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The Role of Thalamocortical Networks in the Symptomatology of Autism Spectrum Disorders

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The Role of Thalamocortical Networks in the Symptomatology of Autism Spectrum Disorders

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor in Philosophy

in

Clinical Psychology

by

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The Dissertation of Aarti Nair is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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ABSTRACT OF THE DISSERTATION

The Role of Thalamocortical Networks in the Symptomatology of Autism Spectrum Disorders

by

Aarti Nair

Doctor in Philosophy in Clinical Psychology

University of California, San Diego, 2015

San Diego State University, 2015

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Rationale: The present dissertation project specifically sought to understand brain networks connecting with the thalamus, an important subcortical relay structure through which almost all sensory information is routed. In view of the known fundamental importance of thalamocortical connectivity for the development of regional functional specialization in cerebral cortex, it is surprising how little firm knowledge is available about the thalamus and its connections with cortex in Autism Spectrum Disorders (ASD). Therefore, it is crucial to examine the role of the thalamus in regulating these functions for an improved understanding of neurodevelopmental mechanisms associated with ASD.

Design: The first study of this project examined functional and anatomical connectivity between five broad cortical regions of interests (ROIs; e.g., temporal lobes) and the thalamus for a sample of children and adolescents with ASD (N=26) compared to TD controls (N=27). This first study allowed us to broadly characterize the connectivity between ipsilateral thalamus and the different lobes. In the second study, we delved deeper into the specificity of connections between more narrowly specialized regions (e.g., fusiform gyrus or anterior temporal pole) and the thalamus for a larger sample of children and adolescents with ASD (N=37) compared to TD controls (N=38).

Results: In the first study, we found evidence of both anatomical and functional underconnectivity between the prefrontal, parietal-occipital, motor, and somatosensory cortices with ipsilateral thalamus. The only exception was functional connectivity with the temporal lobe, which was increased in the ASD group, especially in the right hemisphere. Delving deeper into the specificity of these connections in the second study, we found that functional connectivity was atypically reduced in the ASD group for supramodal association cortices involved in higher-order cognition (e.g., language, face processing), but was increased for sensorimotor and limbic regions (e.g., auditory cortex).

Discussions: Our findings provide evidence of regionally specific aberrations of thalamic connectivity in frontal and temporal lobes, with additional involvement of some parieto-occipital ROIs. These findings could be related to comparatively early maturation of limbic and sensorimotor regions in the context of early overgrowth in ASD, at the expense of thalamocortical connectivity with later maturing cortical regions.

INTRODUCTION

The thalamus is a complex brain structure that has been described as the "gateway" to the cortex. It serves as a "relay station" through which all sensory information is routed and, as such, plays an important role in shaping what people see, hear, and feel. Various lines of evidence have mapped the presence of functionally specialized regions within the thalamus based on their connectivity with the cortex. By virtue of its extensive connectivity with the cortex, the thalamus has been implicated in numerous cognitive processes such as sensorimotor function, attention, and multimodal cognition. Thalamic insult or dysfunction has been linked to several clinical conditions. The current dissertation project aims to examine the role of the thalamocortical (TC) networks in the symptomatology of Autism Spectrum Disorders (ASD), which is a highly prevalent neurodevelopmental disorder involving deficits in social cognition, communication, and sensorimotor function (DSM-IV-TR, 2000).

Organization of the thalamus

Traditionally, the thalamus has been divided into three parts: epithalamus, ventral thalamus, and dorsal thalamus (Walker, 1938; Jones, 1985). According to these authors, the epithalamus comprises the anterior and posterior paraventricular nuclei, as well as the habenular nuclei. It appears to have more connections with the hypothalamus compared to the cerebral cortex. The epithalamus does not send or receive fibers to the cerebral cortex (Castro-Alamancos and Connors, 1997). However, there is some increasing evidence that the paraventricular nuclei have axons that ascend to the cerebral cortex, despite its chemical signature being similar to the remainder of the epithalamus (Jones, 2007). The ventral thalamus comprises the reticular nucleus and

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the ventral lateral geniculate nucleus, and receives fibers from the cerebral cortex but send no fibers to it in return (Sherman, 2001).

