THE NEUROPATHOLOGY OF AUTISM: A REVIEW OF THE CURRENT LITERATURE

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Abstract

The neuropathology of autism is punctuated by a heterochronicity of brain development. There is overgrowth of the brain at early stages of childhood with a disproportionate increase in its white matter. Parcellation of the white matter has found an increase in its outer radiate matter (e.g., arcuate fibers) with reductions in its inner compartment (e.g., corpus callosum). These changes may be the result of supernumerary periventricular germinal cell divisions which manifests itself as migratory deficits and a minicolumnopathy. Other findings such as loss of Purkinje cells and evidence of neuroinflammation may be the result of agonal or preagonal changes. Findings suggest that in autism there is a bias in connectivity favoring short connections at the expense of longer ones. Postmortem neuropathological studies in autism are based on reports of a very small number of brains. Due to the broad age spectrum as well as clinical diversity of ASD, the pattern of neuropathological changes is incomplete and inconsistent.

Running title: neuropathology

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Magnetic resonance imaging (Sack et al., 1998) and postmortem neuropathological studies indicate that ASD is characterized by dynamic age-specific structural and functional abnormalities. Developmental heterochronicity, wherein various brain regions grow at different rates compared to controls, is a defining anatomical feature associated with the disorder (Carper & Courchesne, 2005; Carper et al., 2002; Courchesne et al., 2001; Sparks et al., 2002). Topographic change caused by developmental heterochronicity likely produces the cytoarchitectural alterations that delineate a
distinct neuropathology in autism. The extent of deviation from the normal trajectory of brain development may be used as a diagnostic tool of subtype specificity in the future (Courchesne et al., 2003). Impairments in both local and global connectivity have been described, with an over-development of local connectivity networks at the expense of long distance connectivity (Casanova et al., 2006; Courchesne & Pierce, 2005). The developmental abnormalities that typify ASD, outlined below, are sources of structural and functional change that generate the clinical phenotype.

Young children with ASD are macrocephalic and macroencephalic, two features which manifest prior to and during the time clinical diagnosis is ascertained. Although controversial, at least one longitudinal study has shown that at birth, head circumferences of ASD children are significantly smaller than those of neurotypical children (Courchesne et al., 2003). However, by 6-14 months of age head circumferences of ASD individuals are significantly larger (Courchesne et al., 2003). Head circumference values are considered an accurate index of brain size, and MRI-based studies reveal that autistic children have significantly increased brain volumes compared to controls (Bartholomeusz et al., 2002; Piven et al., 1996). Brain volumes of autistic children increase the most between the ages of 2 and 4.5 years, whereas cerebellar and cerebral white matter (WM) account for the majority of growth (Courchesne et al., 2001). This macroencephaly does appear to have regional specificity, but volumetric studies are inconsistent in their findings. For example, one study indicated that the greatest increase in WM volume takes place in the frontal lobes, and the least in the occipital lobes (Carper et al., 2002). Still others report that the greatest generalized volume increase occurs in the occipital and parietal lobes (Filipek, 1996; Piven et al., 1996). Brain overgrowth may be related to genetic polymorphisms of select key neurotransmitters (Wassink et al., 2007; Davis et al., 2008; Razanahan et al., 2009)

