASDs.
both from their unaffected siblings and from matched control participants, suggesting that activation of this region may be related to phenotypic expression of social deficits in ASDs rather than genetic liability.55

Another area of inquiry has been functioning of the mirror neuron system (including, in humans, the pars opercularis in the inferior frontal gyrus). This system is active during imitation, action observation, intention understanding, and understanding emotional states of others.66 The inferior frontal gyrus has been reported to be relatively less active in ASDs during imitation and observation of faces57-59 and during imitation and observation of emotional expressions in ASDs,48,60 suggesting that mirror neuron dysfunction may account for social deficits in ASDs, though this contention has been questioned.61 Additionally, a recent meta-analysis of fMRI studies of social processing in ASDs revealed hypoactivation of the right anterior insula across studies (but see ref 62 for an exception), a region that is believed to be a relay station for projections from the IFG to the amygdala.63

Cognitive control

Restricted and repetitive behaviors and interests constitute a multifaceted symptom domain in ASDs that comprises both lower-order motoric repetitive behaviors (eg, body rocking, hand flapping) as well as higher-order cognitive manifestations (eg, a need for predictability).64 Because fMRI requires minimal motion from research subjects, cognitive manifestations of restricted and repetitive behaviors have been the focus of fMRI research. Such studies have mostly relied on tasks requiring cognitive control because of linkages between deficits on neuropsychological cognitive control tasks and symptoms of restricted and repetitive behaviors and interests in ASDs.65 Animal lesion and nonclinical human neuroimaging studies indicate that cognitive control is mediated by frontostriatal brain systems, including the lateral prefrontal cortex, the inferior frontal cortex (including the insular cortex), the anterior cingulate cortex, the intraparietal sulcus, and the striatum.66 Functional MRI studies of cognitive control in ASDs have revealed anomalous activation in frontostriatal brain regions (Table III), including inferior and middle frontal gyri, dorsal anterior cingulate cortex, and the basal ganglia during cognitive control tasks. Such findings have been reported using go/no-go, Stroop, and switching tasks,87 tasks that require interference inhibition,62-72 response monitoring,71 novelty detection,74-77 spatial attention,68 working memory,76,77 and saccadic eye movements.78 These findings have been interpreted to reflect deficits in behavioral inhibition and/or generation of adaptive behaviors linked to the expression of restricted and repetitive behavior and interests. Although the direction of effects has varied across studies (ie, frontostriatal hyperactivation vs hypoactivation), likely due to task demands and analysis methods, anomalous frontostriatal activation during tasks requiring cognitive control has been a consistent result in ASD samples, with the majority of findings indicating frontostriatal hyperactivation that has been interpreted to reflect a neurofunctional compensatory mechanisms to overcome cortical inefficiency.70

Communication

Investigations of communication deficits in ASDs have focused predominantly on brain regions mediating language perception, comprehension, and generation. The left hemisphere is typically language-dominant, and speech production is mediated by Broca’s area at the junction of the frontal, parietal, and temporal lobes, whereas speech comprehension is mediated by Wernicke’s area in the posterior temporal lobe.79 Heschl’s gyrus, in the dorsal temporal lobe, contains primary auditory cortex as well as the angular gyrus, involved in higher-order language comprehension and cross-modal integration, and the inferior parietal lobule, involved in processing semantic content.80 fMRI studies of communication functions in ASDs have used tasks requiring listening to speech sounds,54,81,82 sentence comprehension,83-85 verbal fluency,86 pragmatic language comprehension,87 semantic judgments,88 response-naming,89 and viewing body gestures90-91 (Table IV). Overall, findings indicate differential lateralization patterns in ASDs (ie, reduced left > right lateralization),82,84,86,87,90 decreased synchrony of brain regions processing language,83,84 decreased automaticity of language processing,90 greater neurofunctional deficits for speech than songs,94 and recruitment of brain regions that do not typically process language.93 A recent methodological innovation in the domain of language-based fMRI studies in ASDs has been to present speech stimuli to very young children with ASDs (as young as 12 months old) while asleep.82,98 Although the diagnostic stability of ASDs for children in this age range must be considered, this approach has the potential to leverage task-based fMRI
in far younger children with ASDs to examine altered developmental trajectories associated with impaired receptive language skills. Additionally, sleep fMRI would appear to be well suited to studying early emerging functional brain activation properties linked to speech processing in infant high-risk paradigms.

**Reward processing**

The social-communication deficits that characterize ASDs may reflect decreased motivation to engage in social behaviors in early childhood. This decreased motivation may result in fewer experiences with the social environment, further compounding social-communicative deficits. Reward processing is mediated primarily by dopaminergic projections from the ventral tegmental area to the striatum, orbitofrontal cortex, ventromedial prefrontal cortex, and the anterior cingulate cortex, forming a mesolimbic dopamine reward pathway. Emerging evidence suggests that the neural circuits that mediate reward processing may have evolved, at least in part, to facilitate social attachment, and reward mechanisms serve to encode and consolidate positive memories of social experiences, facilitating social functioning abilities hypothesized to be impaired in ASDs.

Reward processing deficits in ASDs have been assessed in six fMRI studies to date (Table V). Schmitz and colleagues reported decreased left anterior cingulate gyrus and left midfrontal gyrus activation to rewarded trials during a sustained attention task in ASDs and that anterior cingulate gyrus activation predicted social symptom severity. Scott-Van Zeeland and colleagues reported ventral striatal hypoactivation during social and nonsocial learning in ASDs. During a rewarded go/no-go paradigm, Kohls and colleagues found ventral striatal hypoactivation to monetary rewards and amygdala and anterior cingulate cortex hypoactivation to monetary and social rewards in children with ASDs. Cascio and colleagues reported increased bilateral insula and anterior cingulate cortex activation to images of food in children with ASDs who had fasted for at least 4 hours. Two studies by Dichter and colleagues, using incentive delay tasks, found decreased nucleus accumbens activation during monetary anticipation, bilateral amygdala hyperactivation during face anticipation that predicted social symptom severity (Figure 1), insular cortex hyperactivation during face outcomes, and

![Figure 1](image-url)
ventromedial prefrontal cortex hyperactivation while viewing images related to circumscribed interests in ASDs. Taken together, these results suggest that reward network dysfunction in ASDs may not be constrained to responses to social rewards, but rather may be characterized by anomalous responsivity that is contingent on the type of reward processed. When considered in light of empirical findings of dysfunctional reward circuitry in a number of psychiatric conditions, including substance use disorders, schizophrenia, affective disorders, and attention deficit/hyperactivity disorder, abnormal mesolimbic responses to rewards appears to be a common endophenotype that may cut across diagnostic boundaries.

**Functional connectivity**

Whereas task-based fMRI studies focus on activity within specific brain regions evoked by cognitive tasks, studies of functional connectivity speak to the temporal dynamics of brain network activity. The integrity of brain connections affects integration and synchronization of information processing, and the study of functional connectivity in ASDs addresses circuitry-level questions believed to be central to dysfunction in ASDs. There is a confluence of evidence that ASDs are characterized by decreased connectivity, in particular between frontal and posterior-temporal cortical systems that play key roles in processing social-affective information. Although initial studies highlighted cortical underconnectivity in ASDs, more recent data suggests that ASDs may be characterized by both local overconnectivity and long-distance underconnectivity. It has been suggested that a cortical underconnectivity account of ASDs may address heterogeneity as well as broad information processing deficits in general, rather than the expression of specific core symptoms.

**Task-based functional connectivity**

The majority of task-based studies in ASDs have documented reduced functional connectivity between frontal and parietal regions as well as between frontal and temporal and/or occipital regions. Tasks have included language comprehension, cognitive control, mentalizing, social processing, working memory, and visuospatial processing. A number of these studies have also indicated smaller and less synchronized cortical networks in ASDs. It should be noted, however, that some task-based studies have found long-range over-connectivity between subcortical and cortical regions as well as between frontal and temporal regions. Other studies have examined connectivity during task-related paradigms by filtering out task-related activity to examine connectivity patterns that are task-independent, and found evidence of decreased and increased functional connectivity.

**Resting-state functional connectivity**

Relatively fewer studies have examined brain connectivity in ASDs during resting state fMRI scans (Table VI). Cherkassky and colleagues reported decreased frontal-posterior default network connectivity during task-based inter-trial intervals (see also refs 126-128) while others have found lower default-mode network connectivity at rest in ASDs. There are also reports of decreased connectivity between the anterior and posterior insula and a number of social processing brain regions in ASDs and less coherent endogenous low-frequency oscillations across multiple cortical and subcortical regions in ASDs. von dem Hagen and colleagues reported reduced functional connectivity within and between resting state networks incorporating “social brain regions” including the insula and amygdala within the default-mode and salience networks, respectively, and Di Martino and colleagues reported increased connectivity between multiple striatal regions and striatal hyperconnectivity with the pons. Monk and colleagues reported positive correlations between repetitive behavior symptoms and resting state connectivity between posterior cingulate cortex and the right parahippocampal gyrus in adults with ASDs, despite increased connectivity between the posterior cingulate cortex, the right temporal lobe, and the right parahippocampal gyrus, although Weng and colleagues found correlations between social and repetitive behavior symptoms and a number of resting connectivity metrics in adolescents with ASDs.

**Structural MRI**

Functional MRI results should ultimately be considered within a broader neuroimaging literature addressing brain structure and white matter connectivity in ASDs. Structural MRI yields information about brain anatomy, including gray- and white-matter volumes as well as...
gyrus and sulcus development, and this approach is well-suited for studies seeking to predict future ASDs diagnoses in infants. Very briefly, the structural MRI literature indicates accelerated brain growth during early development in ASDs. There are reports of significantly large head circumference and brain volume in children with autism. Longitudinal studies indicate that ASDs are characterized by an early transient period of postnatal brain overgrowth evident in 70% of children with ASDs before age 2 that is not present in adolescence and adulthood. Evidence of enlarged total brain size in ASDs is accompanied by studies showing smaller cerebellar vermis, amygdala, and hippocampus. Increased brain size in young children with ASDs has also been linked to increased frontal lobe white matter followed by reduced white matter in early and late adolescence and adulthood.

**Diffusion tensor imaging**

Because the contrast properties of structural MRI are suboptimal for differentiating still-myelinating white matter from surrounding gray matter in children, diffusion tensor imaging (DTI), a measure of microstructural properties of white matter fibers, has emerged as a valuable tool to assess white-matter structure in very young samples. There is evidence of widespread abnormalities in white-matter fiber tract integrity in ASDs, but the extent and developmental course of these differences remains unclear. Two- to three-year-old children with ASDs are characterized by increased fractional anisotropy (an index of white matter fiber density) in the frontal lobes and in the corpus callosum, but in 5-year-old children with ASDs fractional anisotropy was reduced in frontal lobe tracts and no different from controls in tracts connecting frontal and posterior regions. In 10- to 18-year-old children with ASDs, there is evidence of reduced fractional anisotropy in frontal-posterior tracts and in hemispheric fractional anisotropy lateralization in the arcuate fasciculus, but fractional anisotropy was found to be reduced in adolescents with ASDs in prefrontal cortex and tempoparietal junction. It thus appears that young children with ASDs are characterized by increased fractional anisotropy in brain areas mediating social communication, whereas adolescents and adults with ASDs are characterized by generally lower fractional anisotropy, a pattern that recapitulates patterns of brain overgrowth discussed earlier.

Finally, a prospective DTI study of 6- to 24-month-old infants at high-risk of developing ASDs found that fractional anisotropy trajectories for 12 of 15 fiber tracts examined differed between infants who later were identified as having an ASD and those who did not. Infants who went on to have a diagnosis of an ASD had fiber tracts characterized by higher fractional anisotropy at 6 months of age, slower change between 6 and 24 months of age, and lower fractional anisotropy at 24 months of age.

**Summary**

The goal of this review is to highlight consistencies in the ASD fMRI literature. Given the array of imaging tasks reviewed, it is perhaps not surprising that findings are heterogenous. Despite variations in findings, there is a sufficient degree of consistency to draw a number of substantive conclusions. Studies of social processes have generally found evidence of hypoactivation in nodes of the “social brain,” including the medial prefrontal cortex, the inferior frontal gyrus and the anterior insula, the posterior superior temporal sulcus, the interparietal sulcus, the amygdala, and the fusiform gyrus. Studies addressing cognitive control, designed to address neural mechanisms underlying restricted and repetitive behaviors and interests, have converged on aberrant fronto-striatal functioning in ASDs, specifically in inferior and middle frontal gyri, anterior cingulate cortex, and the basal ganglia. Communication impairments in ASDs have been linked to differential patterns of language function lateralization, decreased synchrony of brain regions processing language, and recruitment of brain regions that do not typically processing language. Reward processing studies have highlighted mesolimbic and mesocortical impairments when processing both social and nonsocial incentives in ASDs. Finally, task-based functional connectivity studies in ASDs have reported local overconnectivity and long-distance (ie, between frontal and posterior regions) underconnectivity, whereas resting state connectivity studies indicate decreased anterior-posterior connectivity and less coherent endogenous low-frequency oscillations across multiple regions.