The cortical and thalamic afferents to the reticular nucleus are mostly excitatory, and the axons that go back from the reticular nucleus to the thalamus are inhibitory (Jones, 1985). The dorsal thalamus is the largest part of this division of the thalamus. It is most closely related to the development of the cerebral cortex in its size and complexity (Sherman, 2001). It sends fibers to, and receives fibers from the cerebral cortex and to a lesser extent the striatum (Jones, 2007). The dorsal thalamic nucleus is differentiated into two groups – allothalamus and isothalamus; with the allothalamic region further divided into the intralaminar nuclei - which projects to the striatum and cortex, the non-intralaminar nuclei - which projects only to the cortex, and the paraventricular region that receives afferents from the amygdala (Herrero *et al.*, 2002). Additionally the dorsal thalamus is also connected with the amygdala, hippocampus, and basal ganglia (Jones, 1985). Some of the connections appear to be more diffuse, but most axonal projections between the dorsal thalamus and the cortex are constrained by cytoarchitectonic borders in the cortex (Jones *et al.*, 1976, Hendrickson *et al.*, 1978).

In recent years, with the availability of more sensitive connection-mapping techniques, these basic subdivisions of the thalamus have been revised. Instead, it has become more popular to perceive thalamic subdivisions based on their projections to and from specific regions of the cortex (Figure 1). These projections are largely constrained to the dorsal thalamic nucleus, relaying through the ventral reticular nucleus (Sherman, 2001). A structural classification of the thalamus is based on the termination of its projections in layers of the cortex, arising from animal models (Herkenham *et al.*, 1986). According to this classification, the thalamic nuclei can be divided into three groups based on main layers of termination. The first group comprises the specific

nuclei, with cortical projections terminating in layers IV, lower layer III, and less dense projections in upper layer VI. The second group is the non-specific deep-layer projecting nuclei, also known as intralaminar nuclei, with cortical projections terminating in layers V, VI, and I. The third group is the non-specific projecting nuclei or paralaminar nuclei, with cortical projections terminating in layer I. Another structural classification of the thalamus is based on projection patterns to the cortex in cats (Macchi *et al.*, 1983). These consists of four distinctive groups: nuclei projecting densely into single cortical fields, nuclei projecting densely into one area and diffusively into the other, nuclei projecting diffusely into several cortical fields but with regional concentrations, and nuclei projecting diffusely into widespread areas.

Jones et al. (2007) discuss reciprocal connections in non-human primates between the prefrontal cortex and mediodorsal nucleus, the motor and premotor cortex with ventral anterior and ventral lateral nuclei, the somatosensory cortex with ventral posterior nucleus, the temporal cortex with medial pulvinar and medial geniculate nucleus (MGN), occipital cortex with the lateral geniculate nucleus (LGN), and occipital and parietal cortex with the inferior pulvinar. Behrens et al. (2003) used diffusion tensor imaging (DTI) to segment the thalamus based on its gray matter connectivity with the cerebral cortex. They found that these connections between the thalamus and cortex in humans were similar to non-human primates.

