Delayed Development of the Claustrum in Autism

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AUTISM CLINICAL DIAGNOSIS AND PREVALENCE

Autism is a severe developmental disorder that is characterized by:

- qualitative impairments in reciprocal social interactions,
- qualitative impairments in verbal and nonverbal communication,
- restricted repetitive and stereotyped patterns of behavior, interests and activities, and
- onset prior to the age of 3 years (American Psychiatric Association, 2000).

The 2008 study of 8.4 percent of the US population of 8-year-old children reported a 1 in 88 overall prevalence of autism spectrum disorder (ASD), with a 1 in 54 prevalence for males and a 1 in 252 prevalence for females (male to female ratio of 4.7:1) (US Department of Health and Human Services, 2012). Of children diagnosed with ASD, 38 percent...
are classified as having intellectual disability, having an IQ of less than 70, and 24 percent were in the borderline range with an IQ of 71–85. Approximately 33 percent of individuals with autism are diagnosed with epilepsy (Tuchman and Rapin, 2002).

AUTISM NEUROPATHOLOGY

The clinical understanding of autism is based on the examination of thousands of patients, but post-mortem neuropathological studies have only been undertaken on a small number of brains. Between 1980 and 2003 only 58 brains were examined (Palmen et al., 2004). Recent studies expanded this number by more than 30 subjects with idiopathic autism (Casanova et al., 2006; Courchesne et al., 2011; Jacot-Descombes et al., 2012; Santos et al., 2011; Schuman and Amaral, 2006, Van Kooten et al., 2008; Wegiel et al., 2010, 2012; Whitney et al., 2008, 2009; Yip et al., 2007, 2008) and 10 with autism associated with duplications 15q11.2-q13 (Wegiel et al., 2012). However, morphological markers and neuropathological diagnostic criteria of autism are not established. The concept that autism is associated with neuropathological changes was explored in the first studies reported between 1980 and 1989 (Damasio et al., 1980; Bauman and Kemper, 1985; Ritvo E.R. et al., 1986; Courchesne et al., 1987; Gaffney et al., 1987; Hashimoto et al., 1989; Murakami et al., 1989). This view was expanded by detection of global markers of abnormal brain development, including accelerated brain growth in the first year of life (Courchesne et al., 2003), a slower rate of brain growth between 2 and 4 years of age (Carper et al., 2002; Courchesne et al., 2001), and the link between an altered trajectory of brain development and severity of autism (Courchesne et al., 2003). Overgrowth of the frontal and temporal lobes and the amygdala, which are involved in cognitive, social and emotional functions, and language development, suggests contribution of these developmental alterations to the clinical features of autism (Carper et al., 2002, Courchesne et al., 2001, Sparks et al., 2002).

The diversity of neuropathological findings corresponds to developmental impairments in many interacting brain networks and to an expansion of autism pathology from “local” abnormalities to global defects of the cognitive system. Localizing models are still the main tools for identification of pathological changes as a component of the networks of structural and functional abnormalities (Müller, 2007).

CLAUSTRUM CONNECTIVITY

In 2005 Crick and Koch proposed the claustrum as the ideal candidate for the brain’s “consciousness” center because it acts like a conductor in an
Orchestra to integrate information from various modalities. The claustrum has extensive reciprocal connections to and from almost all brain regions (Fernández-Miranda et al., 2008). The information from the various brain regions is segmented topographically in the claustrum in a partially overlapping manner. The anterior claustrum projects to and receives signals from the frontal cortex. The middle claustrum is associated with the parietal cortex. The posterior/inferior claustrum is associated with the temporal and occipital cortices. The dorsal claustrum forms a visual loop with Brodmann area (BA) 17 (Fernández-Miranda et al., 2008, Mory et al., 1993, Pearson et al., 1982). The claustrum also projects to the amygdala (Amaral and Insausti, 1992), the hippocampus (Amaral and Cowan, 1980), and the striatum (Arikuni and Kubota, 1985, Crick and Koch, 2005). Social brain circuitry (orbitofrontal cortex, superior temporal gyrus and amygdala) (Brothers et al., 1990) projects to the claustrum and receives claustral connections (Fernández-Miranda et al., 2008).

**CLAUSTRUM FUNCTIONING IN NORMAL AND PATHOLOGICAL CONDITIONS**

The claustrum is involved in:

- high-order cognitive functions such as fear recognition (Stein et al., 2007),
- experiential dread (Berns et al., 2006),
- cognitive impairment (Dubroff et al., 2008),
- memory storage (Mory et al., 1996),
- associative learning (Chachich and Powell, 2004),
- repetitive behaviors and addiction (Mory et al., 1996; Naqvi et al., 2007),
- multimodal processing of olfactory, auditory, visual, and tactile information, and of emotional and behavioral responses (Bennet and Baird, 2006),
- suppression of natural urges (Lerner et al., 2009),
- seizures (Zhang et al., 2001) and
- psychoses (Sperner et al., 1996).

Almost all of these functions are modified in autistic subjects and all of these alterations are present in autism.