**Future directions**

Most studies reviewed here focus on adulthood or adolescence, yet ASDs are present from very early child-
hood. It will be critical to address developmental profiles in children with ASDs to disambiguate proximal effects of altered brain function from downstream effects on learning and motivation. There also may be critical periods during early development when brain dysfunction creates a predisposition to develop a number of disorders, and understanding factors that influence these processes will be essential for the prevention of symptom onset. Indeed, emerging techniques allow for functional brain imaging in children as young as 12 months old, and future studies that focus on young samples are needed. Additionally, most studies reviewed here contain small samples, and larger samples will be needed to identify meaningful subgroups and track developmental profiles. Given the high costs associated with brain imaging and challenges recruiting large pediatric patient samples, it will be critical to leverage available bioinformatics tools to facilitate data sharing across research groups. Such tools are under development and the National Institutes of Health recently established a database for sharing ASDs neuroimaging data.

There is also a need to move to designs that incorporate psychiatric comparisons to delineate brain activation patterns in ASDs that diverge and converge with other disorders characterized by social communication impairments and repetitive behaviors. Similarly, ASDs are commonly comorbid with other psychiatric and neurodevelopmental conditions, possibly due to shared genetic etiology and common socioenvironmental determinants, and thus it will be important to examine ASD samples with and without comorbid conditions to refine our understanding of neural endophenotypes in ASDs. Finally, the literature reviewed here is cross-sectional. Though these studies have elucidated aberrant patterns of brain activation in ASDs, these paradigms have rarely been applied to longitudinal treatment outcome studies aimed at understanding mechanisms of action of treatment response in ASDs. As neuroimaging and data-sharing techniques evolve, functional brain imaging will continue to improve our understanding of the pathophysiology of ASDs, with the ultimate goal of improved ASD identification and treatment.

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La resonancia magnética funcional en los trastornos del espectro autista

Esta revisión entrega una panorámica acerca de los hallazgos de la resonancia magnética funcional en los trastornos del espectro autista (TEA). Aunque existe bastante heterogeneidad en los resultados de los estudios han aparecido aspectos comunes que incluyen: 1) hipoactivación en los nodos del “cerebro social” durante las tareas de procesamiento cognitivo, que incluyen regiones dentro de la corteza prefrontal, el sulcus temporal superior posterior, la amígdala y el giro fusiforme, 2) activación frontoestriatal aberrante durante las tareas de control cognitivo, relacionadas con los intereses y las conductas restringidas y repetitivas, y que incluyen regiones dentro de la corteza prefrontal dorsal y los ganglios basales, 3) lateralización y activación diferencial de las regiones relacionadas con el procesamiento neuronal y la producción del lenguaje durante las tareas de comunicación, 4) respuestas mesolímbicas anómalas a las recompensas sociales y no sociales, 5) hipoconectividad funcional a largo plazo e hiperconectividad a corto plazo frente a tareas y 6) disminución de la conectividad funcional antero-posterior durante los estados de reposo. Estos hallazgos aportan razones mecanicistas para la fisiopatología de los TEA y sugieren orientaciones para las futuras investigaciones encaminadas a aclarar los modelos etiológicos y desarrollar tratamientos que puedan ser específicos y obtenerse racionalmente.

Imagerie par resonancia magnétique fonctionnelle dans les troubles autistiques

Cet article présente une synthèse des résultats de l’imagerie par résonance magnétique fonctionnelle dans les troubles autistiques (TA). En dépit d’une grande hétérogénéité due aux résultats des études, des thèmes communs ressortent comme : 1) une hypoactivation des nœuds du « cerveau social » au cours des tâches sociales, qui concerne les régions du cortex préfrontal, du sillon temporal postéro-supérieur, de l’amygdale, et du gyrus fusiforme ; 2) une activation fronto-striatale aberrante du cortex dorsal préfrontal et des noyaux gris centraux lors des tâches de contrôle cognitif se rapportant à des intérêts et à des comportements restreints et répétitifs ; 3) uneactivation et une latéralisation différencielle des régions de production et de traitement du langage au cours des tâches de communication ; 4) des réponses mésolimbiques anormales aux récompenses sociales et non sociales ; 5) une hypoconnectivité fonctionnelle à longue distance et une hyperconnectivité de courte distance basées sur les tâches ; 6) une connectivité fonctionnelle antéro-postérieure diminuée pendant les états de repos. Ces résultats donnent un aperçu mécaniste de la physiopathologie des TA et suggèrent des directions pour la recherche future afin d’élaborer des modèles etiológiques et de développer de façon rationnelle des traitements ciblés et dérivés.
References:

36. Jones W, Carr K, Klin A. Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-old toddlers with autism spectrum disorder. Arch Gen Psychiatry. 2008;65:946-954.

37. Schultz RT, Grelotti DJ, Klin A, et al. The role of the fusiform face area in social cognition: implications for the pathobiology of autism. Philos Trans R Soc Lond B Biol Sci. 2003;358:415-427.

38. Kleinheins NM, Richards T, Johnson LC, et al. fMRI evidence of neural abnormalities in the subcortical face processing system in ASD. Neuroimage. 2011;54:697-704.

39. Monk CS, Weng SJ, Wiggins JL, et al. Neural circuitry of emotional face processing in autism spectrum disorders. J Psychiatry Neurosci. 2010;35:105-114.

40. Weng SJ, Carrasco M, Swardt JR, et al. Neural activation to emotional faces in adolescents with autism spectrum disorders. J Child Psychol Psychiatry. 2011;52:296-305.

41. Perlman SB, Hudac CM, Pegors T, Minshew NJ, Pelphrey KA. Experimental manipulation of face-evoked activity in the fusiform gyrus of individuals with autism. Soc Neurosci. 2011;6:22-30.

42. Kleinheins NM, Johnson LC, Richards T, et al. Reduced neural habituation in the amygdala and social impairments in autism spectrum disorders. Am J Psychiatry. 2009;166:467-475.

43. Baillargeon R, Scott RM, He Z. False-belief understanding in infants. Trends Cogn Sci. 2007;11:110-118.

44. Blakemore SJ. Imaging brain development: the adolescent brain. Neuroimage. 2012;61:397-406.

45. Davis M, Whalen PJ. The amygdala: vigilance and emotion. Mol Psychiatry. 2001;6:13-34.

46. Baron-Cohen S, Ring HA, Bullmore ET, Ashwin C, Williams SC. The amygdala theory of autism. Neurosci Biobehav Rev. 2000;24:355-364.

47. Baron-Cohen S, Ring HA, Wollrighth S, et al. Social intelligence in the normal and autistic brain: an fMRI study. Eur J Neurosci. 1999;11:1891-1898.

48. Dapretto M, Davies MS, Pfeifer JH, et al. Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. Nat Neurosci. 2006;9:28-30.

49. Dichter GS, Richey JA, Rittenberg AM, Sabatino A, Bodfish JW. Reward circuitry function in autism during face anticipation and outcomes. J Autism Dev Disord. 2012;42:147-160.

50. Pelphrey KA, Shultz S, Hudac CM, Vander Wyk BC. Research review: constraining heterogeneity: the social brain and its development in autism spectrum disorder. J Child Psychol Psychiatry. 2011;52:631-644.

51. Pelphrey KA, Morris JP, McCarthy G. Neural basis of eye gaze processing deficits in autism. Brain. 2005;128(Pt 5):1038-1048.

52. Pitskel NB, Bolling DZ, Hudac CM, et al. Brain mechanisms for processing direct and averted gaze in individuals with autism. J Autism Dev Disord. 2011;41:1686-1693.

53. Castelli F, Frith C, Happe F, Frith U. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. Brain. 2002;125:1839-1849.

54. Boddart N, Belin P, Chabane N, et al. Perception of complex sounds: abnormal pattern of cortical activation in autism. Am J Psychiatry. 2003;160:2057-2060.

55. Kaiser MD, Hudac CM, Shultz S, et al. Neural signatures of autism. Proc Natl Acad Sci U S A. 2010;107:21223-21228.

56. Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc Natl Acad Sci U S A. 2003 Apr 29;100:5497-5502.

57. Leslie KR, Johnson-Frey SH, Grafton ST. Functional imaging of face and hand imitation: towards a motor theory of empathy. Neuroimage. 2004;21:601-607.

58. Iacoboni M. Imitation, empathy, and mirror neurons. Annu Rev Psychol. 2009;60:653-670.

59. Williams JA, Whiton A, Suddendorf T, Perrett DI. Imitation, mirror neurons and autism. Neurosci Biobehav Rev. 2001;25:287-295.

60. Iacoboni M, Dapretto M. The mirror neuron system and the consequences of its dysfunction. Nat Rev Neurosci. 2006;7:942-51.

61. Southgate V, Hamilton AF. Unbroken mirrors: challenging a theory of Autism. Trends Cogn Sci. 2008;12:225-229.
85. Wang A, Dapretto M, Hariri A, Sigman M, Bookheimer SY. Processing affective and linguistic prosody in autism: an fMRI study. Neuroimage. 2001;13:5621.

86. Kleinhans NM, Muller RA, Cohen DN, Courchesne E. Atypical functional lateralization of language in autism spectrum disorders. Brain Res. 2008;1211:115-125.

87. Tesink CMJY, Buitelaar JK, Petersson KM, et al. Neural correlates of pragmatic language comprehension in autism spectrum disorders. Brain. 2009;132:1941-1952.

88. Just MA, Cherkassky VL, Keller TA, Minshew NJ. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain. 2004;127:1811-1821.

89. Knaus TA, Silver AM, Lindgren KA, Hadjikhani N, Tager-Flusberg H. fMRI activation during a language task in adolescents with ASD. J Int Neuropsychol Soc. 2008;14:967-979.

90. Grezes J, Wicker B, Berthoz S, de Gelder B. A failure to grasp the affective meaning of actions in autism spectrum disorder subjects. Neuropsychologia. 2009;47:1816-1825.

91. Hadijkhani N, Joseph RM, Manoach DS, et al. Body expressions of emotion do not trigger fear contagion in autism spectrum disorder. Soc Cogn Affect Neurosci. 2009;4:70-78.

92. Catarino A, Luke L, Waldman S, Andrade A, Fletcher PC, Ring H. An fMRI investigation of detection of semantic incongruities in autistic spectrum conditions. Eur J Neurol. 2011;18:558-567.

93. Eigsti IM, Schu J, Menc E, Schultz RT, Paul R. The neural underpinnings of prosody in autism. Child Neuropsychol. 2011. In press.

94. Lai G, Pantazatos SP, Schneider H, Hirsch J. Neural systems for speech and song in autism. Brain. 2012;135:961-975.

95. Groen WB, Tesink C, Petersson KM, et al. Semantic, factual, and social language comprehension in adolescents with autism: an fMRI study. Cortex. 2010;20:1937-1945.

96. Kana RK, Wadsworth HM. "The archeologist's career ended in ruins": hemispheric differences in pun comprehension in autism. Neuroimage. 2012;62:77-86.

97. Mizonu A, Liu Y, Williams DL, Keller TA, Minshew NJ, Just MA. The neural basis of deictic shifting in linguistic perspective-taking in high-functioning autism. Brain. 2011;134:2422-2435.

98. Eyler LT, Pierce K, Courchesne E. A failure of left temporal cortex to specialize for language is an early emerging and fundamental property of autism. Brain. 2012;135:949-960.

99. Gervais H, Belin P, Boddart N, Leboyer M, Coez A, Sfaello I, et al. Abnormal cortical voice processing in autism. Nat Neurosci. 2004;7:801-802.

100. Dawson G, Webb SJ, McPartland J. Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. Dev Neurosci. 2005;27:403-424.

101. Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: ‘liking’, ‘wanting’, and learning. Curr Opin Pharmacol. 2009;9:65-73.

102. Insel TR. Is social attachment an addictive disorder? Physiol Behav. 2003;79:351-357.

103. Schultz W. Multiple reward signals in the brain. Nat Rev Neurosci. 2000;1:199-207.

104. Schmitz N, Rubia K, van Amelsvoort T, Daly E, Smith A, Murphy DG. Neural correlates of reward in autism. Br J Psychiatry. 2008;192:19-24.

105. Scott-Van Zeelnd AA, Dapretto M, Ghahremani GD, Poldrack RA, Bookheimer SY. Reward processing in autism. Autism Res. 2010;3:53-67.

106. Kohls G, Schulte-Ruther M, Nehrkorn B, et al. Reward system dysfunction in autism spectrum disorders. Soc Cogn Affect Neurosci. 2012. In press.

107. Cascarci CJ, Foss-Seig RH, Heacock JL, et al. Response of neural reward regions to food cues in autism spectrum disorders. J Neurodev Disord. 2012;4.

108. Dichter GS, Felder JN, Green SR, Rittenberg AM, Sasso JN, Bodfish JW. Reward circuitry function in autism spectrum disorders. Social Cogn Affect Neurosci. 2012;7:160-172.

109. Dichter GS, Damiano CA, Allen JA. Reward circuitry dysfunction in neurodevelopmental and psychiatric disorders: animal models and clinical findings. J Neurodev Disord. In press.

110. Vissers ME, Cohen MX, Geurts HM. Brain connectivity and high-functioning autism: a promising path of research that needs refined models, methodological convergence, and stronger behavioral links. Neurosci Biobehav Rev. 2012;36:604-625.
Clinical research

135. Hazlett HC, Poe MD, Gerig G, et al. Early brain overgrowth in autism associated with an increase in cortical surface area before age 2 years. Arch Gen Psychiatry. 2011;68:467-476.