Functional classifications of the thalamic nuclei are based on the type of information (e.g., visual, somatic, motor, auditory etc.) relayed to the cortex. Such functional classifications can distinguish between nuclei that convey specific information of one modality (primary) and nuclei that convey information of multiple modalities (secondary; (Castro-Alamancos and Connors, 1997). In studies using resting state functional connectivity, parietal-occipital cortical regions showed maximal connections

with the lateral pulvinar, temporal cortices corresponded most strongly with the medial pulvinar, prefrontal cortex showed maximal correlations with mediodorsal and anterior nuclear areas, somatosensory cortices seemed to correspond most to the ventral posterior nucleus, and the motor cortices correlated with a large region of the thalamus including the ventral lateral, ventral anterior, and parts of mediodorsal nuclei (Zhang *et al.*, 2008, Zhang *et al.*, 2010). In a related study examining maturational trajectories of these functional connections of thalamus and cortex in children, adolescents, and adults, Fair et al. (2010) found a progressive strengthening of functional connectivity of the frontal cortex with dorsal/anterior subdivisions of the thalamus. This was in contrast to a systematic weakening of temporal lobe connectivity with ventral/midline/posterior subdivisions of the thalamus. Additionally, premotor-motor and somatosensory cortical subdivisions also showed increased connectivity in lateral/inferior portions of the thalamus and decreased connectivity in medial/dorsal portions of the thalamus with age, but occipital–parietal correlations with the thalamus were relatively stable across the age groups.

Synaptic processes in the thalamus

Development and pruning of synaptic connections are essential steps in the formation of neuronal networks. As our brain mature from infancy to early adulthood, neurons form synapses with a large number of other neurons, and over time many of these initial connections are pruned while the remaining connections are further strengthened (Goda and Davis, 2003; Luo and O'Leary, 2005). The connections that are spared and strengthened are those that are important for function. As we learn behaviors or skills, neurons involved in that function alter their structure to strengthen that connection over time (Kandel & Schwartz, 1985). Just as the cortex becomes parcellated into cytoarchitectonically different areas, the thalamus evolves into distinct

subdivisions that relays inputs to the cortex during development (Rakic, 1988; O'Leary and Stanfield, 1989). Ghosh et al. (1993) argue that subplate neurons are a necessary component in this selective process for thalamic axons to appropriately identify cortical target regions. Subplate neurons are the first to be generated and mature physiologically in the cerebral cortex (Kanold and Luhmann, 2010). They receive glutamatergic input from the thalamus (Hanganu *et al.*, 2002), and serves as a "waiting station" for the ingrowing TC axons (Kanold and Luhmann, 2010). Subplate neurons serve as an integrating element by collecting these incoming information and distributing them effectively throughout the cortical region (Voigt *et al.*, 2001).

In further understanding the formation and organization of thalamic circuitry, one must distinguish between the afferents that bring information to be relayed, called the drivers, from other inputs, called the modulators (Sherman, 2001; Sherman, 2007). Various lines of evidence suggest that drivers have relatively large terminals with a characteristic fine structural appearance, resembling the mossy axon terminals of the cerebellum (Guillery and Sherman, 2002). They make multiple complex contacts with dendrites of relay cells and interneurons, and are usually involved in the visual, auditory, and somatosensory thalamic relays, also known as primary driving afferents (Guillery and Sherman, 2002). These drivers are glutamatergic (Sherman, 2001), have ascending features, and can be distinguished from modulators because when they are turned off, the receptive field properties of the higher order thalamic relays are lost (Bender, 1981); (Diamond *et al.,* 1992).

Modulators, on the other hand, are innervations in the thalamus from the brain stem, the thalamic reticular nucleus, local interneurons, and layer 6 of the cortex (Sherman, 2001). The brain stem innervations are cholinergic, the interneuronal innervations are GABAergic, and the cortical innervations are mostly glutamatergic.

They have a characteristic light and electron microscopic appearance, and contact

peripheral dendritic regions in contrast to drivers which contact proximal dendritic

regions (Vidnyanszky and Hamori, 1994; Erisir *et al.*, 1997). Essentially, drivers carry the

information that is transmitted to the cortex, but form a relatively small portion of

established thalamic synapses. Modulators, which make up the majority of the thalamic

synapses, change the nature of the thalamic transmission, without changing the

information being transmitted (Guillery and Sherman, 2002). Modulators do so by

changing the relay mode of thalamic cells between tonic mode (depolarization) or burst

mode (bursts of action potential; (Guillery and Sherman, 2002). The interplay of the

drivers and modulators indicate that TC networks are connected with the cortex on two

levels: first order pathways passing information to cortical processing regions (e.g.,

motor cortex, visual cortex), and higher order pathways connected with cortical regions

involved in monitoring of information being relayed (e.g., prefrontal cortex) and

intercommunication between cortical areas (Guillery and Sherman, 2002).