The claustrum receives inputs from many cortical areas, integrates multiple inputs into a new signal, and redirects sensory information throughout the striatum and thalamus. Interconnectivity with subcortical nuclei and sensory cortical areas indicates the claustrum’s involvement in sensorimotor integration, and potentially in the most complex human brain function – consciousness – as well as in higher orders of functionality that enable the organism to adapt rapidly to the changing environment.
(Edelstein and Denaro, 2004). The attraction to routines and sameness appears to be one of the very striking behavioral alterations characteristic of autism. It appears that claustrum immaturity, reflected in the neuronal soma deficit of 29 percent in children and of 17 percent in adults, and the very striking deficit of neuronal nucleus volume (42% and 22% respectively), may be responsible for the claustrum neurons’ functional impairment and deficits in adaptability and consciousness.

VARIATIONS IN THE CLAUSTRUM ASSOCIATED WITH AUTISM

Clastral Volume

The claustrum is a thin ribbon of gray matter located between the insular cortex and the striatum, closely associated with the amygdale, and built of five types of cells of both cortical and subcortical origin. The vast majority of neurons in the claustrum (94%) have numerous coarse pigment granules, long projections and spiny dendrites (Braak and Braak, 1982).

Our study compared the brain hemispheres of autistic and control subjects aged from 4 to 36 years (nine hemispheres in each group). The mean claustral volume of those with autism in the subgroup whose ages ranged from 4 to 8 years (388 mm$^3$) was 22 percent less than in the control subjects (494 mm$^3$). In the older subgroup, the volume of the claustrum in the autistic subjects increased by 18% (to 472 mm$^3$), which was insignificantly more than in age-matched controls (452 mm$^3$).

This observation is consistent with MRI studies of 16 high-functioning (IQ 85) autistic and 14 control males ranging from 7 to 12 years of age, which revealed that those with autism had a smaller claustral volume (555 mm$^3$) than the control subjects (701 mm$^3$) (Davies, 2008). The smaller volumes detected in post-mortem study in comparison to clinical MRI are the result of brain tissue shrinkage during dehydration.

NUMBER OF NEURONS IN THE CLAUSTRUM

The mean numerical density of neurons was almost identical in the autistic (29,156/mm$^3$; $n = 9$) and control subjects (29,260/mm$^3$; $n = 9$). The mean total number of neurons in the nine autistic subjects (12.5 million) was insignificantly less (by 8%) than in the control subjects (13.6 million). Brain region-specific modifications in the number of neurons reveal a 67 percent increase in the number of neurons in the prefrontal cortex (Courchesne et al., 2011), and a 53 percent increase in the ratio between von Economo neurons (mirror neurons) and pyramidal neurons in the
fronto-insular cortex (Santos et al., 2011), but a reduced number of neurons in the fusiform gyrus involved in face recognition (Van Kooten et al., 2008), a regional decrease of the number of Purkinje cells (Fatemi et al., 2002, Lee et al., 2002, Whitney et al., 2008), and most likely prenatal loss of Purkinje cells (Whitney et al., 2008, 2009). Striking differences between the almost normal number of neurons in the claustrum overall and the reported changes in the number of neurons in cortical projection areas may reflect desynchronized development of structures contributing to a broad spectrum of clinical manifestations of autism.

Mean Neuronal Volume

The mean volume of the neuronal body in the 4- to 8-year-old autistic children was 29 percent less (1,410 μm³, n = 4) than in the control group (1,999 μm³, n = 4; P < 0.001); however, in 13- to 36-year-old autistic subjects it was only 17 percent less (1,582 μm³; n = 5) than in the controls (1,904 μm³; n = 5; P < 0.001).

In the 4- to 8-year-old autistic children the mean volume of the neuronal nucleus (234 μm³, n = 4), was 42 percent less than in the control group (400 μm³, n = 4; P < 0.001) whereas, in 13- to 36-year-old autistic subjects, it was 22% less (266 μm³) than in the control group (342 μm³). The initial, very severe, volume deficit in the younger group with autism, and the reduction of this deficit (by 38% in the cell soma volume and by 48% in the neuronal nucleus volume) in the subjects who were more than 8 years old, suggest delay of neuron growth in the younger group and abnormal acceleration in late childhood. The volume deficit in the youngest children indicates altered regulation of neuron growth before the age of 4 years, resulting in lifelong structural and functional abnormalities.

