Altered Immune Function Associated with Neurophysiological Abnormalities and Executive Function Deficits in Children with Autism

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Introduction

Considerable evidence suggests that there is an association between immune functions and cognitive and emotional states in humans (Ashwood and Van de Water 2004). An individual's cognitive and emotional states can compromise immune function, and correspondingly, the biochemical balance or imbalance of the immune system can alter brain function and behavior, suggesting that there is a bidirectional communication between the brain and the immune system (Ashwood et al. 2006; Sperner-Unterweger 2005). For example, immune products such as cytokines have been shown to influence the neural plasticity that underlies learning and memory (Pugh et al. 2001), and circulating cytotoxic T lymphocytes have been shown to enter the central nervous system (CNS) when activated and cause axonal damage in the brain (Neumann et al. 2002). Furthermore, peripheral T-cell deficiency has been hypothesized to be related to cognitive dysfunction and abnormal behavior in schizophrenia (Kipnis et al. 2004). Indeed, changes in immune function have been suggested to underlie a wide array of neurodevelopmental disorders, including autism (Hornig and Lipkin 2001; Boulanger and Shatz 2004).

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Executive Function Deficits Fundamental to Cognitive Impairments in ASD

Children with ASD are characterized by marked impairment in social, behavioral, and cognitive function (Lord et al. 2000). Abnormalities are also found in higher cognitive functions, where some individuals with ASD show severe impairments and mental retardation, while others show isolated cognitive dysfunctions, such as stereotyped behavior and memory impairments (Chan et al. 2011b; Cheung et al. 2010). The presence of restricted and repetitive stereotyped behaviors and uncontrollable temper outbursts are commonly manifested in children with ASD. It has been suggested that impairment in executive function is fundamental to these cognitive and behavioral problems. Executive function is a broadly defined cognitive domain that includes a multidimensional set of abilities required to perform complex behaviors in order to attain a future goal (Donders 2002). Executive function is generally understood to be an umbrella term covering a number of distinct but related cognitive processes, such as planning, cognitive flexibility, generativity, and self-monitoring, as well as the inhibition of inappropriate actions (Ozonoff et al. 2004).

Executive dysfunction can be seen to underlie many of the key characteristics of individuals with autism and include disorganized actions and strategies typified by decreased initiative, perseveration, difficulties in forming novel concepts, and a lack of judgment, insight, and ability to inhibit inappropriate actions (Hill 2004; Schmitz et al. 2006). Thus, individuals with ASD are often rigid and have a narrow focus of attention on uniqueness rather than similarity, preventing them from noticing the larger picture of the situation or understanding perspectives different from their own (Klinger et al. 2000). Individuals with ASD are deficient in the ability to integrate information across contexts. Specifically, they have difficulty learning the relationships between different parts of stimuli as well as perceiving relationships across multiple experiences; they tend to compensate for this cognitive impairment by memorizing ritual details or individual rules from each situation that they encounter. The impaired ability to attend to and integrate information from the environment may also explain why individuals with ASD show a strong liking for repetitive behaviors and elaborate rituals. Many children with autism follow routines in precise detail and show great distress over trivial changes in the environment.

Neural Basis of Executive Dysfunction in ASD

Although the neurobiological determinants of the executive system have not been clearly delineated, it is widely accepted that the frontal cortex is one of the major brain regions implicated in the cognitive impairments and repetitive stereotyped behaviors commonly seen in ASD (Schroeter et al. 2004). Structural abnormalities, including significant enlargement of the frontal lobe (Belmonte et al. 2004;

Carper et al. 2002) and increased brain volume of the dorsolateral and medial frontal regions (Carper and Courchesne 2005), have been reported in individuals with ASD. Results from behavioral and neurobiological studies on individuals with ASD have revealed abnormal neurobiological processes in the frontal lobe that underlie their cognitive deficits (Mundy 2003; Ozonoff et al. 2004; Schmitz et al. 2006). Functional imaging studies have also found altered patterns of activation, perfusion, and glucose metabolism in different areas of the frontal lobe during neuropsychological tasks of executive function (Chan et al. 2011a; Hazlett et al. 2004; Harmony et al. 2009). Furthermore, a recent study (Chan et al. 2009) has shown that the deficits in inhibitory control and executive function are significantly correlated with the degree of functional abnormalities in the frontal area of autistic brains (Fig. 1 and Table 1).