TC circuits are also dependent on arousal state, and tend to be more efficient in

transmitting information when the individual is awake and alert rather than drowsy,

inattentive, or asleep (Livingstone and Hubel, 1981). During the latter states, the

brainstem drive is weakened, neurons are hyperpolarized, and the influence of the

reticular nucleus (burst mode) is at its peak (Jones, 2009). In contrast, when

awake/alert, the reticular nucleus is depolarized, and cortically projecting neurons in the

thalamus are capable of relaying information from peripheral sense organs without

affecting the temporal and spatial properties of the information, or its sensory quality

(Jones, 2009).

Information is relayed to the thalamus mainly through the excitatory action of

glutamatergic synapses (Castro-Alamancos and Connors, 1997). For instance,

glutamatergic neurons excite TC cells in the perigeniculate nucleus (PGN) and lateral

geniculate nucleus (LGN), which in turn relay information to the visual cortex (Sanchez-

Vives and McCormick, 1997). The action of glumatergic synapses on TC pathways may

be viewed as the first-order innervations passing on information from thalamus to cortex.

TC circuits are also heavily influenced by the action of GABAergic cells innervating the

thalamic reticular nucleus (RN) and PGN (Kim *et al.*, 1997). GABAergic neurons are the

main inhibitory neurotransmitter in the brain. Activation of GABAergic neurons inhibit

postsynaptic cells (tonic mode), but can sometimes also generate burst discharges of

action potential (burst mode;(Jones, 2009). Input coming from to the dorsal thalamus

from other brain structures excite relay neurons, which in turn excite cortically projecting

axons, and project back to the dorsal thalamus forming an inhibitory feedback

connection to the relay cells (Kim *et al.*, 1997). This forms a synchronous and

bidirectional cortico-thalamo-cortical circuitry crucial in understanding thalamic function

(Jones, 2009), and is analogous with the higher order innervations monitoring and

regulating information exchange.

Connections to and from the thalamus abide by some constraints of laterality.

According to Jones et al. (2007), input from the body or extrapersonal space is primarily

contralateral to left or right thalamus. Additionally, inputs from subcortical sites to the

thalamus are mostly unilateral (e.g., crossed input from dentatothalamic tract, uncrossed

input from superior colliculus) with some bilateral loops (e.g., retinal inputs to LGN,

brainstem inputs, corticothalamic input). However, output of the thalamus is strictly

unilateral, and one side of the thalamus projects only to cortex and striatum of the same

side (Jones, 2007).

Thalamus and cognition

The thalamus has been extensively studied in terms of its anatomical

organization, efferent and afferent connectivity patterns, basic neural response

properties, and synaptic, biochemical, and molecular characteristics (Jones, 2007;

Sherman and Guillery, 2006). Its role in perception and cognition, on the other hand, has

remained relatively poorly understood. However, in recent years, growing interest in the

thalamus as much more than a sensorimotor structure, as well as methodological

advances such as high-resolution functional magnetic resonance imaging of the

thalamus and improved electrode targeting to subregions of thalamic nuclei using

electrical stimulation and diffusion tensor imaging, have fostered research into thalamic

contributions to cognition. Initial pathophysiological studies of the thalamus focused on

sensorimotor disturbances and pain sensation (Dejerine and Roussy, 1906). Human

neuroimaging studies also have heavily emphasized the functions of cortical rather than

subcortical networks, partially due to technical limitations in terms of spatial resolution.