Brain growth acceleration precedes and is associated with the onset of clinical symptoms, and the specific pattern of growth reflects the severity of ASD diagnosis (Courchesne et al., 2003; Dawson et al., 2007; Dementieva et al., 2005). ASD brain growth trajectories appear to decelerate after the first year of life, plateau during adolescence, and be comparable to controls in adulthood (Redclay & Courchesne, 2005). The functional consequences of abnormal brain development observed in autism explain many of the behavioral characteristics that define the disorder (Cohen, 2007). Although adult brain sizes are comparable between autistic subjects and matched controls, a core neuropathology remains present, and indicates that functional connectivity in different regions is diminished.
MRI-based studies reveal multiple distinguishing neuranatomical features associated with autism, and the foremost of these involves a significant increase in WM volume. While WM makes up less than a third of total cerebral volume, it accounts for 65% of the volume increase reported in the brain tissue of autistic subjects over controls (Herbert et al., 2003). After adjusting for total brain volume, autistic subjects maintain a significantly greater WM volume compared to age-matched controls, which suggests that this WM volume increase is a specific feature associated with autism rather than a reflection of macrocephaly (Bigler et al., 2010; Herbert et al., 2003). When cerebral WM areas were parcellated into an outer zone of radiate WM composed of intrahemispheric corticocortical connections and an inner zone of bridging and sagittal compartments, the outer radiate WM was increased in all cerebral lobes with frontal lobe predominance while the inner zone WM showed no increase in autism (Herbert et al., 2004). Relative reduction in various areas of the corpus callosum is a consistent finding in autism when compared to controls (Hardan et al., 2000; Hardan et al., 2009; Piven et al., 1997). As with findings in overall brain enlargement, WM concentrations are not as large compared to controls in older autistic individuals (Chung et al., 2004; Waiter et al., 2005). The overgrowth of specific WM regions is part of a pathologic process that disrupts the development of normal brain structure and function in autism, although the underlying molecular mechanisms by which this occurs are currently not understood.

Volumetric analyses indicate that abnormalities in multiple cortical and subcortical structures are associated with autism. The limbic system, known for its role in emotion, memory and motivation, is consistently affected. Several studies report reductions in the size of the amygdala and hippocampus in autistic subjects, as well as poorer performance on neuropsychological tasks associated with each structure (Aylward et al., 1999; Herbert et al., 2003; Loveland et al., 2008; Saitoh et al., 2001). Still other studies report that children with autism have larger hippocampi compared to controls, while the amygdala is enlarged in only young autistic children (Schumann et al., 2004). While these limbic structures may be larger in autistic children, they have been found to be smaller in adults when compared to controls (Aylward et al., 1999). Thalamic abnormalities have also been observed, and include increased cell packing density, decreased cell size, and an overall decrease in thalamic volume in autistic individuals (Hardan et al., 2006; Schultz et al., 1999; Tsatsanis et al., 2003). Increased parieto-temporal lobe and cerebellar hemisphere volumes are associated with autism (Brambilla et al., 2003). Overgrowth of the frontal and temporal lobes and amygdala are synchronized with the abnormally accelerated brain growth that occurs between the ages of 2-4 years in autistic children (Carper et al., 2002; Hazlett et al., 2005; Sparks et al., 2002).
While cortical thinning typically occurs with age, this process appears to be accelerated in autistic individuals (Hustler et al., 2007). According to voxel-based MRI analysis, gray matter is reduced in a regionally specific manner and CSF total volume is significantly increased in autistic patients when compared to controls (McAlonan et al., 2005). Other studies report gray matter volumetric increases in specific areas in autism (Rojas et al., 2006). While some MRI studies have produced discordant findings, they reveal a deregulation of brain growth in early childhood in autism, wherein growth trajectories are atypical and regionalized.

The first studies to reveal neuropathological changes in autism were performed in the 1980s by numerous groups (Bauman & Kemper, 1985; Courchesne et al., 1988; Gaffney et al., 1987; Ritvo et al., 1986). Five neuropathological features, in particular, are associated with autistic disorder: increased brain weight and WM volume during childhood, reduced neuronal size and increased cell packing density in the forebrain limbic system, reduced numbers of Purkinje cells in the cerebellum, age-related changes in cell size and numbers in the nucleus of the diagonal band of Broca, deep cerebellar nuclei and inferior olive, and malformations of cerebral cortex and brainstem (Bauman & Kemper, 2005). The most consistent finding across postmortem studies in autism is the significant decrease in cerebellar Purkinje cells when compared to controls (Arin et al., 1991; Bailey et al., 1998; Ritvo et al., 1986). Purkinje cells are also smaller in size in autism compared to age and sex-matched controls (Fatemi et al., 2002). Abnormalities in size and number of neurons in the fastigial, globose and emboliform nuclei have also been shown, and appear to change with age (Bauman & Kemper, 1994). What follows is a summary of the collection of neuropathological features in autism that have been observed by different groups.