In addition to the frontal lobe, increasing evidence shows that executive function involves the integrated action of multiple brain areas (Osaka et al. 2004; Sauseng et al. 2005). It has been widely suggested that disordered neural connectivity between the frontal cortex and its distributed network may underlie the unusual cognitive processing and resultant behavioral symptoms associated with ASD (Fletcher and Henson 2001; Rippon et al. 2007; Weiss and Rappelsberger 2000). In support of this association, diffusion tensor imaging (DTI) studies of individuals with autism have found reduced myelin integrity in the ventromedial prefrontal cortex and at the temporoparietal junctions (Barnea-Goraly et al. 2004; Lewis and Elman 2008). Results from functional MRI studies have shown lower synchronization in the inhibitory networks during response inhibition tasks, indicating that the inhibitory deficit is associated with decreased functional cortical connectivity in these individuals (Kana et al. 2007). Similarly, electroencephalography (EEG) and functional imaging studies have also provided evidence of disordered connectivity across neural systems in ASD patients compared to controls on tests of memory (Chan et al. 2011b), sentence comprehension (Just et al. 2004), social cognition (Castelli et al. 2002), and working memory (Luna et al. 2002). Interestingly, recent studies reported that executive function deficits varied with the level of general intellectual functioning in children with ASD (Han 2010, unpublished data); low-functioning children with ASD showed the poorest performance in executive function tasks, typically developing children showed the highest performance, and high-functioning counterparts performed in between these two groups (Table 2). Furthermore, a related study (Chan et al. 2011b) demonstrated that the severity of the executive dysfunctions in children with ASD was closely related to the degree of disordered neural connectivity; increased EEG coherence in the theta band was seen between the frontal cortex and its distributed network (Fig. 2).

Immunologic Abnormalities in ASD

Although the cause of the reported abnormal neural connectivity in ASD is not well understood, increasing evidence has indicated that immunological factors are involved (Ashwood and Van de Water 2004; Pardo et al. 2005). Increased incidence