136. Hazlett HC, Poe M, Gerig G, et al. Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. Arch Gen Psychiatry. 2005;62:1366-1376.

137. Vaidya CJ, Foss-Feig J, Shook D, Kaplan L, Kenworthy L, Gaillard WD. Controlling attention to gaze and arrows in childhood: an fMRI study of typical development and Autism Spectrum Disorders. Dev Sci. 2011;14:911-924.

138. Sparks BF, Friedman SD, Shaw DW, et al. Brain structural abnormalities in young children with autism spectrum disorder. Neurology. 2002;59:184-192.

139. Courchesne E, Pierce K. Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. Int J Dev Neurosci. 2005;23:153-170.

140. Lainhart JE. Advances in autism neuroimaging research for the clinician and geneticist. Am J Med Genet C Semin Med Genet. 2006;142C:33-39.

141. Akshoomoff N, Lord C, Lincoln AJ, et al. Outcome classification of preschool children with autism spectrum disorders using MRI brain measures. J Am Acad Child Adolesc Psychiatry. 2004;43:349-357.

142. Carper RA, Moses P, Tigue ZD, Courchesne E. Cerebral lobes in autism: early hyperplasia and abnormal age effects. Neuroimage. 2002;16:1038-1051.

143. Herbert MR, Ziegler DA, Makris N, et al. Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol. 2004;55:530-540.

144. Courchesne E, Karns CM, Davis HR, et al. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology. 2001;57:245-254.

145. Waiter GD, Williams JH, Murray AD, Gilchrist A, Perrett DI, Whiten A. Structural white matter deficits in high-functioning individuals with autistic spectrum disorder: a voxel-based investigation. Neuroimage. 2005;24:455-461.

146. Levitt JG, Blanton RE, Smalley S, et al. Cortical sulcal maps in autism. Cereb Cortex. 2003;13:728-735.

147. Cascio CJ, Gerig G, Piven J. Diffusion tensor imaging: application to the study of the developing brain. J Am Acad Child Adolesc Psychiatry. 2007;46:213-223.

148. Hong S, Ke X, Tang T, et al. Detecting abnormalities of corpus callosum connectivity in autism using magnetic resonance imaging and diffusion tensor tractography. Psychiatry Res. 2011;194:333-339.

149. Alexander AL, Lee JE, Lazar M, et al. Diffusion tensor imaging of the corpus callosum in Autism. Neuroimage. 2007;34:61-73.

150. Barnea-Goraly N, Lotspeich LJ, Reiss AL. Similar white matter aberrations in children with autism and their unaffected siblings: a diffusion tensor imaging study using tract-based spatial statistics. Arch Gen Psychiatry. 2010;67:1052-1060.

151. Cheon KA, Kim YS, Oh SH, et al. Involvement of the anterior thalamic radiation in boys with high functioning autism spectrum disorders: a Diffusion Tensor Imaging study. Brain Res. 2011;1417:77-86.

152. Ben Bashat D, Kronfeld-Duenias V, Zachor DA, et al. Accelerated maturation of white matter in young children with autism: a high b value DWI study. Neuroimage. 2007;37:40-47.

153. Sundaram SK, Kumar A, Makki MI, Beben ME, Chugani HT, Chugani DC. Diffusion tensor imaging of frontal lobe in autism spectrum disorder. Cereb Cortex. 2008;18:2659-2665.

154. Sahyoun CP, Belliveau JW, Mody M. White matter integrity and pictorial reasoning in high-functioning children with autism. Brain Cogn. 2010;73:180-188.

155. Fletcher PT, Whitaker RT, Tao R, et al. Microstructural connectivity of the arcuate fasciculus in adolescents with high-functioning autism. Neuroimage. 2010;51:1117-1125.

156. Knauz TA, Silver AM, Kennedy M, et al. Language laterality in autism spectrum disorder and typical controls: a functional, volumetric, and diffusion tensor MRI study. Brain Lang. 2010;112:113-120.

157. Barnea-Goraly N, Kwon H, Menon V, Eliez S, Lotspeich L, Reiss AL. White matter structure in autism: preliminary evidence from diffusion tensor imaging. Biol Psychiatry. 2004;55:323-326.

158. Wolff JJ, Gu H, Gerig G, Elison JT, Styner M, Gouttard S, et al. Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. Am J Psychiatry. 2012;169:589-600.

159. Glover GH, Mueller BA, Turner JA, et al. Function biomedical informatics research network recommendations for prospective multicenter functional MRI studies. J Magn Reson Imaging. 2012;36:39-54.

160. Hall D, Huerta MF, McAuliffe MJ, Farber GK. Sharing heterogeneous data: The National Database for Autism Research. Neuroinformatics. In press.

161. Holtzheimer PE, Kelley ME, Gross RE, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch Gen Psychiatry. 2012;69:150-158.

162. Dichter GS, Sikich L, Song A, Vovodyc J, Bodfish JW. Functional neuroimaging of treatment effects in psychiatry: methodological challenges and recommendations. Int J Neurosci. 2012;122:483-493.
REFERENCES FOR THE TABLES

1. Ashwin C, Baron-Cohen S, Wheelwright S, O’Riordan M, Bullmore ET. Differential activation of the amygdala and the ‘social brain’ during fearful face-processing in Asperger Syndrome. Neuropsychologia. 2007;45:2-14.

2. Bird G, Catmur C, Silani G, Frith C, Frith U. Attention does not modulate neural responses to social stimuli in autism spectrum disorders. Neuroimage. 2006;31:1614-1624.

3. Bookheimer SY, Wang AT, Scott A, Sigman M, Dapretto M. Frontal contributions to face processing differences in autism: evidence from fMRI of inverted face processing. J Int Neuropsychol Soc. 2008;14:922-932.

4. Corbett BA, Carmane V, Ravizza S, et al. A functional and structural study of emotion and face processing in children with autism. Psychiatry Res. 2009;173:196-205.

5. Coutanche MN, Thompson-Schill SL, Schultz RT. Multi-voxel pattern analysis of fMRI data predicts clinical symptom severity. Neuroimage. 2011;57:113-123.

6. Dalton KM, Nacewicz BM, Johnstone T, et al. Gaze fixation and the neural circuitry of face processing in autism. Nat Neurosci. 2005;8:519-526.

7. Deeley Q, Daly EM, Surguladze S, et al. An event related functional magnetic resonance imaging study of facial emotion processing in Asperger syndrome. Biol Psychiatry. 2007;62:207-217.

8. Greimel E, Schulte-Ruther M, Kircher T, et al. Neural mechanisms of empathy in adolescents with autism spectrum disorder and their fathers. Neuroimage. 2010;49:1055-1065.

9. Hadjikhani N, Joseph RM, Snyder J, et al. Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. Neuroimage. 2004;22:1141-1150.

10. Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H. Abnormal activation of the social brain during face perception in autism. Hum Brain Mapp. 2007;28:441-449.

11. Hall GB, Szechtman H, Nahmias C. Enhanced salience and emotion recognition in Autism: a PET study. Am J Psychiatry. 2003;160:1439-1441.

12. Hall GB, Doyle KA, Goldberg J, West D, Szatmari P. Amygdala engagement in response to subthreshold presentations of anxious face stimuli in adults with autism spectrum disorders: preliminary insights. PloS One. 2010;5:e10804.

13. Hubl D, Bolte S, Feineis-Matthews, S, et al. Functional imbalance of visual pathways indicates alternative face processing strategies in autism. Neurology. 2003;61:1232-1237.

14. Humphreys K, Hassen U, Avidan G, Minshew N, Behrmann M. Cortical patterns of category-selective activation for faces, places and objects in adults with autism. Autism Res. 2008;1:52-63.

15. Kleinhans NM, Richards T, Sterling L, et al. Abnormal functional connectivity in autism spectrum disorders during face processing. Brain. 2008;131(Pt 4):1000-1012.

16. Kleinhans NM, Johnson LC, Richards T, et al. Reduced neural habituation in the amygdala and social impairments in autism spectrum disorders. Am J Psychiatry. 2009;166:467-475.

17. Kleinhans NM, Richards T, Weaver K, et al. Association between amygdala response to emotional faces and social anxiety in autism spectrum disorders. Neuropsychologia. 2010;48:3665-3670.

18. Kleinhans NM, Johnson LC, et al. fMRI evidence of neural abnormalities in the subcortical face processing system in ASD. Neuroimage. 2011;54:697-704.

19. Koshino H, Kana RK, Keller TA, Cherkassky VL, Minshew NJ, Just MA. fMRI investigation of working memory for faces in autism: visual coding and underconnectivity with frontal areas. Cereb Cortex. 2008;18:289-300.
### Table I. Studies investigating face processing in autism spectrum disorders.

| Citation                                      | ASD† | TYP† | ASD age      | TYP age      | Task(s)                                                                 |
|-----------------------------------------------|------|------|--------------|--------------|------------------------------------------------------------------------|
| Ashwin, Baron-Cohen, Wheelwright, O’Riordan, Bullmore, 2007 [1] | 13 (13) | 13 (13) | 31.2 ± 9.1 | 25.6 ± 5.1 | Viewed facial stimuli known to activate AMY in healthy controls         |
| Bird, Catmur, Silani, Frith, Frith, 2006 [2]   | 16 (14) | 16 (14) | 33.3 ± 11.5 | 35.3 ± 12.1 | Viewed pairs of stimuli (face/ house) in attended /unattended locations |
| Bookheimer, Wang, Scott, Sigman, Dapretto, 2008 [3] | 12 (12) | 12 (12) | 11.3 ± 4.0 | 11.9 ± 2.4 | Inverted or upright face matching                                       |
| Corbett, Carmean, Ravizza, et al, 2009 [4]    | 12 (12) | 15 (13) | 9.01 ± 13.82 | 9.17 ± 1.44 | Face identify and expression matching                                    |
| Coutanche, Thompson-Schill, Schultz, 2011 [5] | 12 (12) | 12 (12) | 13.9 ± 4.48 | 13.6 ± 3.87 | Recognition of emotional facial expressions                              |
| Dalton, Nacewicz, Johnstone, et al, 2005 [6]  | Task 1: 14 (14) | Task 1:12 (12) | 15.9 ± 4.71 | 17.1 ± 2.78 | (1) Facial emotion discrimination                                      |
|                                               | Task 2: 16 (16) | Task 2:16 (16) |              |              | (2) Face recognition                                                   |
| Deeley, Daly, Surguladze, et al, 2007 [7]     | 18 (18) | 9 (9)  | 34 ± 10      | 27 ±5        | Viewed face stimuli with variable emotional expressions                 |
| Greimel, Schulte-Ruther, Kircher, et al, 2010 [8] | 15 (15), 11 (11) (adolescents, fathers) | 15 (15), 9 (9) (adolescents, fathers) | 14.9 ± 1.6, 47.7 ±5.3 (adolescents, fathers) | 15.0 ± 1.4, 43.9 ± 5.1 (adolescents, fathers) | Emotion identification in facial stimuli and in self |
| Hadjikhani, Joseph, Snyder, et al, 2004 [9]   | 11** | 10** | 36 ± 12 | 26 ± 6 | Viewed faces, objects, and scrambled images                            |
| Hadjikhani, Joseph, Snyder, Tager-Flusberg, 2007 [10] | 10** | 7** | 34 ± 11 | 35 ± 12 | Viewed unemotional faces                                               |
| Hall, Szechtman, Nahmias, 2003 [11]           | 8(8) | 8(8) | ** | ** | Emotion and gender recognition tasks                                   |
| Hall, Doyle, Goldberg, West, Szatmari, 2010 [12] | 12 (12) | 12 (12) | 31.8** | 32** | Identified gender of subliminally presented images of anxious faces     |
| Hubl, Bolte, Feineis-Matthews, et al, 2003 [13] | 10 (10) | 10 (10) | 25.3 ± 6.9 | 27.7 ± 7.8 | Viewed faces and complex patterns                                       |

*† Numbers in parentheses indicate sample size.