Cortical and sub-cortical morphological abnormalities associated with autism primarily involve the limbic system. Histological studies have shown that the hippocampus of autistic individuals has reduced cell size and simplified dendritic branching compared to age-matched controls (Raymond et al., 1996). Evidence of neuronal cell size and packing density in autistic amygdale is contradictory. While some studies report a reduction in neuronal size and increased cell packing densities, others find no significant difference in cell size but do report significantly fewer neurons associated with the amygdalae of autistic patients (Bauman & Kemper, 1990; Schumann & Amaral, 2006). Cell packing density was reportedly increased in the hypothalamus and mamillary body (Bauman & Kemper, 1985). Smaller neurons have been reported in the basal ganglia and cerebellum of 4- to 7-year-old children with autism, specifically in Purkinje cells, the dentate nucleus, amygdala, nucleus accumbens, caudate and putamen, with corrections in size by adulthood.
A generalized reduction in density of axons and dendrites in the autistic brain has also been proposed (Guerin et al., 1996). These studies indicate that a delay of neuronal growth evidenced by cortical dysgenesis, which is brain structure-specific, occurs in autism and undergoes modification during the life span.

Several brainstem and cerebellar morphological abnormalities have been revealed in neuropathological studies on autism. Neurons in the inferior olivary nucleus appear more abundant in autism, but their size varies with age in that they are enlarged in children younger than 12 years old but smaller in adults over 21 when compared to age-matched controls (Anderson et al., 1993; Kemper & Bauman, 2002). The pons, medulla, and midbrain midsagittal areas are all smaller in autistic subjects, and the pons seems to develop more rapidly in autism compared to controls (Hashimoto et al., 1995). As mentioned previously, the cerebellum is the most consistent site of neural abnormality in autism. Alterations in Purkinje cell density and number appears to be more prominent in specific regions (Arin et al., 1991). Hyerplasia and hypoplasia in cerebellar vermal regions is evident (Courchesne et al., 1994). These studies indicate atrophy of the neocerebellar cortex, with regionally specific marked loss of Purkinje cells. It seems possible that some of these changes may be the result of agonal or preagonal changes.

A recent survey of brains collected by the Autism Tissue Program (ATP) (n=35) (Casanova, 2007) reveals that approximately one-third of them (n=11) died of drowning (2 received CPR and survived an indeterminate amount of time). Twenty three of the remaining cases died of diverse causes involving hypoxia, e.g., seizures, circulatory failure, sepsis, anoxic encephalopathy, etc. It is likely that either hypoxia or hypoxia-reperfusion injury could account for cell loss in selectively vulnerable populations (e.g., Purkinje cells) or for neuroinflammatory changes. In effect, some of the neuroinflammatory findings (e.g., predominant white matter gliosis) reported in autistic subjects (Vargas et al., 2005) are similar to those reported for delayed death after suffocation or near drowning (Oehmichen et al., 2006). These changes may therefore reflect the way patients died rather than core pathology to autism.

Neocortical minicolumns, the basic architectonic and functional units of the human brain that organize neurons in cortical space, are smaller, more numerous, and less compact in autistic patients compared to controls (Buxhoeveden & Casanova, 2002; Casanova et al., 2002; Casanova et al., 2006). While this minicolumnar pathology has been observed bilaterally in Brodmann cortical areas 3, 4, 9, 17, 21 and 22, the narrowest minicolumns are found in the dorsolateral prefrontal cortex of autistic subjects (Casanova & Trippe, 2009; Casanova et al., 2006). Reduction in size of neocortical
neurons and their nuclei is likely an indicator of reduced or impaired functional connectivity between distant cortical regions with a bias toward local rather than global information processing (Casanova et al., 2006; Just et al., 2004; Koshino et al., 2005). Reductions in corpus callosum and gyral window size confirm that a constrained cortical network of connections exists, which favors short-range corticocortical fibers at the expense of long-range commissural fibers (Casanova et al., 2009). Malformations of cortical development have been observed in disorders caused by abnormalities of cell proliferation, apoptosis, cell migration, cortical organization and axon pathfinding (Hevner, 2007). Thus, the minicolumnar abnormalities seen in autistic individuals suggest that the cause of the underlying pathology likely occurs during fetal or very early postnatal development.