However, in more recent years, there has been an accumulation of compelling evidence

to suggest the involvement of the thalamus in various different cognitive functions

ranging from language to executive functions. For instance, Kinomura et al. (1996)

focused on the effects of attention on thalamic (intralaminar nuclei) and brain stem

(midbrain tegmentum) activity. Their demonstration of attentional effects was interpreted

as evidence that these areas may control the transition from relaxed wakefulness to

higher general attention. Other studies have found activation in the LGN during tasks of

attentional modulation in healthy individuals. These findings of attentional modulation in

the human LGN have been corroborated by a recent single-cell recording study in the

macaque LGN that provides additional support for a thalamic role in attention (McAlonan

et al., 2008). The pulvinar has been implicated in attentional processes in the visual

cortex, and modulates shifts in visuo-spatial attention (Petersen *et al.*, 1987). Other

evidence suggests that the pulvinar is important for filtering distractor information

(Chalupa *et al.*, 1976). Strumpf et al. (2013) found that the BOLD response in pulvinar increased concomitantly with an increased response in visual cortex during a task requiring discrimination of a target amongst distractors. However, it is unclear how the different subdivisions of the pulvinar contribute to these functions. In addition, thalamic involvement has also been reported in perceptual modulation tasks (Saalmann and Kastner, 2009). Neuroimaging studies have shown that activity in the LGN reflects the subjects' reported percept and not necessarily the actual retinal input in tasks of binocular rivalry (Haynes *et al.*, 2005, Wunderlich *et al.*, 2005).

In a number of functional imaging studies thalamic participation in language tasks has been shown. For example, left thalamic activation has been found during the differentiation of distinct speech sounds, alongside with activity in the planum temporale, the superior temporal and Heschl's gyri of the dominant hemisphere (Alain *et al.*, 2005). Even the thalamic first-order auditory nucleus – the MGN - has been shown to be active during the recognition of speech sounds involving cortical feedback loops, a function presumed to be relevant for communication (Arnott *et al.*, 2005). Joint thalamic and frontotemporal involvement has been reported during lexico-semantic operations and object recall (Assaf *et al.*, 2006). These authors have proposed a neuronal circuitry in which spatially distributed cortical language operations are flexibly engaged by various thalamic neuronal assemblies, including anterior, intralaminar, dorsomedial nuclei as well as pulvinar subregions of the dominant hemisphere. In this view, human language is not a hierarchically organized cognitive function, but the compound output of interdependent subcortical and cortical systems, specialized in network activation (Klostermann *et al.*, 2013).

Functional brain imaging studies have also demonstrated that the mediodorsal thalamus participates in working memory processes. Activation of the mediodorsal

thalamus has been observed while subjects performed working memory tasks, such as delayed matching-to-sample tasks and delayed non-matching-to-sample tasks (de Zubicaray *et al.*, 2001). In addition to the temporary maintenance of information in working memory, Monchi et al. (2001) showed that the mediodorsal thalamus participated in other aspects of information processing. Using fMRI, they found that during performance on the Wisconsin card sorting test the mediodorsal thalamus was activated when the subjects received negative feedback. Tasks of sequential processing such as conceptual reasoning, card sorting and Tower of London (first six contrasts of the Problem Solving subsection), consistently engaged basal ganglia, thalamic, and cerebellar regions (Cabeza and Nyberg, 2000). According to the authors, these regions are typical skill learning regions and may reflect the skill-learning aspects of sequential problem solving tasks.

Thalamic strokes can lead to cognitive and behavioral changes that may be symptomatically similar to cortical syndromes, which is why the thalamus may be viewed as a "little brain" in itself (Carrera and Bogousslavsky, 2006). Therefore, it is often difficult to distinguish between thalamic and cortical dysfunction. Since thalamic infarcts are usually not life threatening, postmortem anatomical descriptions of thalamus - to allow for more definitive inferences between thalamic lesions and specific behavioral or cognitive changes - are rare (Carrera and Bogousslavsky, 2006). Imaging techniques such as MRI or PET, however, are able to provide a better understanding of the role of the thalamus in cognition.