** Table I. Studies investigating face processing in autism spectrum disorders.
### Table I. Continued

| Core findings in ASD group (relative to controls) | Conclusions |
|--------------------------------------------------|-------------|
| Differential activation to faces; ↑ACG, superior temporal cortex; No difference in AMY activation between angry and frightened faces | Different activation of social brain during face processing; Absence of response to varying emotional intensity of facial stimuli |
| Attention modulation present only to house images (rather than to both houses and faces) | Social stimuli less salient for individuals with ASD |
| ↓Frontal cortex across all conditions, particularly left hemisphere, dorsal IFG (i.e. mirror neurons); ↓AMY; ↑Precuneus | Faces processed as objects; Behavioral differences in processing upright vs inverted faces implicates a social rather than visual processing impairment |
| ↓AMY during expression matching; ↓FG during identity matching | ASD recruits frontal and parietal lobes, but not AMY, for face expression matching; ASD processes faces less efficiently and less effectively; AMY fails to provide socioemotional context during social interactions |
| Multi-voxel pattern analysis classification negatively correlated with symptom severity (activation levels did not); Searchlight analysis across the ventral TL identified regions with relationships between classification performance and symptom severity | Clinical severity was more classifiable from MVPA than from FG patterns; MVPA can identify regions not found using mean activation; ITG may play a role in ASD face processing |
| ↓Bilateral FG, occipital gyri, MFG; ↑Left AMY, OFG; FG and AMY activation correlated with time fixating on eye regions in the ASD group | Diminished gaze fixation may account for FFG hypoactivation results in the literature |
| Fusiform, extrastriate hyporesponsiveness across emotion and intensity levels | While fusiform and extrastriate regions are activated to social stimuli in ASD, it is less so than in typical development |
| ↓FG correlated with social deficits; ↓IFG during self-task; Fathers of ASD performed similarly to fathers of controls, but showed ↓FG | FG impairment shared between first-degree relatives is a fundamental feature of ASD; FG impairment during face processing related to empathy deficits |
| No FFA activation differences when viewing faces | Face processing abnormalities not due to dysfunction in the FFA, but to abnormalities in surrounding networks involved in social cognition |
| No differences in FFA, inferior occipital gyrus activation; ↓Right AMY, IFC, STS, somatosensory cortex, PMC | Atypical activation in a broader face-processing network outside of FFA and inferior occipital gyrus; Suggests mirror neuron system disturbance during face-processing in ASD |
| ↓IFA, FG; ↑right ATL, ACG, THAL | Recognition of emotions in ASD achieved through recruitment of brain regions concerned with attention, perceptual knowledge, and categorization |
| ↓FFA; No AMY differences between groups | Transmission of social information along subcortical pathways intact, but signaling to downstream structures as well as the mechanisms of subsequent processing are impaired |
| ↓FG, esp. during face processing; ↑Medial occipital gyrus, superior parietal lobule, medial frontal gyrus | Deficits in face-specific regions, but overdevelopment in areas of visual search; Predisposed for local processing, rather than global |
| Citation                          | ASD  | TYP  | ASD age  | TYP age  | Task(s)                                                                                                                                 |
|----------------------------------|------|------|----------|----------|------------------------------------------------------------------------------------------------------------------------------------------|
| Humphreys, Hasson, Avidan, Minshew, Behrmann, 2008 [14] | 13   | 15   | 27 ± 10  | 29 ± 10  | Viewed faces, buildings, objects and patterns in controlled and naturalistic settings                                                   |
| Kleinhans, Richards, Sterling, et al, 2008 [15]          | 19‡  | 21‡  | 23.57 ± 6.6 | 23.32 ± 5.15 | Viewed familiar faces, houses                                                                                                           |
| Kleinhans, Johnson, Richards, et al, 2009 [16]          | 19‡  | 20‡  | **       | **       | Viewed neutral faces                                                                                                                    |
| Kleinhans, Richards, Weaver, et al, 2010 [17]          | 31 (29) | 25 (23) | 23.57 ± 6.6 | 23.32 ± 5.15 | Matched facial expressions of fear or anger                                                                                             |
| Kleinhans, Richards, Johnson, et al, 2011 [18]          | 31 (29) | 25 (23) | 23.57 ± 6.6 | 23.32 ± 5.15 | Viewed images of faces and houses                                                                                                        |
| Koshino, Kana, Keller, et al, 2008 [19]       | 11   | 11   | 24.5 ± 10.2 | 28.7 ± 10.9 | Working memory tasks using faces                                                                                                         |
| Loveland, Steinberg, Pearson, Mansour, Reddoch, 2008 [20] | 5 (4) | 4 (3) | 18 ± 1.3 | 17 + 1.1 | Auditory and visual emotional congruence task                                                                                             |
| Monk, Weng, Wiggins, et al, 2010 [21]          | 12‡  | 12‡  | 26 ± 6   | 27 ± 6   | Probe detection with different emotional expressions                                                                                     |
| Morita, Kosaka, Saito, et al, 2011 [22]          | 15 (14) | 15 (13) | 23.7 ± 4.3 | 23.3 ± 3.6 | Rated photogenicity of faces                                                                                                             |
| Ogai, Matsumoto, Suzuki, et al, 2003 [23]     | 5**  | 9**  | 21.8 ± 5.9 | 23.0 ± 5.2 | Facial expression recognition                                                                                                            |
| Pelphrey, Morris, McCarthy, Labar, 2007 [24]     | 8 (6) | 8 (6) | 24.5 ± 11.5 | 24.1 ± 5.6 | Dynamic and static face processing                                                                                                        |
| Perlman, Hudac, Pegors, Minshew, Pelphrey, 2011 [25] | 12 (11) | 7 (7) | 25.5 ± 7.47 | 28.57 ±5.74 | Viewed faces while compelled to look at eyes                                                                                              |
| Pierce, Muller, Ambrose, Allen, Courchesne, 2001 [26] | 6 (6) | 8 (8) | 29.5 ± 8  | 28.3‡    | Face perception with gender identification                                                                                              |
| Pierce, Haist, Sedaghat, Courchesne, 2004 [27]     | 7 (7) | 9 (9) | 27.1 ± 9.2 | **       | Familiar versus unfamiliar face processing                                                                                               |
| Pierce, Redcay, 2008 [28]                     | 11 (9) | 11 (9) | 9.9 ± 2.1 | 9.8 ± 1.8 | Matched faces of mothers, other children, adult strangers                                                                               |
| Pinkham, Hopfinger, Pelphrey, Piven, Penn, 2008 [29] | 12‡  | 12‡  | 24.08 ± 5.71 | 27.08 ± 3.99 | Free-viewing face processing                                                                                                             |

Table I. Continued
### Table I. Continued

| Core findings in ASD group (relative to controls) | Conclusions |
|---------------------------------------------------|-------------|
| ↓FFA, occipital face area, STS in response to faces; No group differences in place-related or object-related processing | Differential organization of ventral visual cortex; Developmental effects of lower functional connectivity have a more pronounced effect on later-developing systems, like face-processing, than for early-developing systems, like object- and place-processing |
| Reduced functional connectivity FFA-AMY, FFA-PCC, FFA-THAL; Greater social impairment correlated with worse connectivity FFA-AMY, FFA-right IFC | Abnormal connectivity in limbic system underlies social deficits in ASD |
| Reduced bilateral AMY habituation; No group differences in FG habituation | AMY hyperarousal to socially relevant stimuli; Sustained AMY arousal may contribute to social deficits |
| ↓Left PFC; ↑Occipital lobe; Social anxiety correlated with ↑right AMY, ↑left middle temporal gyrus, ↓FFA | Social anxiety mediates emotional face perception |
| No activation in right AMY, right pulvinar, or bilateral superior colliculi to faces; | Rapid face identification but failure to engage subcortical brain regions involved in face detection and automatic emotional face processing. |
| ↓Inferior left PFC, right posterior temporal; Activation in a different FFA location; Lower FFA-frontal connectivity | Faces processed as objects; Working memory of faces not mediated by typical frontal regions |
| During emotion trials, ↓OFC, STG, PHG, posterior cingulate gyrus, occipital gyrus | Fronto-limbic and superior temporal activity differences during integration of auditory and visual emotional stimuli |
| ↑Right AMY to emotional faces; Greater right AMY and VMPFC coupling; Weaker positive right AMY and TL coupling | Attention must be factored into any model of neural circuitry in ASD; Overconnectivity may underlie greater emotional responses in ASD |
| ↓Self-related activity in PCC; ↓Right IC and lateral OFC to embarrassment; ↓IC activity to self-face images associated with weak coupling between cognitive evaluation and emotional responses to self-face | Decoupling between evaluation of self-face images and emotional response; Dysfunction in PCC and IC contributes to lack of self-conscious behaviors in response to self-reflection |
| ↓Left insula, left IFG, left putamen during recognition of disgust and fear | Difficulty understanding facial expressions in others and, therefore, in manipulating social information |
| ↓AMY, STS, FG to dynamic faces | Dysfunctions in these component areas may contribute to problems in social and emotional processing |
| Right FG activity normalized by following predetermined scan paths to eyes, but AMY response unaffected | Rather than an underdeveloped FFA as a result of not focusing on faces during development, FFA appears functional; Impaired mechanism of appropriately directing gaze |
| ↓Bilateral FG, left AMY; 50% of group showed atypical FG activation to faces | ASD is associated with aberrant locations of maximal activations to faces |
| No group difference in extent of FFA activation to faces; ↑FFA to familiar faces; Right hemisphere dominance to both types of faces; Limited response in the posterior cingulate, AMY, MFL | FFA hypoactivation to faces in ASD may be specific to unfamiliar faces; ASD may be characterized by anomalous FFA modulation by faces, rather than hypoactivation |
| Normal FG response to face of mother or other children; ↓FG to stranger adult faces | Selective reduction in FG activity in response to strangers may be a result to reduced attention and interest in those conditions |
| ↓Right AMY, FFA; ↓Left VLPFC compared to non-paranoid individuals with schizophrenia | Potential common substrates of impaired social cognition in ASD and schizophrenia |
Clinical research

20. Loveland KA, Steinberg JL, Pearson DA, Mansour R, Reddoch S. Judgments of auditory-visual affective congruence in adolescents with and without autism: a pilot study of a new task using fMRI. Perceptual Motor Skills. 2008;107:557-575.

21. Monk CS, Weng SJ, Wiggins JL, et al. Neural circuitry of emotional face processing in autism spectrum disorders. J Psychiatry Neurosci. 2010;35:105-114.

22. Morita T, Kosaka H, Saito DN, et al. Emotional responses associated with self-face processing in individuals with autism spectrum disorders: an fMRI study. Soc Neurosci. In press.

23. Ogai M, Matsumoto H, Suzuki K, et al. fMRI study of recognition of facial expressions in high-functioning autistic patients. Neuroreport. 2003;14:559-563.

24. Pelphrey KA, Morris JP, McCarthy G, Labar KS. Perception of dynamic changes in facial affect and identity in autism. Soc Cogn Affect Neurosci. 2007;2:140-149.

25. Perlman SB, Hudac CM, Pegors T, Minshew NJ, Pelphrey KA. Experimental manipulation of face-evoked activity in the fusiform gyrus of individuals with autism. Soc Neurosci. 2011;6:22-30.

26. Pierce K, Muller RA, Ambrose J, Allen G, Courchesne E. Face processing occurs outside the fusiform ‘face area’ in autism: evidence from functional MRI. Brain. 2001;124(Pt 10):2059-73.

27. Pierce K, Haist F, Sedaghat F, Courchesne E. The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. Brain. 2004;127( Pt 12):2703-2716.

28. Pierce K, Redcay E. Fusiform function in children with an autism spectrum disorder is a matter of “who”. Biol Psychiatry. 2008;64:552-560.

29. Pinkham AE, Hopfinger JB, Pelphrey KA, Piven J, Penn DL. Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. Schizophr Res. 2008;99:164-176.

30. Rudie JD, Shehzad Z, Hernandez LM, et al. Reduced functional integration and segregation of distributed neural systems underlying social and emotional information processing in autism spectrum disorders. Cereb Cortex. In press.

31. Scherf KS, Luna B, Minshew N, Behrmann M. Location, location, location: alterations in the functional topography of face- but not object- or place-related cortex in adolescents with autism. Front Hum Neurosci. 2010;4:26.

32. Schultz RT, Gauthier I, Klin A, et al. Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. Arch Gen Psychiatry. 2000;57:331-340.

33. Uddin LQ, Davies MS, Scott AA, et al. Neural basis of self and other representation in autism: an fMRI study of self-face recognition. PloS One. 2008;3:e3526.

34. Wang AT, Dapretto M, Hariri AR, Sigman M, Bookheimer SY. Neural correlates of facial affect processing in children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2004;43:481-490.

35. Welchew DE, Ashwin C, Berkouk K, et al. Functional disconnectivity of the medial temporal lobe in Asperger’s syndrome. Biol Psychiatry. 2005;57:991-998.

36. Weng SJ, Carrasco M, Swartz JR, et al. Neural activation to emotional faces in adolescents with autism spectrum disorders. J Child Psychol Psychiatry. 2011;52:296-305.

37. Baron-Cohen S, Ring HA, Wheelwright S, et al. Social intelligence in the normal and autistic brain: an fMRI study. Eur J Neurosci. 1999;11:1891-1898.

38. Castelli F, Frith C, Happe F, Frith U. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. Brain. 2002;125(Pt 5):1839-1849.

39. Dapretto M, Davies MS, Pfeifer JH, et al. Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. Nat Neurosci. 2006;9:28-30.

40. Kaiser MD, Hudac CM, Shultz S, et al. Neural signatures of autism. Proc Natl Acad Sci U S A. 2010;107:21223-21228.

41. Hadjikhani N, Joseph RM, Manoach DS, et al. Body expressions of emotion do not trigger fear contagion in autism spectrum disorder. Soc Cogn Affect Neurosci. 2009;4:70-78.

42. Pitskel NB, Bolling DZ, Hudac CM, et al. Brain mechanisms for processing direct and averted gaze in individuals with autism. J Autism Dev Disord. 2011;41:1686-1693.

43. Konishi S, Nakajima K, Uchida I, Kikyo H, Kamiyama M, Miyashita Y. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. Brain. 1999;122(Pt 5):981-991.