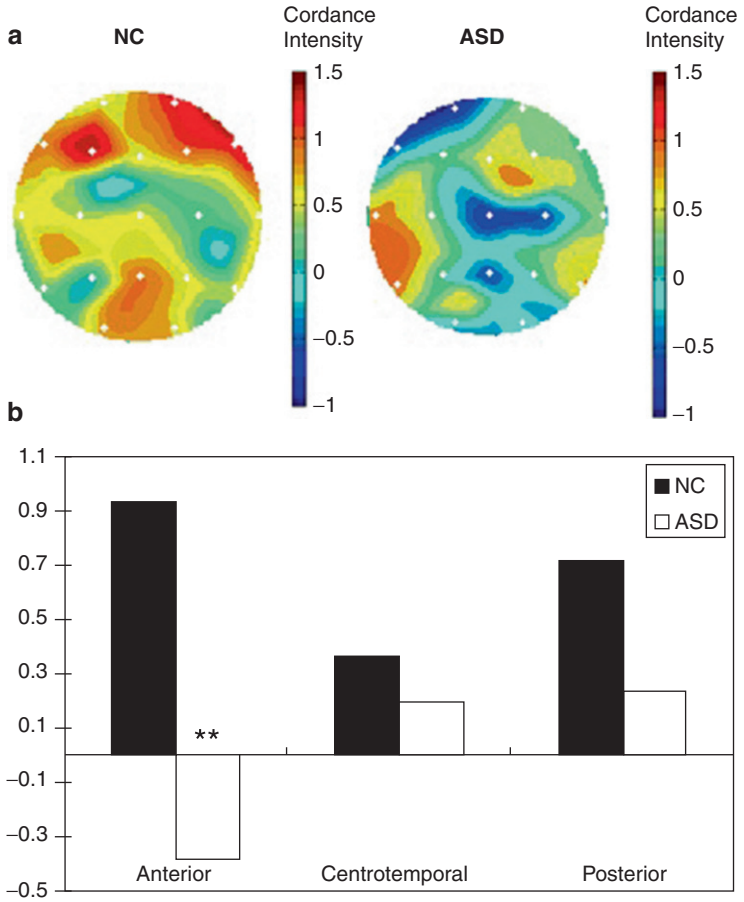

Fig. 1 Topographical maps demonstrating the averaged values for cordance intensity for typically developing children (NC) and children with autistic spectrum disorder (*ASD*). (**a**) Cordance is an indirect measure of brain perfusion. *White dots* indicate the spherical positions of the recording sites (nose at top) derived from triangle-based cubic interpolations. *Orange-red* indicates higher cordance value, and *green-blue* indicates lower cordance value. (**b**) Children with autistic spectrum disorder (*ASD*) showed significantly lower mean cordance value at theta frequency band in the anterior, but not centrotemporal and posterior, regions than those of normal controls (*NC*). $^{**}p < 0.001$ (Source: From Chan et al. 2009)

of immunological disorders, such as heightened autoimmunity, reduced immune functions, and altered peripheral lymphocyte numbers, has been reported in autistic patients and their first-degree relatives, suggesting that there is a genetic link in the pathogenesis of ASD (Ashwood et al. 2003; Connolly et al. 1999; Molloy et al. 2006; Singer et al. 2006). In addition, some maternal viral infections were reported to increase the risk for ASD. Maternal influenza infection in mice was associated

Table 1 Correlations between anterior cordance value, general intelligence (IQ), and measures of executive functioning (EF) of IQ-matched children with ASD and their typically developing counterparts ($n = 42$)

EF measures	Anterior cordance
TONI-III (IQ)	0.06
HKLLT delayed intrusion	−0.43*
HKLLT false alarm	−0.14
OR false alarm	−0.40*
BRIEF behavioral regulation	−0.32*
BRIEF metacognition	−0.32*
BRIEF global composite	−0.35*

Source: From Chan et al. 2009
Cordance is a quantitative derivative of scalp EEG power that was found to show a strong correlation with cerebral perfusion. Greater brain perfusion is indicated by increased cordance value. Anterior cordance: cordance value in the frontal region of the brain. *TONI-III* test of nonverbal intelligence, *HKLLT* Hong Kong list learning test (executive task of memory), *OR* object recognition test (false alarms as measure of intrusion), *BRIEF* behavior rating inventory of executive function
*$p < 0.05$

with profound anatomical, motor, and other behavioral defects reminiscent of autism, including anxiety in novel situations and early postnatal macrocephaly (Fatemi et al. 2002; Shi et al. 2003). The findings of these studies are consistent with findings from longitudinal clinical and imaging studies describing a pattern of abnormal brain overgrowth in young children with ASD, particularly in the frontal lobe (Carper and Courchesne 2005; Redcay and Courchesne 2005). Retrospective studies of head circumference measurements reported that much of the overgrowth occurs within 6–14 months of age, a critical period that coincides with synaptogenesis, dendritic formation, and ongoing myelination (Belmonte et al. 2004; Courchesne et al. 2003). These findings indicate the occurrence of transient postnatal macrocephaly (Courchesne 2002), in which the deviant brain growth interferes with the normal developmental course of the functional connectivity of the frontal cortex and its distributed networks, resulting in disruption to long-range and localized connectivity between key neural networks in the brains of individuals with ASD (Courchesne and Pierce 2005; Herbert 2005; Just et al. 2007; Rippon et al. 2007). Some researchers have further suggested that the systematic, immunologic aberrations in ASD are linked with autoimmunity; the production of autoantibodies directed against central nervous system (CNS) proteins results in the destruction of neural tissues in individuals with ASD (Korvatska et al. 2002).

Although deleterious agents in the blood are restricted from entering the brain by the blood-brain barrier, recent studies have demonstrated that products of immune activation such as cytokines can gain access to the brain through active transport, or they can impair blood-brain barrier function directly by binding to receptors on brain endothelial cells (Ashwood and Van de Water 2004; Wilson et al. 2002).

