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BRAIN RESEARCH

Research Report

Brain growth across the life span in autism: Age-specific changes in anatomical pathology

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ARTICLE INFO

Article history:
Accepted 25 September 2010
Available online 1 October 2010

Keywords:
Autism
Overgrowth
Magnetic resonance imaging
Development
Degeneration

ABSTRACT

Autism is marked by overgrowth of the brain at the earliest ages but not at older ages when decreases in structural volumes and neuron numbers are observed instead. This has led to the theory of age-specific anatomic abnormalities in autism. Here we report age-related changes in brain size in autistic and typical subjects from 12 months to 50 years of age based on analyses of 586 longitudinal and cross-sectional MRI scans. This dataset is several times larger than the largest autism study to date. Results demonstrate early brain overgrowth during infancy and the toddler years in autistic boys and girls, followed by an accelerated rate of decline in size and perhaps degeneration from adolescence to late middle age in this disorder. We theorize that underlying these age-specific changes in anatomic abnormalities in autism, there may also be age-specific changes in gene expression, molecular, synaptic, cellular, and circuit abnormalities. A peak age for detecting and studying the earliest fundamental biological underpinnings of autism is prenatal life and the first three postnatal years. Studies of the older autistic brain may not address original causes but are essential to discovering how best to help the older aging autistic person. Lastly, the theory of age-specific anatomic abnormalities in autism has broad implications for a wide range of work on the disorder including the design, validation, and interpretation of animal model, lymphocyte gene expression, brain gene expression, and genotype/CNV-anatomic phenotype studies.

1. Introduction

Recent research has led to the theory of age-specific anatomic abnormalities in autism (Courchesne et al., 2001, 2007; Courchesne and Pierce, 2005) (see Fig. 1). At early ages, there is abnormal overgrowth of the brain in autism, but during adolescence and young adulthood, there may be abnormal decline and possible degeneration (Fig. 1). Because early abnormal overgrowth occurs at the time of the first detectable behavioral and clinical signs of autism (Pierce et al. 2009; Pierce, in review) (Table 1), neural defects that cause overgrowth may be the neural bases of autism.

This theory was originally based on evidence from four studies in the early 2000s. First, in an MRI study, Courchesne et al. (2001) reported evidence of an unusual brain growth trajectory in autism. They discovered abnormal brain and cerebrum enlargement in autistic 2- to 4-year olds, but also observed slightly smaller overall brain volumes in autistic 12 to 16 year olds (Fig. 2). Subsequent studies also reported brain or cerebral overgrowth in autistic 2- to 4-year olds (Carper et al.

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doi:10.1016/j.brainres.2010.09.101

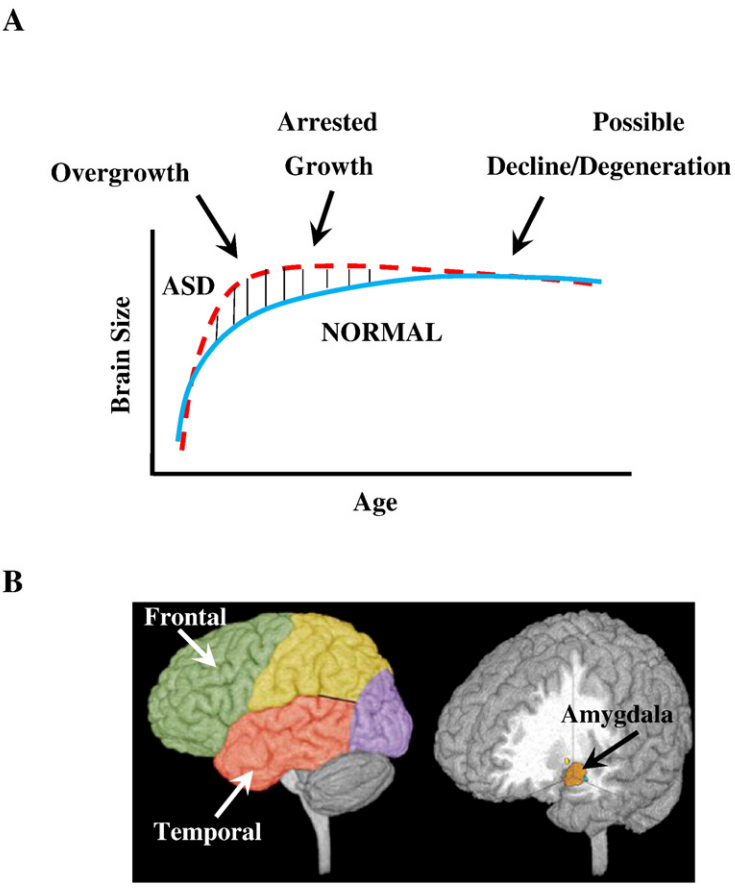

Fig. 1 – Three phases of growth pathology in autism. (A) Model of early brain overgrowth in autism that is followed by arrest of growth. Red line represents ASD, while blue line represents age-matched typically developing individuals. In some regions and individuals, the arrest of growth may be followed by degeneration, indicated by the red dashes that slope slightly downward. (B) Sites of regional overgrowth in ASD include frontal and temporal cortices and amygdala (from Courchesne et al., 2007).

2002; Sparks et al., 2002; Hazlett et al., 2005; Bloss and Courchesne 2007; Schumann et al. 2010), while autistic adolescents and adults have been reported to display cortical atrophy (Hadjikhani et al., 2006) and reduction in amaygdala (Aylward et al., 1999; Pierce et al., 2004) and frontal cortex volumes (Kosaka et al., 2010) (reviews: Amaral et al., 2008; Courchesne et al., in press). Moreover, meta-analyses of MRI brain volume in the autism literature (Redcay and Courchesne, 2005; Stanfield et al., 2008) and postmortem autistic brain weight (Redcay and Courchesne, 2005) also confirm early brain overgrowth in autism by 2 to 6 years of age.

Table 1 – Red flags of autism spectrum disorder by 1 to 2 years of age.

Reduced social interest and affect
Lack of warm, joyful emotional expressions
Lack of sharing emotional enjoyment or interest
Lack of response to name
Lack of showing and interacting
Abnormal language development
Lack of coordination of gaze, facial expression, gesture, and sound during interactions

Second, based on analyses of head circumference (HC), it was discovered that this abnormal brain enlargement is not present at birth in most cases but instead begins during the

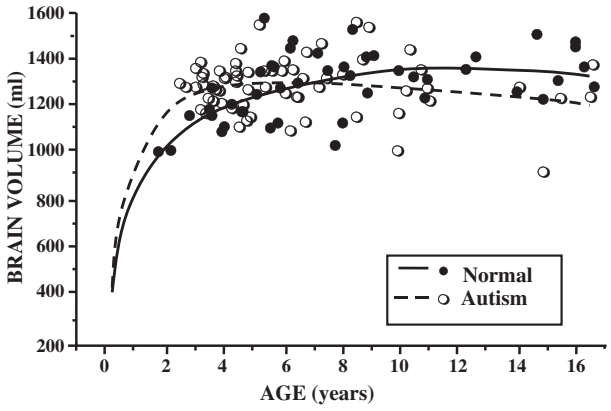

Fig. 2 – Brain growth in autism through 16 years. Data plot shows larger MRI-based volumes in autistic 2- to 4-year-old males as compared to normal 2- to 4-year-old males and smaller overall brain volumes in autistic 8–16 year olds as compared to normal (from Courchesne et al. 2001).