44. Pelphrey KA, Morris JP, McCarthy G. Neural basis of eye gaze processing deficits in autism. Brain. 2005;128(Pt 5):1038-1048.

45. Silani G, Bird G, Brindley R, Singer T, Frith C, Frith U. Levels of emotional awareness and autism: an fMRI study. Soc Neurosci. 2008;3:97-112.

46. Wang AT, Lee SS, Sigman M, Dapretto M. Reading affect in the face and voice: neural correlates of interpreting communicative intent in children and adolescents with autism spectrum disorders. Arch Gen Psychiatry. 2007;64:698-708.

Table I. Continued
47. Wicker B, Fonlupt P, Hubert B, Tardif C, Gepner B, Deruelle C. Abnormal cerebral effective connectivity during explicit emotional processing in adults with autism spectrum disorder. Soc Cogn Affect Neurosci. 2008;3:135-143.

48. Allen G, Courchesne E. Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: an fMRI study of autism. Am J Psychiatry. 2003;160:262-273.

49. Allen G, Muller RA, Courchesne E. Cerebellar function in autism: dysfunctional magnetic resonance imaging activation during a simple motor task. Biol Psychiatry. 2004;56:269-278.

50. Agam Y, Joseph RM, Barton JJ, Manoach DS. Reduced cognitive control of response inhibition by the anterior cingulate cortex in autism spectrum disorders. Neuroimage. 2010;52:336-347.

51. Belmonte MK, Yurgelun-Todd DA. Functional anatomy of impaired selective attention and compensatory processing in autism. Brain Res Cogn Brain Res. 2003;17:651-664.

52. Damari SR, Keller TA, Kana RK, et al. Cortical underconnectivity coupled with preserved visuospatial cognition in autism: evidence from an fMRI study of an embedded figures task. Autism Res. 2010;3:273-279.

53. Dichter GS, Belger A. Social stimuli interfere with cognitive control in autism. Neuroimage. 2007;35:1219-1230.

54. Dichter GS, Belger A. Atypical modulation of cognitive control by arousal in autism. Psychiatry Res. 2008;164:185-197.

55. Dichter GS, Felder JN, Bodfish JW. Autism is characterized by dorsal anterior cingulate hyperactivation during social target detection. Soc Cogn Affect Neurosci. 2009;4:215-226.

56. Gilbert SJ, Bird G, Brindley R, Frith CD, Burgess PW. Atypical recruitment of medial prefrontal cortex in autism spectrum disorders: an fMRI study of two executive function tasks. Neuropsychologia. 2008;46:2261-2291.

57. Gilbert SJ, Meuwese JDI, Towgood KJ, Frith CD, Burgess PW. Abnormal functional specialization within medial prefrontal cortex in high-functioning autism: a multi-voxel similarity analysis. Brain. 2009;132:869-878.

58. Gomot M, Belmonte MK, Bullmore ET, Bernard FA, Baron-Cohen S. Brain hyper-reactivity to auditory novel targets in children with high-functioning autism. Brain. 2008;131(Pt 9):2479-2488.

59. Haist F, Adamo M, Westerfield M, Courchesne E, Townsend J. The functional neuroanatomy of spatial attention in autism spectrum disorder. Dev Neuropsychol. 2005;27:425-458.

60. Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. Functional and anatomical cortical underconnectivity in autism: evidence from an fMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex. 2007;17:951-961.

61. Kana RK, Keller TA, Minshew NJ, Just MA. Inhibitory control in high-functioning autism: decreased activation and underconnectivity in inhibition networks. Biol Psychiatry. 2007;62:198-206.

62. Keen M, Brenner L, Palmer E, Lincoln AJ, Muller RA. Functional brain organization for visual search in ASD. J Int Neuropsychol Soc. 2008;14:990-1003.

63. Kennedy DP, Redcay E, Courchesne E. Failing to deactivate: resting functional abnormalities in autism. Proc Nat Acad Sci U S A. 2006;103:8275-8280.

64. Lee PS, Yerys BE, Della Rosa A, et al. Abnormal cerebral effective connectivity during explicit emotional processing in autism spectrum disorder. Soc Cogn Affect Neurosci. 2007;35:1219-1230.

65. Lee PS, Foss-Feig J, Henderson JG, et al. Atypical neural substrates of Embedded Figures Task performance in children with Autism Spectrum Disorder. Neuroimage. 2007;38:184-1893.

66. Liu Y, Cherkassky VL, Minshew NJ, Just MA. Autonomy of lower-level perception from global processing in autism: evidence from brain activation and functional connectivity. Neuropsychologia. 2011;49:2105-2111.

67. Luna B, Minshew NJ, Garver KE, et al. Neocortical system abnormalities in autism: an fMRI study of spatial working memory. Neurology. 2002;59:834-840.

68. Manjaly ZM, Bruning N, Neufang S, et al. Neurophysiological correlates of relatively enhanced local visual search in autistic adolescents. Neuroimage. 2007;35:283-291.

69. Mizuno A, Villalobos ME, Davies MM, Dahl BC, Muller RA. Partially reduced thalamocortical functional connectivity in autism. Brain Res. 2006;1104:160-174.

70. Muller RA, Kleinmans N, Kemimoto N, Pierce K, Courchesne E. Abnormal variability and distribution of functional maps in autism: an fMRI study of visuomotor learning. Am J Psychiatry. 2003;160:1847-1862.

71. Muller RA, Cauchi C, Rubio MA, Mizuno A, Courchesne E. Abnormal activity patterns in premotor cortex during sequence learning in autistic patients. Biol Psychiatry. 2004;56:323-332.

72. Muller RA, Pierce K, Ambrose JB, Allen G, Courchesne E. Atypical patterns of cerebral motor activation in autism: a functional magnetic resonance study. Biol Psychiatry. 2001;49:665-676.

| Core findings in ASD group (relative to controls) | Conclusions |
| --- | --- |
| Reduced functional integration: AMY-secondary visual areas, PO-parietal cortex; Reduced segregation: AMY-DLPFC, PO-VMPFC; Reduced integration: PO-FC, within right NAC | Reduced functional integration and segregation of large-scale brain networks during face viewing |
| ↓FG, occipital face area, STS to faces; ↑Ventral posterior FG to faces | Selective ventral visual pathway disruption; Face-processing alteration present in early adolescence; Face perception in ASD akin to object perception in typical development |
| ↑Right FG; ↑Right ITG | Brain activation in the ASD group during face discrimination was consistent with feature-based strategies |
| ↑Right premotor/prefrontal during presentation of “other” faces | Functional dissociation between the representation of self versus others suggests a neural substrate of self-focus and decreased social understanding |
| ↓FG and ↑precuneus during matching facial expressions; Lack of modulation by task demands in the AMY | Recruited different neural networks and relied on different strategies when processing facial emotion |
| Abnormal AMY—parahippocampal connectivity | Difficulty in grasping facial expressions in others and, therefore, in manipulating interpersonally derived information |
| ↑AMY, ventral PFC and striatum, particularly to sad faces; Negative correlation between age, pubertal status, and AMY activation | Greater activation in social-emotional processing regions when viewing faces |

Table I. Continued
Clinical research

73. Noonan SK, Haist F, Muller RA. Aberrant functional connectivity in autism: evidence from low-frequency BOLD signal fluctuations. *Brain Res.* 2009;1262:48-63.

74. Ring HA, Baron-Cohen S, Wheelwright S, et al. Cerebral correlates of preserved cognitive skills in autism: a functional MRI study of embedded figures task performance. *Brain.* 1999;122( Pt 7):1305-1315.

75. Solomon M, Ozonoff SJ, Ursu S, et al. The neural substrates of cognitive control deficits in autism spectrum disorders. *Neuropsychologia.* 2009;47:2515-2526.

76. Schmitz N, Rubia K, Daly E, Smith A, Williams S, Murphy DG. Neural correlates of executive function in autistic spectrum disorders. *Biol Psychiatry.* 2006;59:7-16.

77. Shafritz KM, Dichter GS, Baranek GT, Belger A. The neural circuitry mediating shifts in behavioral response and cognitive set in autism. *Biol Psychiatry,* 2008;63:974-980.

78. Silk TJ, Rinehart N, Bradshaw JL, et al. Visuospatial processing and the function of prefrontal-parietal networks in autism spectrum disorders: a functional MRI study. *Am J Psychiatry.* 2006;163:1440-1443.

79. Takarae Y, Minshew NJ, Luna B, Sweeney JA. Atypical involvement of frontostriatal systems during sensorimotor control in autism. *Psychiatry Res.* 2007;156:117-127.

80. Thakkar KN, Polli FE, Joseph RM, et al. Response monitoring, repetitive behavior and anterior cingulate abnormalities in autism spectrum disorders (ASD). *Brain.* 2008;131(Pt 9):2464-2478.

81. Anderson JS, Lange N, Froehlich A, et al. Decreased left posterior insular activity during auditory language in autism. *Am J Neuroradiol.* 2010;31:131-139.

82. Boddart N, Belin P, Chabane N, et al. Perception of complex sounds: abnormal pattern of cortical activation in autism. *Am J Psychiatry.* 2003;160:2057-2060.

83. Catarino A, Luke L, Waldman S, Andrade A, Fletcher PC, Ring H. An fMRI investigation of detection of semantic incongruities in autistic spectrum conditions. *Eur J Neurosci.* 2011;33:558-567.

84. Eigsti IM, Schuh J, Mendl E, Schultz RT, Paul R. The neural underpinnings of prosody in autism. *Child Neuropsych.* In press.

85. Eyler LT, Pierce K, Courchesne E. A failure of left temporal cortex to specialize for language is an early emerging and fundamental property of autism. *Brain.* 2012;135(Pt 3):949-960.

86. Grezes J, Wicker B, Berthoz S, de Gelder B. A failure to grasp the affective meaning of actions in autism spectrum disorder subjects. *Neuropsychologia.* 2009;47:1816-1825.

87. Groen WB, Tesink C, Petersson KM, et al. Semantic, factual, and social language comprehension in adolescents with autism: an fMRI study. *Cereb Cortex.* 2010;20:1937-1945.

88. Harris GJ, Chabris CF, Clark J, Urban T, Aharon I, Steele S, et al. Brain activation during semantic processing in autism spectrum disorders via functional magnetic resonance imaging. *Brain Cognition.* 2006;61:54-68.

Citation | ASD †† | TYP †† | ASD age | TYP age | Task(s)
---|---|---|---|---|---
Baron-Cohen, Ring, Wheelwright, et al, 1999 [37] | 6 (4) | 12 (6) | 26.3 ± 2.1 | 25.5 ± 2.8 | Inferred mental states from images of eyes
Castelli, Frith, Happe, Frith, 2002 [38] | 10** | 10** | 33 ± 7.6 | 25 ± 4.8 | Viewed animated sequence of geometric shapes
Dapretto, Davies, Pfeifer, et al, 2006 [39] | 10 (9) | 9 (9) | 12.05 ± 2.5 | 12.38 ± 2.22 | Imitation and observation of emotional expressions
Kaiser, Hudac, Shultz, et al, 2010 [40] | 25 (20) | 17 (12) (no sibling with ASD); 20 (9) (sibling with ASD) | 11.8 ± 3.6 | 10.9 ± 3.1 (no sibling with ASD); 11.3 ± 2.8 (sibling with ASD) | Viewed biological motion clips and scrambled motion clips
Hadjikhani, Joseph, Manoach, et al, 2009 [41] | 9** | 11 (8) | 30 ± 11 | 31 ± 14 | Emotion processing of body expressions
Pitskel, Bolling, Hudac et al, 2011 [42] | 15 (15) | 14 (13) | 23.4 ± 6.9 | 24.2 ± 7.4 | Viewed direct and averted gaze of virtual human face
Konishi, Nakajima, Uchida, et al, 1999 [43] | 18 (12) | 18 (12) | 35.6 ± 12.4 | 33.0 ± 10.7 | Imitation inhibition task
Pelphrey, Morris, McCarthy, 2005 [44] | 10 (9) | 9 (8) | 23.2 ± 9.9 | 23.4 ± 5.8 | Viewing congruent and incongruent eye gaze shifts
Silani, Bird, Brindley, et al, 2008 [45] | 15 (13) | 15 (13) | 36.6 ± 11.7 | 33.7 ± 10.3 | Emotion introspection task
Wang, Lee, Sigman, Dapretto, 2007 [46] | 18 (18) | 18 (18) | 12.4 ± 2.9 | 11.8 ± 1.9 | Processed potentially ironic remarks
Wicker, Fonlupt, Hubert et al, 2008 [47] | 12 (11) | 14 (14) | 27 ± 11 | 23.4 ± 10 | Emotion and age discrimination