Table 2 Mean performance and standard deviation (*SD*) on the measures of executive functioning in typical developing children (*NC*), high-functioning autistic (*HFA*) children, and low-functioning autistic (*LFA*) children with autism spectrum disorders (*ASD*)

Measures	NC ($n = 28$) M (SD)	HFA ($n = 19$) M (SD)	LFA ($n = 19$) M (SD)	*F*-value	Group difference
HKLLT – total learning	25.64 (4.75)	18.11 (8.18)	8.05 (5.91)	45.15**	NC > HFA** NC > LFA** HFA > LFA**
HKLLT – discrimination %	93.07 (8.31)	70.56 (33.11)	21.92 (30.07)	48.08**	NC > HFA** NC > LFA** HFA > LFA**
D2 – concentration performance	164.8 (53.72)	118.1 (55.24)	30.26 (44.01)	38.62**	NC > HFA** NC > LFA** HFA > LFA**
FP – unique design	23.64 (10.86)	22.74 (11.05)	5.95 (6.83)	20.62**	NC > LFA** HFA > LFA**
CCTT – T2: time (in seconds)[a]	44.4 (18.86)	73.76 (68.61)	172.4 (109.0)	19.66**	NC > LFA** HFA > LFA *
ToC – achievement score	9.57 (2.75)	7.57 (4.59)	2.37 (1.98)	28.75**	NC > LFA** HFA > LFA**
Go/No-Go – commission errors[a]	9.0 (6.09)	10.05 (7.55)	15.18 (11.89)	3.02	

Source: From Han 2010

D2 = D2 test of attention, *FPT* five-point test (mental flexibility), CCTT – T2: time = total completion time in Trail 2 of the Children's Color Trail Test (mental flexibility), *ToC* Tower of California Test (planning), Go/No-Go = Go/No-Go test of inhibition

$^{**}p < 0.001$; $^{*}p < 0.007$

[a]Lower value indicates better performance

Indeed, a number of studies have reported the presence of anti-CNS autoantibodies in children with ASD (Plioplys et al. 1989; Singh et al. 1993). In addition, postmortem studies of brain tissues in some individuals with ASD showed clear signs of inflammation, supporting the idea that ASD may be associated with the activation of the brain's immune system (Vargas et al. 2005). Vargas et al. (2005) also found significantly elevated levels of cytokines and chemokines in the cerebrospinal fluid (CSF) of children with ASD; products of immune activation including cytokines can alter brain function and affect cognitive and emotional processing (Ashwood et al. 2006). For example, cytokine IL-1b has been shown to influence the neural plasticity that underlies learning and memory (Pugh et al. 2001). Similarly, circulating cytotoxic T lymphocytes (CTL) were shown to enter the CNS when activated and can cause axonal damage to neurons (Neumann et al. 2002). Together, these findings suggest that neuroimmune abnormalities occur in the brain of individuals with ASD, and these abnormalities may be associated with the behavioral and cognitive problems observed in ASD patients (Pardo et al. 2005).

