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An MRI and proton spectroscopy study of the thalamus in children with autism

Antonio Y. Hardan[a,*], Nancy J. Minshew[b], Nadine M. Melhem[b], Sumana Srihari[b], Booil Jo[a], Rahul Bansal[c], Matcheri S. Keshavan[c], Jeffrey A. Stanley[c]

[a]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA
[b]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh, PA, USA
[c]Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, USA

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Abstract

Thalamic alterations have been reported in autism, but the relationships between these abnormalities and clinical symptoms, specifically sensory features, have not been elucidated. The goal of this investigation is to combine two neuroimaging methods to examine further the pathophysiology of thalamic anomalies in autism and to identify any association with sensory deficits. Structural MRI and multi-voxel, short echo-time proton magnetic resonance spectroscopy (^{1}H MRS) measurements were collected from 18 male children with autism and 16 healthy children. Anatomical measurements of thalamic nuclei and absolute concentration levels of key ^{1}H MRS metabolites were obtained. Sensory abnormalities were assessed using a sensory profile questionnaire. Lower levels of *N*-acetylaspartate (NAA), phosphocreatine and creatine, and choline-containing metabolites were observed on the left side in the autism group compared with controls. No differences in thalamic volumes were observed between the two groups. Relationships, although limited, were observed between measures of sensory abnormalities and ^{1}H MRS metabolites. Findings from this study support the role of the thalamus in the pathophysiology of autism and more specifically in the sensory abnormalities observed in this disorder. Further investigations of this structure are warranted, since it plays an important role in information processing as part of the cortico–thalamo–cortical pathways.

Keywords: Sensory profile questionnaire (SPQ); Sensory abnormalities; *N*-Acetylaspartate (NAA)

1. Introduction

Autism is a pervasive developmental disorder characterized by impairment in the development of reciprocal social interactions and communication abilities, and the presence of stereotyped/repetitive behaviors (APA, 2000). In addition to these core deficits, abnormalities in the motor and sensory domains have also been reported. While not necessary to make the diagnosis, these features are clinically important because of their impact on function and quality of life. This is particularly true for the sensory disturbances, where recent evidence pointed to their usefulness in distinguishing autism from mental

* Corresponding author. 401 Quarry Road, Stanford, CA 94305. Tel.: +1 650 724 8919; fax: +1 650 724 7389.
E-mail address: hardanay@stanford.edu (A.Y. Hardan).

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retardation in very young children with pervasive developmental disorders (Gillberg et al., 1990). However, a limited number of studies have focused on the neurobiological basis of these deficits, and further investigations of their pathophysiology are needed if more effective therapeutic strategies are to be developed.

Sensory abnormalities in autism were initially reported by Kanner (1943) in 7 of his 11 original cases, when he described children who were experiencing fascination with visual stimuli and hypersensitivity to noise. Recent work has focused on examining the characteristics of these alterations by assessing their frequency and course in patient populations with different age ranges and variable level of illness severity. These features appear to be common, with a reported prevalence rate ranging from 30% to 88% and even 100% (Kientz and Dunn, 1997; Dawson and Watling, 2000). Sensory abnormalities are also quite diverse, with 39% of individuals with autism exhibiting a hypo-responsive pattern, 19% experiencing a hyper-responsive pattern and 36% displaying a mixed response (Greenspan and Wieder, 1997). Interestingly, the consistency of these patterns over time in the same individuals has been questioned with evidence of variability with age (Cesaroni and Garber, 1991). However, the most critical and informative characteristics appear to be related to the relationship between these sensory abnormalities and the core symptoms. Some investigators have reported on links between sensory features and different aspects of social development, such as joint attention (Dahlgren and Gillberg, 1989; Baranek, 1999). Others have suggested a relationship between auditory abnormalities and the development of language and communication (Rapin, 1997; Dawson et al., 1989). In contrast, other studies have associated sensory anomalies and rigidity/repetitive behaviors, and suggested that both types of symptoms might share common pathophysiologic pathways driven by chronic hypo- or hyper-arousal (Rogers and Ozonoff, 2005).

The neural basis of sensory processing has been investigated in animal models and more recently in humans with the advent of non-invasive magnetic resonance technologies. Sensory-specific areas have been described with, for example, specialized brain regions in the occipital cortex, the superior temporal gyrus, and the post-central gyrus responsible for processing visual, auditory and tactile information, respectively. However, this regional specialization becomes more difficult to delineate with the processing of multisensory information such as examining a visual stimulus when it is accompanied with a tactile or auditory stimulus. Such complex events are initially processed in sensory-specific areas and later on by common multisensory representations in association cortices such as the ventral intraparietal areas (Duhamel et al., 1998) and posterior temporal cortex (both tactile and visual stimulation) (Macaluso and Driver, 2001). While several brain regions are variably involved in simple and complex sensory information, virtually all sensory systems pass through the thalamus, which is reciprocally connected through projections to the cerebral cortex. An additional crucial attribute of the thalamus is that it appears to be much more than a key-link in this process since it actively filters the flow of information to the cortex. These characteristics have prompted several investigators in the field of autism, using different methodologies including imaging techniques, to link sensory abnormalities observed in this disorder to the thalamus, but no direct evidence supporting this association has, to date, been reported (Baranek, 2002; Tsatsanis et al., 2003; Hardan et al., 2006).

The focus on the thalamus in the neuroimaging literature has recently increased. Studies investigating the structural and functional integrity of the thalamus in autism have been reported. Two recent morphometric studies in individuals with autism have observed an abnormal relationship between total brain size and thalamic volumes in patients, in the absence of volumetric differences between autistic and control subjects (Tsatsanis et al., 2003; Hardan et al., 2006). An MRI and ^{1}H spectroscopy study of the thalamus examined a sample of 32 children with autism and 15 controls (Perich-Alsina et al., 2002). No structural differences were found between the two groups, but *N*-Acetylaspartate(NAA)/phosphocreatine plus creatine (PCr+Cr) ratios, a marker of functioning neuroaxonal tissue (Birken and Oldendorf, 1989; Pouwels et al., 1999), were found to be decreased in the oldest patient subgroup (8–13 years). Additional evidence implicating the thalamus in the pathophysiology of autism comes from a positron emission tomography (PET) study examining a sample of 17 adolescents and adults with autism and 17 healthy matched controls while subjects were performing a serial verbal learning task. No volumetric alterations in the thalamus were observed between the two groups, but lower relative glucose metabolic rates were found in the thalamus and other brain regions in patients with autism spectrum disorders compared with controls (Haznedar et al., 2006).

While the above investigations provide evidence of abnormalities in the thalamus in autism, they offer little support to the link between this structure and the clinical manifestations of autism, particularly the sensory abnormalities. Therefore, we conducted this investigation