Desynchronized Development of Claustral Circuitry

The study of 16 brain subdivisions in 14 autistic and 14 control subjects revealed: (a) brain-structure-specific delay in the rate of neuronal growth and (b) desynchronization of neuronal growth in the brains of autistic subjects. Desynchronization is reflected in striking differences of neuronal volume deficit in early childhood, including a very severe (>30%) deficit in the nucleus accumbens and Purkinje cells; severe deficit (20% to 30%) in the claustrum, thalamus, caudate nucleus, globus pallidus, dentate nucleus, entorhinal cortex, amygdala, magnocellular basal complex (including in the nucleus basalis of Meynert and the Ammons horn); moderate deficit (10% to 20%) in the putamen, inferior olive and magnocellular lateral geniculate body (LGB); and mild deficit (4% to 5%) in the parvocellular LGB and substantia nigra (P < 0.001). The function of the examined structures suggests that delayed and desynchronized development of the
affected networks contributes to all three diagnostic domains of autism, including disrupted social and communication development, restricted repetitive and stereotyped patterns of behavior, and intellectual deficits. The conspicuous differences in the developmental volume deficits of neurons in the claustrum, and in brain structures receiving projections from the claustrum and projecting to the claustrum, that were detected in 4- to 8-year-old autistic children are signs of desynchronization of claustral-circuit development. The detected pattern of developmental delays suggests that a number of physiologic processes that collectively ensure the maintenance of undisturbed contact with the environment are altered in early childhood and that the claustrum is one of the most severely modified brain structures in early and late childhood (Wegiel et al., submitted).

Executive functions, cognitive processes that allow complex goal-directed behavior including spatial working memory and response inhibition, are impaired in autism (Minshew et al., 1999; Hill, 2004; Ozonoff et al., 2004).

Altered Claustrum Connectivity in Autism

The very noticeable range of developmental delays in the claustral neurons, and in the neurons receiving projections from the claustrum and projecting to the claustrum, suggest that claustral dysfunction is associated with or caused by a desynchronized development of the subcomponents of these multifunctional networks.

The claustrum is involved in long-term response potentiation within the claustral-entorhinal-hippocampal system (Wilhite et al., 1986) and neuronal volume deficits of 29%, 23% and 4%, respectively, are found in these three compartments in people with autism (Wegiel et al., submitted). The frontal, temporal, parietal and occipital cortex project to the claustrum (Druga, 1968; LeVay and Sherk, 1981), whereas the dorsocaudal claustrum (visual claustrum) projects to the visual cortex. The slight reduction of neuronal volume in BA17 in the occipital cortex (Casanova et al., 2006) and a significant reduction in the mean perikaryal volume of the neurons in layers V and VI (by 21.1% and 13.4%, respectively) in the fusiform gyrus (Van Kooten et al., 2008) are indicative of desynchronized development of the claustrocortical networks in autism. It may affect the role of the claustrum as an integrator of input from the somatosensory, auditory and visual cortices, as well as from the respective diencephalic relays (Spector, 1969). The 12% and 5% deficits in the neuronal volume of the magnocellular and parvocellular lateral geniculate nuclei, respectively, and the 27% deficit in neuronal volume in the thalamus (Wegiel et al., submitted) indicate developmental desynchronization of other claustrum-related regions. The rostral portion of the claustrum projects to the caudate nucleus (Arikuni and Kubota, 1985), which is also affected by a 16% deficit in neuronal volume (Wegiel et al., submitted).
THEORIES OF AUTISM AND THE ROLE OF THE CLAUSTRUM IN AUTISM

Functional MRI and post-mortem studies are the foundation for several theories of autism, including a theory of a deficit of long-range connectivity but increased short-range connectivity, disrupted cortical synchronization (Belmonte et al., 2004; Courchesne et al., 2004; Frith, 2004; Hughes, 2007; Rippon et al., 2007), and a defective theory of mind (Baron-Cohen et al., 1985, 1999; Frith, 2001; Frith et al., 1994; Kobayashi et al., 2007).

The hypothesis of a deficit of long-range connectivity is based on detection of modified activity between distant, but functionally and anatomically related, cortical regions (Anderson et al., 2011; Cherkassky et al., 2006; Coben et al., 2008; Dinstein et al., 2011; Just et al., 2007; Kennedy and Courchesne, 2008). Regional increase of the white-matter volume suggests an increase in local short-range connections (Herbert et al., 2003, 2004). The theory of “a developmental disconnection syndrome” (Courchesne and Pierce, 2005; Frith, 2004) is supported by new data indicating a failure of development of connections rather than loss of connection (Geschwind and Levitt, 2007). Concentration of functional MRI studies on the cortex supports a corticocentric theory of autism, but the complexity of the autistic phenotype suggests involvement of the subcortical structures, including the claustrum, interacting with such subcortical subdivisions as the amygdala, which is involved in processing social information, emotional interpretation, fear and anxiety (Amaral et al., 2003; Baron-Cohen et al., 2000; Winston et al., 2002); the thalamus, involved in language functions, attention, and anxiety (Ojemann, 1977; Ojemann and Ward, 1971); and the striatum, involved in repetitive motor behaviors and rituals (Day and Carelli, 2007; Salamone, 1994; Sears et al., 1999). The detected deficits of neuronal growth in 16 subcortical structures, including claustrum, expand the corticocentric model of developmental alterations in autism and support a model of global developmental encephalopathy characterized by delayed and desynchronized development of neurons in interacting structures of the cortex and subcortex (Wegiel et al., submitted).

References


8. DELAYED DEVELOPMENT OF THE CLAUSRUM IN AUTISM