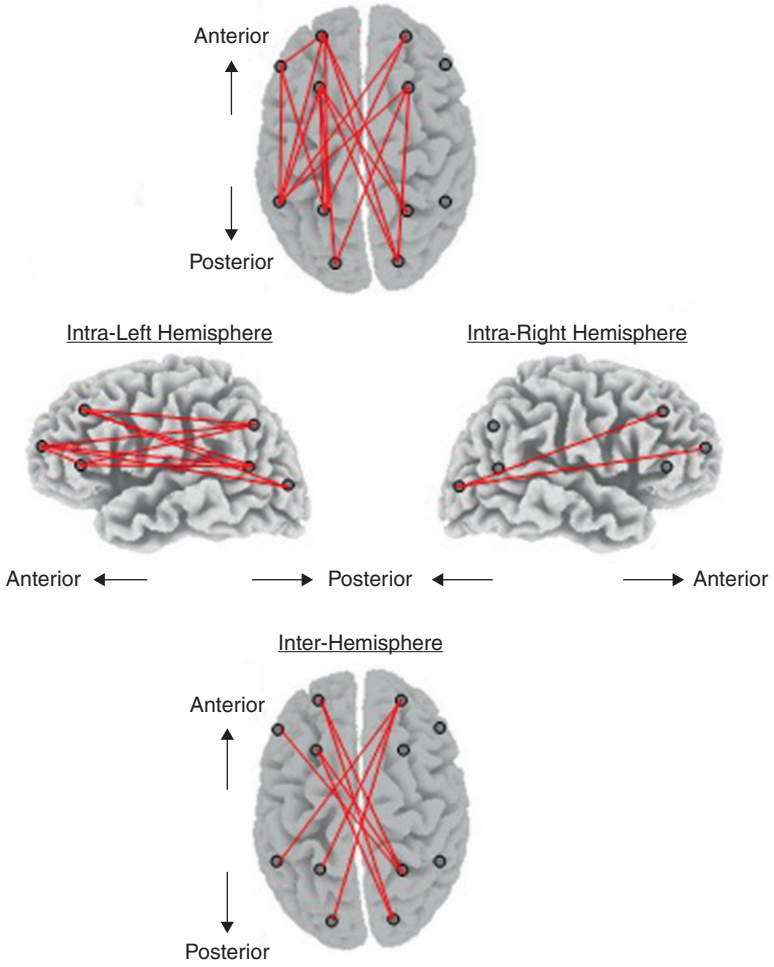

Fig. 2 Graphical representation of the between-subject differences in intra – and interhemispheric theta coherence during object recognition task. *Red lines* linking the electrode pairs (*grey dots*) represent significantly higher coherence values in children with autistic spectrum disorder (*ASD*) than the typically developing controls (NC) (Source: From Chan et al. 2011b)

Lymphocyte Subset Alterations Related to Neurophysiologic Abnormalities and Executive Function Deficits in ASD

While studies suggest the involvement of immunologic factors in the pathogenesis of ASD, relatively little empirical evidence indicates that altered immune functions may contribute to the disordered neural connectivity and diversity of autistic phenotypes. A recent study reported that deficits in general intelligence, executive

Table 3 The absolute numbers and percentage values of lymphocyte subsets in the peripheral blood of high-functioning autistic (*HFA*) and low-functioning autistic (*LFA*) children with ASD

Variable	HFA ($n = 18$) M (SD)	LFA ($n = 19$) M (SD)	*t*-value
Absolute number of lymphocytes			
Total lymphocytes (cells/ml)	2,527.4 (708.1)	3,136.2 (924.9)	−2.07*
T lymphs (cells/ml)	1,683.8 (465.9)	2,138.3 (606.1)	−2.55*
Th lymphs (cells/ml)	834.3 (232.4)	955.5 (225.7)	−1.74
Suppressor/cytotoxic T lymphs (cells/ml)	659.4 (182.7)	964.3 (393.5)	−3.05**
B lymphs (cells/ml)	455.6 (164.4)	578.4 (232.0)	−1.85
NK cells (cells/ml)	388.3 (307.9)	361.4 (245.5)	1.32
Percentages within lymphocytes			
T lymphs (%)	65.8 (6.6)	68.5 (4.8)	−1.45
Th lymphs (%)	33.6 (7.6)	31.4 (5.8)	0.96
Suppressor/cytotoxic T lymphs (%)	25.8 (3.1)	30.2 (5.0)	−3.17**
B lymphs (%)	17.7 (5.2)	18.5 (5.5)	−0.46
NK cells (%)	14.3 (9.4)	10.9 (5.3)	1.32