*Table II.* Studies investigating theory of mind and mental inference-making in autism spectrum disorders.
89. Hesling I, Dihlarreguy B, Peppe S, Amirault M, Bouvard M, Alliard M. The integration of prosodic speech in high functioning autism: a preliminary FMRI study. PloS One. 2010;5:e11571.
90. Just MA, Cherkassky VL, Keller TA, Minshew NJ. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain. 2004;127(Pt 8):1811-1821.
91. Kana RK, Keller TA, Cherkassky VL, Minshew NJ, Just MA. Sentence comprehension in autism: thinking in pictures with decreased functional connectivity. Brain. 2006;129(Pt 9):2484-2893.
92. Kana RK, Wadsworth HM. “The archeologist’s career ended in ruins”: Hemispheric differences in pun comprehension in autism. Neuroimage. In press.
93. Kleinans NM, Muller RA, Cohen DN, Courchesne E. Atypical functional laterization of language in autism spectrum disorders. Brain Res. 2008;1221:115-125.
94. Knaus TA, Silver AM, Lindgren KA, Hadjikhani N, Tager-Flusberg H. fMRI activation during a language task in adolescents with ASD. J Int Neuropsychol Soc. 2008;14:967-979.
95. Knaus TA, Silver AM, Kennedy M, et al. Language laterality in autism spectrum disorder and typical controls: a functional, volumetric, and diffusion tensor MRI study. Brain Lang. 2010;112:113-120.
96. Lai G, Schneider HD, Schwarzenberger JC, Hirsch J. Speech stimulation during functional MR imaging as a potential indicator of autism. Radiology. 2011;260:521-530.
97. Lai G, Pantazatos SP, Schneider H, Hirsch J. Neural systems for speech and song in autism. Brain. 2012;135(Pt 3):961-75.
98. Mizuno A, Liu Y, Williams DL, Keller TA, Minshew NJ, Just MA. The neural basis of deictic shifting in linguistic perspective-taking in high-functioning autism. Brain. 2011;134(Pt 8):2422-2435.
99. Redcay E, Courchesne E. Deviant functional magnetic resonance imaging patterns of brain activity to speech in 2-3-year-old children with autism spectrum disorder. Biol Psychiatry. 2008;64:589-598.
100. Redcay E, Dodell-Feder D, Mavros PL, et al. Atypical brain activation patterns during a face-to-face joint attention game in adults with autism spectrum disorder. Hum Brain Mapp. In press.
101. Sahyoun CP, Belleiveau JW, Soulieres I, Schwartz S, Mody M. Neuroimaging of the functional and structural networks underlying visuospatial vs. linguistic reasoning in high-functioning autism. Neuropsychologia. 2010;48:86-95.
102. Scott-Van Zeeland AA, McNealy K, Wang AT, Sigman M, Bookheimer SY, Dapretto M. No neural evidence of statistical learning during exposure to artificial languages in children with autism spectrum disorders. Biol Psychiatry. 2010;68:345-351.
103. Tesink CMJY, Buitelaar JK, Petersson KM, et al. Neural correlates of pragmatic language comprehension in autism spectrum disorders. Brain. 2009;132:1941-1952.

### Core findings in ASD group (relative to controls)

| Brain Region | Description |
|--------------|-------------|
| Frontal-temporal regions | Supports amygdala theory of autism |
| ↓AMY | Possible neurofunctional explanation for impaired mentalizing |
| ↓MPFC, STS, temporal poles | Dysfunctional mirror neuron system may underlie social deficits in autism |
| ↓Decreased extrastriate functional connectivity | Identifies non-overlapping regions associated with ASD phenotypes and ASD genetic vulnerability in the absence of ASD symptoms |
| ↓IFG | Emotion perception deficits in ASD may be due to compromised processing of the emotional component of observed actions |
| ↑Right TPJ, right AI, left lateral OC | Brain mechanisms underlying processing gaze direction in ASD |
| ↑Left DLPFC | Highlights contribution of hyperimitation to reduced social cognition |
| ↓STS on incongruent trials | Lack of STS modulation to congruent and incongruent gaze shifts contributes to eye gaze processing deficits |
| ↓Self-reflection/mentalizing regions (MPFC, ACC, precuneus, inferior OFC, temporal poles, cerebellum) during self introspection; AI activity predicted alexithymia and empathy in both groups | Alexithymia and empathy deficits linked to anomalous AI activity |
| ↓MPFC, right STG to irony; MPFC activity in ASD modulated by instructions to attend to faces and tones of voice; MPFC activity inversely related to symptom severity in ASD group | MPFC mediates understanding the intentions of others |
| ↓DMPFC, right VLPCF, right STG; Abnormal connectivity between AMY, VLPCF, DLPFC, posterior occipital-temporal regions | Abnormal connectivity between structures of the social brain could explain social deficits in ASD |

### Table II. Continued
Table III. Studies investigating cognitive control in autism spectrum disorders.

| Citation | ASD **† | TYP **† | ASD age  | TYP age  | Task(s)                                                                 |
|----------|----------|----------|----------|----------|------------------------------------------------------------------------|
| Allen, Courchesne, 2003 [48] | 8 (7)    | 8 (7)    | 26.89 ± 8.59 | 26.77 ± 8.22 | Motor control and attentional control                                  |
| Allen, Muller, Courchesne, 2004 [49] | 8 (7)    | 8 (7)    | 26.89 ± 8.59 | 26.77 ± 8.22 | Repeated button pressing                                                |
| Agam, Joseph, Barton, Manoach, 2010 [50] | 11**     | 14**     | 28 ± 10   | 27 ± 8   | Antisaccade task                                                        |
| Belmonte, Yurgelun-Todd, 2003 [51] | 6 (5)    | 6 (5)    | 32.7 ± 9.8 | 27.2 ± 4.4 | Bilateral visual spatial attention task                                |
| Damarla, Keller, Kana, et al, 2010 [52] | 13 (11)  | 13 (13)  | 19 ± 5.5  | 22.1 ± 4.25 | Embedded figures task                                                   |
| Dichter, Belger, 2007 [53] | 17 (16)  | 15 (14)  | 22.9 ± 5.2 | 24.6 ± 6.5 | Flanker task (interference inhibition)                                 |
| Dichter, Belger, 2008 [54] | 12 (12)  | 22 (22)  | 23.2 ± 5.8 | 25.1 ± 6.0 | Flanker task intermixed with high and low arousal images               |
| Dichter, Felder, Bodfish, 2009 [55] | 15 (14)  | 19 (18)  | 23.3 + 11.1 | 28.0 + 7.9 | Oddball target detection task with social and non-social targets        |
| Gilbert, Bird, Brindley, Frith, Burgess, 2008 [56] | 14 (11)  | 18 (13)  | 38 ± 13   | 32 ± 8   | (1) Random response generation task (2) Selected stimulus-oriented vs stimulus-independent thought |
| Gilbert, Meuwese, Towgood, Frith, Burgess, 2009 [57] | 16 (14)  | 16 (12)  | 32 ± 7.7  | 31 ± 5.7  | (1) Stimulus-oriented spatial task (2) Stimulus-independent spatial task |
| Gomot, Belmonte, Bullmore, Bernard, 2008 [58] | 12 (12)  | 12 (12)  | 13.5 ± 1.6 | 13.8 ± 1  | Auditory novelty detection                                              |
| Haist, Adamo, Westerfield, Courchesne, Townsend, 2005 [59] | 8 (8)    | 8 (8)    | 23.4 ± 11.4 | 25.6 ± 12.5 | Spatial attention task                                                  |
| Just, Cherkassky, Keller, Kana, Minshew, 2007 [60] | 18 (17)  | 18 (15)  | 27.1 ± 11.9 | 24.5 ± 9.9 | Tower of London task                                                   |
| Kana, Keller, Minshew, Just, 2007 [61] | 12 (11)  | 12 (11)  | 26.8 ± 7.7 | 22.5 ± 3.2 | Go/No-go task                                                          |
| Keehn, Brenner, Palmer, Lincoln, Muller, 2008 [62] | 9 (9)    | 13 (13)  | 15.1 ± 2.6 | 14.1 ± 2.1 | Visual search task                                                     |
| Kennedy, Redcay, Courchesne, 2006 [63] | 12**     | 14**     | 25.49 ± 9.61 | 26.07 ± 7.95 | Counting Stroop task                                                   |
| Lee, Yerys, Della Rosa, et al, 2009 [64] | 12 (9)   | 12 (8)   | 10.17 ± 1.57 | 11.01 ± 1.78 | Go/No-go task                                                          |
| Lee, Foss-Feig, Henderson et al, 2007 [65] | 17 (12)  | 14 (11)  | 10.37 ± 1.52 | 10.81 ± 1.47 | Embedded figures task                                                  |
| Liu, Cherkassky, Minshew, Just, 2011 [66] | 15 (14)  | 15 (15)  | 25.2 ± 7.6  | 26.3 ± 8.2  | (1) Line-counting task (2) Judged whether a 3D object was possible      |
| Core findings in ASD group (relative to controls)                                                                 | Conclusions                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| ↑Motor regions;                                                                                                     | Developmental cerebellar abnormality has differential functional implications for cognitive and motor systems                               |
| ↓Cerebellar attention                                                                                                | Cerebellar dysfunction that is a reflection of abnormal anatomy                                                                        |
| ↑Ipsilateral anterior cerebellar hemisphere                                                                         | Functional neural abnormalities in volitional ocular-motor control linked to repetitive behaviors                                          |
| ↓Frontal eye field, dorsal ACC; Decreased frontal eye field—dorsal ACC connectivity; Both findings associated with repetitive behavior symptoms |                                                                                                                                           |
| ↓Left VOC; ↑Left IPS                                                                                                 | Neurofunctional basis of impaired selective attention                                                                                 |
| ↓Left DLPFC, inferior parietal areas; ↑Visuospatial areas; Decreased frontal—visuospatial connectivity               | Cortical underconnectivity despite preserved visuospatial performance                                                                   |
| ↓Prefrontal, parietal regions during the incongruent social condition only                                             | Social stimuli interfere with brain regions mediating cognitive control                                                                 |
| ↓Right MFG on conflict trials preceded by high arousal images only                                                 | Abnormal modulation of regions mediating cognitive control in context of high arousal                                                  |
| ↑Right IFG, DMPFC to social targets; DMPFC activation to social targets predicted severity of social impairments       | DMPFC hyperactivation during cognitive control of social stimuli contributes to expression of social deficits                           |
| Task 1: ↓Cerebellum, left lateral temporal cortex; Task 2: ↑Medial rostral PFC                                        | Impaired cognitive control in is associated with task-specific functional changes                                                        |
| Similar activation patterns; Multi-voxel similarity analyses revealed found abnormal functional specialization within medial rostral PFC | Abnormal functional specialization within medial rostral PFC                                                                         |
| ↑Right PFC-premotor, left inferior parietal regions                                                                  | Cognitive control associated with activation of a more widespread network of regions                                                   |
| ↓Frontal, parietal, occipital, within the IPL; ↑SPL and extrastriate cortex                                         | Deficit in automatic spatial attention abilities and aberrant voluntary spatial attention skills                                         |
| Similar activation in DLPFC between groups; Lower frontal—parietal connectivity                                     | Cognitive control deficits may be preferentially linked to lower cortical integration of information                                     |
| ↓Left ACG, left precuneus, right AG, premotor areas; Lower connectivity between ACG, MCG, right MFG, IFG, inferior parietal regions | Inhibition circuitry is activated atypically and is less synchronized, leaving inhibition to be accomplished by strategic control rather than automatically |
| ↑Occipital and frontoparietal regions                                                                              | Enhanced discrimination and increased top-down modulation of attention processes                                                        |
| Decreased deactivation of resting network regions (MPFC/rostral ACC, PCC)                                           | Lack of deactivation indicates abnormal internally directed processes at rest and may be compensatory                                     |
| Age-moderated decreased connectivity in IFC, motor planning regions                                                 | Atypical developmental connectivity trajectories for IFC with other neural regions supporting response inhibition                        |
| ↑Dorsomedial premotor, left superior parietal, right occipital cortex                                               | Reduced cortical activation suggests that disembedded visual processing is performed sparingly                                          |
| ↓Medial frontal to possibility task; Decreased frontal—posterior connectivity                                       | Less effort for lower-level processing;                                                                                                 |
| Decreased effort for lower-level processing; Reduced global-to-local interferences                                    |                                                                                                                                           |
104. Tesink CM, Buitelaar JK, Petersson KM, van der Gaag RJ, Teunisse JP, Hagoort P. Neural correlates of language comprehension in autism spectrum disorders: when language conflicts with world knowledge. *Neuropsychologia*. 2011;49:1095-1104.

105. Vaidya CJ, Foss-Feig J, Shook D, Kaplan L, Kenworthy L, Gaillard WD. Controlling attention to gaze and arrows in childhood: an fMRI study of typical development and Autism Spectrum Disorders. *Dev Sci*. 2011;14:911-924.

106. Cascio CJ, Foss-Feig JH, Heacock JL, et al. Reward circuitry function in autism spectrum disorders. *J Neurodev Disord*. In press.

107. Dichter GS, Richey JA, Rittenberg AM, Sabatino A, Bodfish JW. Reward circuitry function in autism during face anticipation and outcomes. *J Autism Dev Disord*. 2012;42:147-160.

108. Dichter GS, Felder JN, Green SR, Rittenberg AM, Sasson NJ, Bodfish JW. Reward circuitry function in autism spectrum disorders. *Soc Cogn Affect Neurosci*. 2012;7:160-172.

109. Kohls G, Schulte-Ruther M, Nehrkorn B, et al. Reward system dysfunction in autism spectrum disorders. *Br J Psychiatry*. 2008;192:19-24.

110. Schmitz N, Rubia K, van Amelsvoort T, Daly E, Smith A, Murphy DG. Neural correlates of reward in autism. *Br J Psychiatry*. 2008;192:19-24.