Studies of clinicopathological correlations in autism reveal a link between several domains of functional deficits and primary neuropathology. One of the core features of ASD symptomatology involves deficient verbal abilities related to the understanding of semantics and social pragmatics (Wetherby et al., 1998). Studies of language-related neocortex reveal reduced neuronal density in Wernicke’s area (BA 22) and gyrus angularis (BA 39) and increased glial cell density in both of these regions as well as in Broca’s area (BA 44) in autistic subjects when compared to controls (Lopez-Hurtado & Prieto, 2008). Investigators hypothesize that structural alterations in language-related cortical areas contributes to the communication impairment in autism.

Another core feature of ASD behavior includes abnormalities in social reciprocity, eye contact, and facial expression. It has been established that patients with autism have deficits in face processing, perception and recognition (Grelotti et al., 2001; Joseph & Tanaka, 2003). Functional magnetic resonance imaging (fMRI) studies have shown that the fusiform gyrus, which is involved in face-processing, is hypoactive in autistic patients (Pierce et al., 2004). It is believed that this hypoactivation is associated with the failure of autistic subjects to make direct eye contact (Dalton et al., 2005). Neuropathological studies reveal reduced neuronal number and volume in the fusiform gyrus and suggest that an underdevelopment of connections between primary visual cortex (BA 17) and the fusiform gyrus may contribute to abnormal face perception in autism (van Kooten et al., 2008).

Impairments in gross and fine motor function as well repetitive and stereotyped behaviors are common findings in patients with autism. It has been proposed that sensorimotor deficits may be associated with pathological changes in the basal ganglia and cerebellum (Bailey et al., 1998; Sears
A positive correlation between caudate volume and repetitive behavior scores has been reported in autism (Hollander et al., 2005). Cerebellar findings including a decrease in the number of GABAergic Purkinje cells and increased feed-forward inhibition from basket cells indicate altered inhibition of cerebellar nuclei which could directly affect cerebellocortical output and lead to changes in motor behavior and cognition (Arin et al., 1991; Yip et al., 2008).

A particular range of cognitive deficits in autism demonstrate that performance IQ is generally higher than verbal IQ and that comprehension is usually low on intelligence tests (Siegel et al., 1996). These cognitive deficits are likely related to abnormalities in the memory and limbic systems. Size reductions in the hippocampal formation and amygdala in autism have been reported, as well as reduced complexity of dendritic arbors in the hippocampus (Aylward et al., 1999; Bauman & Kemper, 1985). The anterior cingulate gyrus is reduced in volume and positron emission tomography (PET) activity in subjects with autism is decreased (Haznedar et al., 1997). The caudate nucleus is involved in learning, short- and long-term memory, planning and problem solving, thus observed caudate volume changes in autistic children may also explain cognitive deficits that typify autism (Fuh & Wang, 1995; Poldrack et al., 1999; Schmidtke et al., 2002).

Neuroanatomical and neuropathological studies have revealed an atypical pattern of development in ASD. The brains of autistic subjects are generally larger during the onset of clinical symptoms when compared to controls, where WM contributes disproportionately to brain volume enlargement in a regionally specific manner. Developmental heterochronicity is a defining feature of ASD, however inconsistencies in findings make cross-study comparison difficult. Multiple factors account for these inconsistencies, most notably among them conflicting subject diagnostic and exclusionary criteria. Statistical problems also exist in data collection, due to small sample size, confounding factors such as comorbidity with other disorders, IQ, postmortem interval, cause of death and medication history. While discordant findings exist, it is clear that characteristic neuropathologies are associated with the core symptoms of ASD. Image analysis can be used to distinguish subjects with autistic disorder, Asperger’s syndrome or PDD-NOS from controls, which may yield significant diagnostic applications (Akshoomoff et al., 2004; El-Baz et al., 2007). Generalized processing abnormalities related to a constrained neural network underlie the observed and defining behaviors found in ASD and lead to the idea of autism as a neural information processing disorder (Gustafsson, 1997; Happe et al., 2001; Herbert, 2005). Precisely how these neurobiological abnormalities relate to the behavioral phenotype is currently under investigation. Taken together, these findings suggest that while abnormalities seen in the brains of autistic
individuals represent an ongoing neuropathology that continues to change through adulthood, this process has a neurodevelopmental component that may be prenatal in origin.
References