Source: From Han et al. 2011
Standard deviations are in parentheses. *Lymphs* lymphocytes
**$p < 0.01$; *$p < 0.05$

functioning, and abnormal repetitive behavior were exacerbated as a function of the level of lymphocyte subsets in children with ASD (Han et al. 2011). In the study, 18 high-functioning autistic (HFA) and 19 low-functioning autistic (LFA) children with ASD, aged 8–17 years, were assessed on executive function using a battery of neuropsychological tests, including the Hong Kong List Learning Test (HKLLT), D2 Test of Concentration (D2), 5-Point Test (5-point), Children's Color Trail Test (CCTT), the Tower of California Test (ToC), and the Go/No-Go task. The children were also assessed on autoimmune symptoms reported by their parents as well as immunological measures, including lymphocyte subset of T lymphocytes (CD3+), B lymphocytes (CD19+), T-helper (Th) lymphocytes (CD3 + CD4+), suppressor/cytotoxic T lymphocytes (CD3 + CD8+), and natural killer (NK) cells (CD3–CD16+ and/or CD56+). The results indicated that low-functioning children with ASD showed more severe deficits in executive functioning and higher levels of lymphocyte subsets compared to high-functioning children with ASD (Table 3). These findings are in line with previous studies that reported immune system abnormalities in children with ASD (Krause et al. 2002; Molloy et al. 2006). In an important extension of previous immunological studies, this study found that executive functions and repetitive stereotyped behavior varied as a function of the increased levels of lymphocyte subsets, in particular, the suppressor/cytotoxic T lymphocytes (CD3 + CD8+) (Table 4). This finding provided initial evidence to support the notion that the predominance of cytotoxic T lymphocytes (CD8 + CTLs) may play a role in the executive dysfunctions and repetitive, stereotyped behaviors in ASD.

CD8 + CTLs are highly potent cells with several distinct cytotoxic functions. It has been reported that CD8 + CTLs are important effectors in several autoimmune

Table 4 Correlations between IQ, measures of executive functions, parent behavioral observations, and peripheral blood lymphocyte subsets in children with ASD ($N = 37$)

Executive function measures	Total lymphocytes	T lymphs	Suppressor/ cytotoxic T lymphs	Suppressor/cytotoxic T lymphs %
IQ	−0.34*	−0.32*	−0.38*	−0.33*
Executive composite score	0.35*	0.36*	0.38*	0.31
HKLLT – total learning	−0.40*	−0.39*	−0.42**	−0.30
HKLLT – discrimination	−0.37*	−0.38*	−0.41**	−0.30
D2 – concentration performance	−0.47**	−0.52**	−0.47**	−0.33*
FPT – unique design	−0.34*	−0.35*	−0.40**	−0.36*
CCTT – T2: time	0.17	0.21	0.21	0.22
ToC – achievement	−0.20	−0.17	−0.20	−0.12
Go/No-Go – commission errors	0.29	0.29	0.29	0.17
ADI-R social interaction	0.19	0.08	0.11	−0.00
ADI-R communication	0.02	−0.01	−0.05	−0.15
ADI-R repetitive behavior	0.45**	0.43**	0.44**	0.27

Source: From Han et al. 2011

Lymphs lymphocytes, *ADI-R* autism diagnostic interview-revised (Lord et al. 1994) is a rating measure completed by the parent on the child's behaviors relevant to the diagnosis of Pervasive Developmental Disorders. It consisted of three scales, Social Interaction, Communication, and Repetitive/Stereotyped Behavior, which correspond with the three diagnostic criteria of autism established in the DSM-IV-TR (American Psychiatric Association 2002)

* $p < 0.05$; ** $p < 0.01$

and degenerative CNS diseases and can cause neuronal tissue destruction. For example, neurites of cultured hippocampal neurons were found to be selectively transected by CD8+ CTLs but not CD4+ lymphocytes (Medana et al. 2000, 2001). In addition, circulating CD8+ CTLs have been shown to cause axonal damage in brain cells (Neumann et al. 2002). Together, these data provide compelling evidence that tissues of the CNS can become CD8+ CTL targets. The ability of autoreactive cytotoxic T cells to direct tissue damage to the CNS (Krause et al. 2002) may explain why a higher level and percentage of circulating suppressor/cytotoxic T lymphocytes (CD3+ CD8+) were found in low-functioning children with ASD compared with their high-functioning counterparts in the abovementioned study, which in turn may account for the more severe executive dysfunctions and abnormal repetitive behavior in the low-functioning group. This finding is supported by another study that further examined the association between the level of circulating CD3+ CD8+ and the documented abnormal neural connectivity in ASD (Han et al. 2013).