111. Scott-Van Zeeland AA, Dapretto M, Ghahremani DG, Poldrack RA, Bookheimer SY. Reward processing in autism. *Autism Res*. 2010;3:53-67.

112. Anderson JS, Nielsens JA, Kroelich AL, et al. Functional connectivity magnetic resonance imaging classification of autism. *Brain*. 2011;134(PT 12):3742-3754.

113. Cherkassky VL, Kana RK, Keller TA, Just MA. Functional connectivity in a baseline resting-state network in autism. *Neuroimage*. 2011;17:1687-1690.

114. Di Martino A, Kelly C, Grzadzinski R, et al. Aberrant striatal functional connectivity in children with autism. *Biol Psychiatry*. 2011;68:847-856.

115. Kennedy DP, Courchesne E. The intrinsic functional organization of the brain is altered in autism. *Neuroimage*. 2008;39:1877-1885.

116. Lai MC, Lombardo MV, Chakrabarti B, et al. A shift to randomness of brain oscillations in people with autism. *Biol Psychiatry*. 2010;68:1092-1099.

117. Monk CS, Peltier SJ, Wiggins JL, et al. Abnormalities of intrinsic functional connectivity in autism spectrum disorders. *Neuroimage*. 2009;47:764-772.

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**Table III. Continued**

| Citation | ASD † | TYP † | ASD age | TYP age | Task(s) |
|----------|-------|-------|---------|---------|---------|
| Luna, Minshew, Garver, et al, 2002 [67] | 11 (9) | 6 (6) | 32.3 ± 9.3 | 30.3 ± 11.8 | (1): Spatial working memory task (2) Guided saccade task |
| Manjaly, Bruning, Neufang et al, 2007 [68] | 12** | 12** | 14.4 ± 2.7 | 14.3 ± 2.7 | Embedded figures task |
| Mizuno, Villalobos, Davies, Dahl, Muller, 2006 [69] | 8 (8) | 8 (8) | 28.4 ± 8.9 | 28.1 ± 8.3 | Visuomotor coordination task |
| Muller, Kleinmans, Kemmotsu, Pierce, Courchesne, 2003 [70] | 8 (8) | 8 (8) | 28.4 ± 8.9 | 28.1 ± 8.3 | 6-digit sequence learning |
| Muller, Cauich, Rubio, Mizuno, Courchesne, 2004 [71] | 8 (8) | 8 (8) | 28.4 ± 8.9 | 28.1 ± 8.3 | 8-digit sequence learning |
| Muller, Pierce, Ambrose, Allen, Courchesne, 2001 [72] | 8 (8) | 8 (8) | 28.4 ± 8.9 | 28.1 ± 8.3 | Visual stimulation using finger movements |
| Noonan, Haist, Muller, 2009 [73] | 10 (10) | 10 (10) | 23 ± 9.9 | 25.8 ± 9.9 | Source recognition task |
| Ring, Baron-Cohen, Wheelwright, et al, 1999 [74] | 6 (4) | 12 (6) | 26.3 ± 2.1 | 25.5 ± 2.8 | Embedded figures task |
| Solomon, Ozonoff, Ursu, et al, 2009 [75] | 22 (17) | 23 (18) | 15.2 ± 1.7 | 16.0 ± 2.0 | Preparing to overcome prepotency task |
| Schmitz, Rubia, Daly, et al, 2006 [76] | 10 (10) | 12 (12) | 38 ± 9 | 39 ± 6 | (1) Go/No-go task (2) Stroop task (3) Cognitive set shifting |
| Shafritz, Dichter, Baranek, Belger, 2008 [77] | 18 (16) | 15 (13) | 22.3 ± 8.7 | 24.3 ± 6.2 | Oddball target detection task |
| Silk, Rinehart, Bradshaw et al, 2006 [78] | 7 (7) | 9 (9) | 14.7 ± 2.9 | 15.0 ± 1.8 | Mental rotation task |
| Takarae, Minshew, Luna, Sweeney, 2007 [79] | 13** | 14** | 24.5 ± 7.7 | 26.6 ± 7.8 | Saccadic eye movement paradigms |
| Thakkar, Polli, Joseph, et al, 2008 [80] | 12 (10) | 14 (8) | 30 ± 11 | 27 ± 8 | Anti-saccade task |
118. Paakki JJ, Rahko J, Long X, et al. Alterations in regional homogeneity of resting-state brain activity in autism spectrum disorders. *Brain Res*. 2010;1321:169-179.
119. von dem Hagen EA, Stoyanova RS, Baron-Cohen S, Calder AJ. Reduced functional connectivity within and between ‘social’ resting state networks in autism spectrum conditions. *Soc Cogn Affect Neurosci*. In press.
120. Weng SJ, Wiggins JL, Peltier SJ, et al. Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders. *Brain Res*. 2010;1313:202-214.
121. Wiggins JL, Peltier SJ, Ashinoff S, et al. Using a self-organizing map algorithm to detect age-related changes in functional connectivity during rest in autism spectrum disorders. *Brain Res*. 2011;1380:187-197.

### Core findings in ASD group (relative to controls)

| Task 1 | ↑DLPFC, PCC; ↑Right PVC, bilateral extrastrate areas; Increased functional connectivity in left insula, right postcentral gyrus, MFG | Neurofunctional basis of impaired working memory |
| Task 2: no differences | | |
| ↑PFC, posterior parietal cortex | Enhanced local processing in early visual areas rather than impaired global processing |
| ↑↑ Right pericentral and PMC; Delayed activation of BA 3, 4, 6 | Underconnectivity hypothesis unsupported; Subcortico-cortical connectivity may be hyperfunctional, potentially compensating for reduced cortico-cortical connectivity |
| ↓Contra-lateral peri-landic cortex, BG, THAL, bilateral supplementary motor area, ipsilateral cerebellum, bilateral DLPFC; ↑Posterior cortex, PFC, extrastrate regions | Disturbances in cerebello-thalamocortical pathways |
| Increased connectivity between left MFG—left superior parietal regions | Atypical use of the primary sensory and premotor cortices during learning |
| ↓Right DLPFC, bilateral parietal cortex; ↑Right ventral occipitotemporal cortex | Abnormal functional variability and less distinct regional activation patterns |
| ↓Anterior frontal, parietal occipital regions; Decreased frontal/parietal/occipital connectivity related to ADHD symptoms | An inefficiency in optimizing network connections during task performance |
| Task 1: ↑↑ left IFG, OFG; Task 2: ↑↑ left insula, AMY-hippocampal junction; Task 3: ↑↑ PL | Object feature analysis, rather than working memory systems, are used for local processing and visual search in autism |
| ↓Frontal, striatal, and parietal regions; ACC activation correlated with repetitive behavior symptoms | Fronto-parietal connectivity deficits contribute to ADHD symptoms in autism |
| ↓lateral and medial PMC, DLPFC, ACG, CN | Cognitive control associated with increased brain activity in multiple regions |
| ↑DLPFC, CN, medial THAL, ACC, PCC, right DN | Cognitive control deficits and repetitive behaviors might be associated with dysfunctions in neural circuitry |
| ↑Rostral ACC; Reduced fractional anisotropy in white matter underlying rostral ACC; Repetitive behaviors correlated with rostral ACC activation | Dysfunctional frontostriatal networks during cognitive control |
| | Cognitive control regions may compensate for lower-level processing difficulties |
| | Rostral ACC abnormalities contribute to repetitive behaviors |

**Table III.** Continued
### Clinical research

| Citation | ASD | TYP | ASD age | TYP age | Task(s) |
|----------|-----|-----|---------|---------|---------|
| Anderson, Lange, Froehlich, et al, 2010 [81] | 26 (26) | 15 (15) | 21.7 ± 6.4 | 22.5 ± 6.3 | (1) Thought about a described word (2) Filled in missing word in a sentence |
| Boddardt, Belin, Chabane, et al, 2003 [82] | 5 (4) | 8 (8) | 19.1 ± 4.5 | 21.9 ± 3.3 | Listened to speech-like sounds |
| Catarino, Luke, Waldman, et al, 2011 [83] | 12 (12) | 12 (12) | 27.0 ± 10 | 34.0 ± 13 | Detected semantic incongruities within written sentences |
| Eigsti, Schuh, Mendl, Schultz, Paul, 2011 [84] | 16** | 11** | ** | ** | Processed linguistic stimuli that varied in emotional and semantic content |
| Eyler, Pierce, Courchesne, 2012 [85] | 40 (40) | 40 (40) | 32.0 mo ± 10.2 | 25.6 mo ± 9.6 | Listened to story with complex, simple, or backward speech during sleep |
| Grezes, Wicker, Berthoz, de Gelder, 2009 [86] | 12 (10) | 12 (12) | 26.6 ± 10.4 | 21.0 ± 1.6 | Viewed fearful or neutral body language |
| Groen, Tesink, Petersson, et al, 2010 [87] | 16 (12) | 26 (21) | 15.3 ± 1.6 | 15.7 ± 1.7 | Sentences congruent or incongruent to speaker |
| Hadjikhani et al, 2009 [41] | 12 (9) | 11 (11) | 30 ± 11 | 35 ± 12 | Recognition of emotional bodies |
| Harris, Chabris, Clark, et al, 2006 [88] | 14 (14) | 22 (22) | 36 ± 12 | 31 ± 9 | Semantic and perceptual word processing |
| Hesling, Dilharreguy, Peppe, et al, 2010 [89] | 8 (8) | 8 (8) | 23.38 ± 2.10 | 23.05 ± 2.02 | Listened to speech stimulus involving variable intonation, rhythm, focus and affect |
| Just, Cherkassky, Keller, Minshew, 2004 [90] | 17 (13) | 17 (12) | 28.0 ± 13.3 | 28.6 ± 10.7 | Identified agent or object in each sentence |
| Kana, Keller, Cherkassky, Minshew, Just, 2006 [91] | 12 (11) | 13 (12) | 22.5 ± 8.8 | 20.3 ± 4.0 | Processed sentences with high or low imagery content |
| Kana, Wadsworth, 2012 [92] | 16 (16) | 16 (16) | 20.0 ± 6.43 | 21.6 ± 2.70 | Processed sentences with puns |
| Kleinhans, Muller, Cohen, Courchesne, 2008 [93] | 14 (14) | 14** | 23.79 ± 9.58 | 22.41 ± 8.67 | (1) Letter fluency task; (2) Category fluency task |
| Knaus, Silver, Lindgren, Hadjikhani, Tager-Flusberg, 2008 [94] | 12 (12) | 12 (12) | 15.46 ± 2.48 | 14.94 ± 2.71 | Reading version of response-naming task |
| Knaus, Silver, Kennedy, et al, 2010 [95] | 14 (14) | 20 (20) | 16.83 ± 2.35 | 14.43 ± 2.47 | (1) Response-naming task; (2) Control letter-judgment task |
| Lai, Schneider, Schwarzenberger, Hirsch, 2011 [96] | 39 (35) | 15 (10) | 12.4 ± 4.7 | 12.13 ± 4.34 | Listened to speech |

**Table IV.** Studies investigating communication in autism spectrum disorders.
### Core findings in ASD group (relative to controls)

| Finding                                                                                     | Conclusions                                                                 |
|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| ↓Left posterior insula, bilateral receptive language areas;                                 | Posterior insula implicated in receptive language impairments               |
| Receptive language correlated with activation of posterior left WA;                         |                                                                             |
| Verbal IQ correlated with activation of bilateral BA, PFC, lateral PMC                    |                                                                             |
| ↑Right MFG                                                                                  | Abnormal auditory cortical processing implicated in language impairments    |
| More spatially restricted activation pattern (only left IFG, left ACC, right FG)            | Impaired integration of multiple neural networks related to difficulties in use of context |
| Affective and grammatical prosodic cues prompted more generalized activation                | Language processing less automatic; Linkages between ToM and language processing deficits; Increased reliance on executive control regions for speech processing |
| ↓Left hemisphere to speech sounds (worsens with age); Abnormally right-lateralized temporal cortex to language (worsens with age) | Lateralized abnormalities of temporal cortex processing of language in toddlers with autism |
| ↓AMY, IFG, PMC to fearful gestures                                                          | Dysfunction in this network may impact the communication deficits present in autism |
| ↓Left IFG for sentences requiring integration of speaker information;                       | ASD recruits left IFG atypically in language tasks that demand integration of social information |
| No difference for semantic- and world-knowledge sentences                                  |                                                                             |
| ↓IFC, AI in response to emotionally neutral gestures                                       | Identifies neural mechanisms of impaired affect communication               |
| During semantic processing, ↓BA, ↑WA;                                                      | Abnormal Broca’s area development that may be linked with language deficits |
| Diminished activation difference between concrete and abstract words                        |                                                                             |
| Abnormal neural network for prosodic speech perception in left supra marginal gyrus;       | Prosodic impairments could not only result from activation pattern abnormalities, but also from an inability to inhibit default network |
| Absence of deactivation patterns in default mode                                            |                                                                             |
| ↑WA; ↓BA;                                                                                 | Decreased information synchronization across the language processing network |
| Decreased functional connectivity between contributing cortical areas                      |                                                                             |
| Language and spatial centers not as synchronized;                                          | Under-integration of language and imagery; Reliance on visualization to support language comprehension |
| ↑Parietal and occipital regions during low-imagery sentences                                |                                                                             |
| ↑Overall, particularly in right hemisphere and posterior areas during pun comprehension;  | Altered neural route in language comprehension in general, and figurative language in particular |
| ↓Left hemisphere                                                                           |                                                                             |
| ↑Right frontal and right superior TL during letter fluency task;                           | Reduced hemispheric differentiation for certain verbal fluency tasks; abnormal functional organization may contribute to the language impairments |
| Decreased lateralization of activation patterns during letter fluency, but not to category |                                                                             |
| ↑BA; Reduced BA left lateralization                                                       | Decreased efficiency of semantic processing                                |
| Atypical language laterality more prevalent in the ASD group                               | Language laterality may be a novel way to subdivide samples, resulting in more homogenous groups |
| ↓Mean amplitude and spread of activity in STG                                              | Possible neurofunctional correlate of language impairment                   |