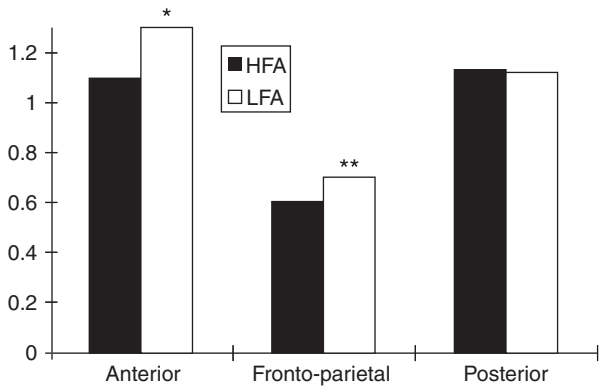

Fig. 3 Mean short – and long-range EEG theta coherences in high-functioning autistic (*HFA*) and low-functioning autistic (*LFA*) children with ASD during eyes-open resting condition. The LFA group showed sharply elevated EEG coherence in the anterior region and also long-range coherence in the frontoposterior connections. No significant difference was found between the two groups in the posterior region. $^{**}p < 0.01$, $^{*}p < 0.05$

Seventeen high-functioning autistic (HFA) and 17 low-functioning autistic (LFA) children with ASD, aged 8–17 years, were compared on their executive functions using a neuropsychological test; a nonexecutive cognitive task, as measured by the Picture Completion Task; neural connectivity, as measured by EEG theta coherence in the anterior and posterior regions; and immunologic function, as measured by the level of circulating CD3 + CD8+ suppressor/cytotoxic T lymphocytes in a blood sample. The results regarding executive function showed that LFA children performed significantly poorer than HFA children. However, there was no group difference on the nonexecutive cognitive Picture Completion Task. The EEG results showed that LFA children had significantly elevated theta coherence in the anterior network, as well as in the long-range coherences in the frontoposterior connections (Fig. 3). Regarding immunologic function, the results showed that LFA children had significantly elevated levels of suppressor/cytotoxic T lymphocytes (CD3 + CD8+) (Fig. 4). While executive dysfunction, disordered neural connectivity, and abnormal immunologic function were found to be associated, no significant correlation was found between the nonexecutive Picture Completion Task and any of the immunologic, neuropsychological, and neurophysiologic measures (Table 5).

Together, the above findings provide important evidence that immunologic factors may play a role in causing neuronal damage in the brains of children with ASD. This has opened up a new direction of research in which behavioral and cognitive dysfunctions may be studied from the perspective of immunologic functions. Moreover, as a new avenue of neuropsychological intervention, future research could determine whether improvements in immunologic functions are associated with corresponding improvements in behavioral and cognitive performance.

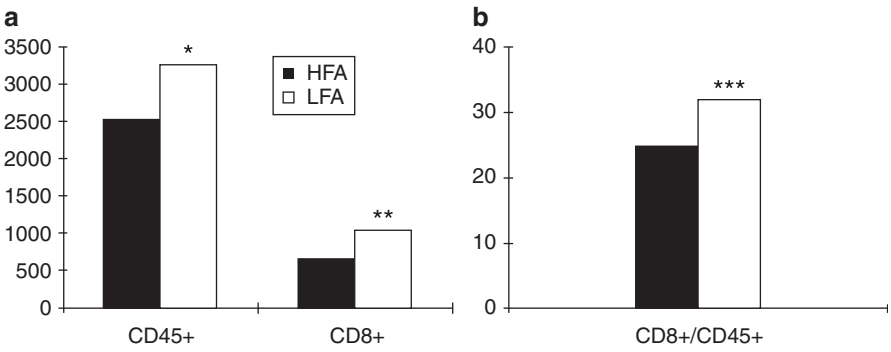

Fig. 4 (**a**) The absolute number and (**b**) percentage value of suppressor/cytotoxic T lymphocytes in the peripheral blood of high-functioning autistic (*HFA*) and low-functioning autistic (*LFA*) children with ASD. CD45+: total lymphocytes; CD8+: suppressor/cytotoxic T lymphocytes; CD8+/CD45+: percentage of suppressor/cytotoxic T lymphocytes. ***$p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Table 5 Correlations between peripheral blood lymphocyte subsets, EEG theta coherence, general intelligence (*IQ*), and executive function (*EF*) in children with ASD ($n = 34$)

	Immunological measures	
	CD8+	CD8+/CD45+
EEG coherence		
Anterior	0.21	0.47**
Frontoposterior	0.08	0.41*
IQ	−0.48**	0.48**
EF composite score	0.51**	0.56**
PicC – repetition priming	0.13	−0.02

EF composite score was derived by summing the Z scores from measures of executive functioning; PicC: nonexecutive Picture Completion Task; CD8+: suppressor/cytotoxic T lymphocytes; CD8+ / CD45+: percentage of suppressor/cytotoxic T lymphocytes
* $p < 0.05$; ** $p < 0.01$

Key Terms

Executive function. Executive function is a broadly defined cognitive domain that includes a multidimensional set of abilities to perform complex behaviors for the attainment of a future goal. It is generally understood to be an umbrella term covering a number of distinct but related cognitive processes such as planning, cognitive flexibility, generativity, and self-monitoring, as well as inhibition of inappropriate actions.

Frontal lobe. The frontal lobe is part of the cerebral cortex and covers about one-third of the brain's structures. It is the main areas documented to be involved in executive function.

Lymphocytes. Lymphocytes are specialized white blood cells of the immune system. The three major types of lymphocytes are T cells, B cells, and natural killer cells. Peripheral T-cell deficiency is related to the cognitive dysfunction and abnormal behaviors in ASD.

Cytotoxic T lymphocytes. A subset of T lymphocytes, cytotoxic T lymphocytes are highly potent cells of the immune system with distinct cytotoxic functions that can cause direct tissue damage to the CNS. They are thought to be important effectors in several autoimmune and degenerative CNS diseases.

Cortical connectivity. Cortical connectivity is the integrated action of different brain areas to transfer information, which can range ranging from local connectivity within neural assemblies to long-range connectivity between different brain areas.

EEG coherence. EEG coherence is an electroencephalography (EEG) measure to estimate the cortical connectivity between different functional areas in the brain. EEG coherence measures the level of synchronization between two brain areas in terms of EEG signals recorded at different sites of the scalp.

Key Facts of the Relationship Between Immunologic Abnormalities and Cognitive Function Deficits

- Products of immune activation can alter brain function and affect cognitive and emotional processing.
- Products of immune activation such as cytokines can gain access to the brain through active transport or impair the brain barrier function directly by binding to the receptors on brain endothelial cells.
- Cytokine IL-1β can influence the neural plasticity that underlies learning and memory.
- When activated, circulating cytotoxic T lymphocytes in the blood can enter the central nervous system and can cause axonal damage of brain cells.
- Peripheral T-cell deficiency is related to the cognitive dysfunction and abnormal behaviors in schizophrenia.
- There is an elevated incidence of immune disorders in individuals with ASD, including abnormal cell-mediated immunity, abnormal T-cell populations and functions, B-cell and natural killer cell dysfunction, high blood monocyte counts, and elevated percentage monocytes to total leukocytes.
- Elevated levels of the cytokines in innate responses were also found in the cerebrospinal fluid of children with ASD.

Summary Points

- This chapter focuses on the relationship between altered immune function and the cognitive function in children with ASD.

- Previous studies have shown that children with ASD have impaired executive function and disordered neural connectivity.
- Increasing evidence suggests that immunological factors are involved in the pathogenesis of ASD.
- Maternal viral infection can increase the risk for ASD.
- Maternal influenza infection in mice has been shown to produce profound anatomical, motor, and other behavioral defects reminiscent of ASD.
- There are anti-CNS autoantibodies and clear signs of inflammation inside the brain and cerebrospinal fluid in individuals with ASD.
- The products of the altered immune system can gain access to the brain and cause direct neural damage, which may lead to the disordered neural connectivity and eventual cognitive dysfunctions and stereotyped behaviors in individuals with ASD.

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