Table IV. Continued
| Citation | ASD *† | TYP *† | ASD age | TYP age | Task(s) |
|----------|--------|--------|---------|---------|---------|
| Lai, Pantazatos, Schneider, Hirsch, 2012 [97] | 36 (32) | 21 (14) | 9.61 ± 4.04 | 10.72 ± 4.42 | Listened to speech and songs |
| Mizuno, Liu, Williams, et al, 2011 [98] | 15 (14) | 15 (15) | 24.7 ± 7.8 | 24.7 ± 7.7 | Linguistic perspective-taking task requiring deictic shifting |
| Redcay, Courchesne, 2008 [99] | 12 (12) | 23 (17) | 34.9 mo ± 7.4 | 19.6 mo ± 4.2 | Listened to forward and backward speech |
| Redcay, Dodell-Feder, Mavros, et al, 2012 [100] | 13 (10) | 14 (11) | 28.0 ± 7.05 | 27.0 ± 5.68 | Interactive face-to-face joint attention game |
| Sahyoun, Belliveau, Soulieres, Schwartz, Mody, 2010 [101] | 12 (10) | 12 (9) | 13.3 ± 2.45 | 13.3 ± 2.07 | Pictorial reasoning with visuospatial processing, semantic processing, or both |
| Scott-Van Zeeland, McNealy, Wang, et al, 2010 [102] | 18 (18) | 18 (18) | 12.62 ± 2.5 | 11.64 ± 1.58 | Listened to two artificial languages and a random speech stream |
| Tesink, Buitelaar, Petersson, et al, 2009 [103] | 24 (16) | 24 (16) | 26.3 ± 6.3 | 26.2 ± 6.0 | Speaker inference task |
| Tesink, Buitelaar, Petersson, et al, 2011 [104] | 24 (16) | 24 (16) | 26.3 ± 6.3 | 26.2 ± 6.0 | Integrated contextual information during auditory language comprehension |
| Vaidya, Foss-Feig, Shook, et al, 2011 [105] | 15 (11) | 18 (14) | 10.78 ± 1.29 | 10.96 ± 1.26 | Responded to target word in presence of congruent or incongruent arrow or averted gaze |

Table IV. Continued
### Core findings in ASD group (relative to controls)

| Finding                                                                 | Conclusions                                                                 |
|------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| ↓Left IFG during speech;                                               | Functional systems that process speech and song more effectively engaged for song than for speech |
| ↑Left IFG during songs;                                                |                                                                             |
| Increased left IFG-STG connectivity for songs;                        |                                                                             |
| Increased frontal—posterior connectivity                               |                                                                             |
| ↑Right AI, precuneus;                                                 | Higher activation compensates for decreased connectivity during deictic shifting |
| Decreased right AI—precuneus connectivity                              |                                                                             |
| ↓Extended network recruited in typical early language acquisition;     | Children with ASDs may be on a deviant developmental trajectory characterized by greater recruitment of right hemisphere regions during speech perception |
| ↑Medial, right GC;                                                     |                                                                             |
| ↑Right hemisphere to forward speech                                    |                                                                             |
| ↓Left posterior STS, DMPFC during joint attention;                     | Failure of developmental neural specialization in STS and DMPFC during joint attention |
| ↑Posterior STS during solo attention                                    |                                                                             |
| ↑Occipito-parietal, ventral temporal areas;                            | Greater visual mediation of language processing                             |
| Reduced inferior frontal - ventral temporal and middle temporal        |                                                                             |
| connectivity                                                           |                                                                             |
| ↑Fronto-temporal-parietal, as number of cues to word boundaries        | Abnormalities in neural regions subserving language-related learning;        |
| increased;                                                            | Communicative impairments linked to decreased sensitivity to the statistical and speech cues in language |
| No learning-related increases for artificial languages in BG, left    |                                                                             |
| temporoparietal cortex;                                                |                                                                             |
| Communicative impairment correlated with signal increases in these    |                                                                             |
| regions to artificial languages                                         |                                                                             |
| ↑Right IFG for speaker-incongruent sentences;                         | Compensatory mechanisms during implicit low-level inferential processes in spoken language |
| Absence of VMPFC modulation to incongruent sentences                   |                                                                             |
| ↓Left, right IFG for sentences with world knowledge anomaly            | Reduced integrative capacity of stored knowledge;                           |
| Congruent: regions associated with attention to gaze (left STS, PMC)    | Atypical functional anatomy to social and nonsocial communicative cues      |
| activated to arrows;                                                   |                                                                             |
| Incongruent: regions associated with arrows (ACC, left DLPFC, right    |                                                                             |
| CN) activated to gaze                                                  |                                                                             |
|                                                                        |                                                                             |

Table IV. Continued
Table V. Studies investigating reward processing in autism spectrum disorders.

| Citation                          | ASD † | TYP† | ASD age | TYP age | Task(s)                                                                 |
|----------------------------------|-------|------|---------|---------|-------------------------------------------------------------------------|
| Cascio, Foss-Feig, Heacock, et al, 2012 [106] | 17 (17) | 23** | 12.8 ± 2.5 | 13.2 ± 3.4 | Viewed images of high-calorie foods after fasting                    |
| Dichter, Richey, Rittenberg, et al, 2012 [107] | 16 (14) | 20 (14) | 26.0 ± 9.1 | 25.4 ± 7.0 | Incentive delay task with monetary and social rewards                |
| Dichter, Felder, Green, et al, 2012 [108] | 15 (15) | 16 (16) | 30.1 ± 11.6 | 27.5 ± 7.5 | Incentive delay task with monetary rewards and rewards related to circumscribed interests |
| Kohls, Schulte-Ruther, Nehrkorn, et al, 2012 [109] | 15 (15) | 17 (17) | 14.6 ± 3.3 | 13.9 ± 3.0 | Go/no-go task with social vs. monetary rewards                          |
| Schmitz, Rubia, van Ameloot, et al, 2008 [110] | 10 (10) | 10 (10) | 37.8 ± 7 | 38.2 ± 6 | Rewarded continuous performance task                                  |
| Scott-Van Zeeland, Dapretto, Ghahremani, 2010 [111] | 16 (16) | 16 (16) | 12.4 ± 2.14 | 12.3 ± 1.76 | Implicit learning task with social vs. monetary rewards                |
### Table V. Continued

| Core findings in ASD group (relative to controls)                                                                 | Conclusions                                                                 |
|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| ↑Bilateral insula along anterior-posterior gradient;                                                             | Abnormally enhanced neural response to primary rewards in ASD                |
| ↑ACC to food cues                                                                                               |                                                                             |
| ↓NAC, OFC during monetary anticipation;                                                                        | Domain-general reward circuitry dysfunction; atypical amygdala activation to social rewards may contribute to social symptom |
| ↑Right insula to face incentives;                                                                               | severity in ASD                                                              |
| ↑Bilateral AMY during face anticipation that correlated with social symptoms                                      |                                                                             |
| ↓NAC during monetary anticipation and outcomes;                                                                  | Reward circuitry hypoactivation to monetary incentives but hyper-            |
| ↑VMPFC to circumscribed interests incentives                                                                    | activation to circumscribed interests in ASD. Possible neural mechanism of  |
| ↓Midbrain, THAL, AMY, striatum, ACC to both rewards;                                                             | circumscribed interests in ASD                                               |
| ↓NAC to monetary reward, but not social reward                                                                   | Domain-general reward system dysfunction in ASD                               |
| ↑Left ACG during reward trials that correlated with social symptom severity;                                      | Reward achievement associated with abnormal activation in areas             |
| ↓VS to both social and monetary rewards (more pronounced to social rewards.                                      | responsible for attention and arousal in ASD                                 |
|                                                                                                                 | Diminished neural responses during social reward learning may contribute to |
|                                                                                                                 | social learning impairments in ASD                                           |
### Table VI. Studies investigating resting state connectivity in autism spectrum disorders.

| Citation | ASD ** | TYP* | ASD age | TYP age | Task(s) |
|----------|--------|------|---------|---------|---------|
| Anderson, Nielsen, Froehlich, et al, 2011 [112] | 40 (40) | 40 (40) | 22.7 ± 7.4 | 21.6 ± 7.4 | 8’ resting scan with eyes open |
| Cherkassky, Kana, Keller, Just, 2006 [113] | 57 (53) | 57 (52) | 24.0 ± 10.6 | 24.0 ± 9 | Periods of rest during task-based scans (duration not specified). |
| Di Martino, Kelly, Grzadzinski, et al, 2011 [114] | 20 (17) | 20 (14) | 10.4 ± 1.7 | 10.9 ± 1.6 | 6’ 38” resting scan with eyes open |
| Kennedy, Courchesne, 2008 [115] | 13 (13) | 12 (12) | 26.9 ± 12.3 | 27.5 ± 10.9 | 7’ 10” resting scan with eyes open |
| Lai, Lombardo, Chakrabarti, et al, 2010 [116] | 18 (18) | 33 (33) | 26.9 ± 7.4 | 28.4 ± 6.1 | 13’ 39” resting scan with eyes closed (only last 512 of 625 volumes analyzed). |
| Monk, Peltier, Wiggins, et al, 2009 [117] | 12 (11) | 12 (10) | 26 ± 5.93 | 27 ± 6.1 | 10’ resting scan with eyes open. |
| Paakki, Rahko, Long et al, 2010 [118] | 28 (20) | 27 (18) | 14.58 ± 1.62 | 14.49 ± 1.51 | 7’ 36” resting scan with eyes open. |
| von dem Hagen, Stoyanova, Baron-Cohen, Calder, 2012 [119] | 18 (18) | 25 (25) | 30 ± 8 | 25 ± 6 | 10’ resting scan with eyes open. |
| Weng, Wiggins, Peltier, et al, 2010 [120] | 16 (14) | 15 (14) | 15.0 ± 1.45 | 16.0 ± 1.44 | 10’ resting scan with eyes open. |
| Wiggins, Peltier, Ashinoff et al, 2011 [121] | 39 (32) | 41 (33) | 14.0 ± 2.08 | 15.3 ± 2.4 | 10’ resting scan with eyes open. |
Core findings in ASD group (relative to controls) | Conclusions
--- | ---
Negatively correlated ROI pairs showed decreased anticorrelation in ASD; Greatest connectivity differences in default mode network, superior parietal lobule, FG and AI | Weaker inhibitory connections, particularly for long connections; Resting state fMRI may be feasible as a diagnostic classifier for ASD
Decreased connectivity in resting-state networks despite similar volume and organization; Decreased posterior—anterior connectivity | Resting state underconnectivity in ASD
Increased connectivity between striatal subregions and heteromodal associative and limbic cortex; Increased pons-striatum and pons-insula connectivity | Increased connectivity in ectopic circuits reflects alternate trajectory of development, rather than immaturity of circuits
Reduced default mode network connectivity | Altered functional organization of the network involved in social and emotional processing
More randomness in midline structures, medial temporal structures, lateral temporal and parietal structures, insula, AMY, BG, THAL, IFG; Social symptoms negatively correlated with randomness in retrosplenial and right anterior IC | ASD associated with small but significant shift towards randomness in endogenous brain oscillations
Decreased PCC-SFG connectivity; Increased connectivity between PCC and right TL and right PHG; Social symptoms correlated with PCC-SFG connectivity; repetitive behaviors correlated with PCC—right PHG connectivity | Altered intrinsic connectivity that was associated with core symptoms
Decreased regional homogeneity in right STS, right IFG, right MFG, bilateral cerebellum, right insula, right postcentral gyrus; Increased regional homogeneity in right THAL, left IFG, left anterior subcallosal gyrus, bilateral cerebellar lobule VIII | Right-dominant alterations of resting state activity
Decreased default mode network connectivity; Decreased connectivity in salience network (includes insula) and a medial TL network (includes AMY) | Reduced connectivity in networks involved with the “social brain”; May be implicated in difficulties with communication and information integration
Decreased connectivity in 9 of 11 default mode areas; Social and repetitive behavior symptoms correlated with decreased connectivity in parts of default mode network; Communication correlated with increased connectivity in parts of default mode network | Decreased default mode network connectivity in adolescents with ASDs than in adults with ASDs
Decreased connectivity between posterior hub of default network and right SFG; Less increase in connectivity with age | Different developmental trajectory of default mode network