Lesions to thalamic subdivisions

This anterior region of the thalamus is connected to the cingulate gyrus, hippocampus, parahippocampal region, orbitofrontal cortex and prefrontal cortex (Yakovlev *et al.*, 1960; Yakovlev and Locke, 1961). Thalamic lesions in the anterior

region account for 12% of all thalamic infarcts (Bogousslavsky *et al.*, 1988). Individuals

with thalamic lesions in this anterior region often demonstrate perseveration, apathy,

memory impairments, anomia, and superposition of unrelated information or

palipsychism (Ghika-Schmid and Bogousslavsky, 2000). Generally, the picture appears

to be one of disorganized expressive language with frequent intrusions of unrelated

topics. This pattern of superposition was more evident in unstructured conversational

speech (e.g., news, current events) compared to performance on automatic tasks

(Ghika-Schmid and Bogousslavsky, 2000). Aphasia appears to be prevalent with this

type of injury, and may be related to disruptions in communication between cortical

language regions and striatum with the anterior region of thalamus (Kennedy and

Murdoch, 1993). These authors also found that naming difficulties were more likely to

occur with thalamic lesions than other subcortical lesions involving structures such as

the basal ganglia. Some patients with anterior infarcts may also demonstrate

confabulations similar to frontal lobe lesions, suggesting disruption of thalamo-frontal

projections (Ghika-Schmid and Bogousslavsky, 2000). Similar to cortical strokes, left

thalamic lesions are likely to lead to verbal impairments, while right thalamic lesions are

likely to lead to visuospatial impairment (Graff-Radford *et al.*, 1984). In terms of the

memory impairments, anterograde amnesia with relatively preserved recognition is an

often-found pattern for anterior thalamic lesions (Clarke *et al.*, 1994). Studies suggest

that this amnesic pattern may be due to interruptions of the mamillothalamic tract and it's

connections to memory regions, such as the hippocampus (Mori and Hashimoto, 2001).

Medial regions of the thalamus receive and/or project to the premotor and motor

cortex, orbitofrontal and mediofrontal cortex, as well as the globus pallidus and

amygdala (Groenewegen and Berendse, 1994). Thalamic lesions in the median region

account for approximately 35% of thalamic infarcts and involve the dorsomedian and

intralaminar nuclei (Bogousslavsky *et al.*, 1988). Lesions in these nuclei are characterized by altered consciousness, vertical gaze paresis, and personality changes such as apathy, amnesia, and loss of self-activation following restoration of normal consciousness (Castaigne *et al.*, 1981). Most notably, disinhibited behavior and distinct personality change appears to be associated with these lesions, which could once again be confused with other pathologies such as schizophrenia, mania, or delirium (Carrera and Bogousslavsky, 2006). Individuals with bilateral median thalamic lesions are more likely to demonstrate severe apathy and lack of spontaneity compared to individuals with unilateral lesions (Carrera and Bogousslavsky, 2006). It appears that the median regions of the thalamus are more involved in executive processes, compared to the anterior part of the thalamus that appear to be more associated with attention and memory (Van der Werf *et al.*, 2003). However, other studies have noted significant memory impairments in individuals with bilateral paramedian thalamic infarctions. Crews et al. (1996) describe a case report of an individual with a similar infarction demonstrating difficulties on measures of executive functions such as sequencing, timed cognitive processing, shifting sets, and inhibition of automatic responses, which they attributed to the lack of motivation or apathy associated with these lesions. Additionally, they also found evidence for some language difficulties especially object naming, impaired bilateral psychomotor speed, impaired recall but adequate recognition on verbal memory tasks, impaired recall on non-verbal memory tasks, and deficient explicit memory but intact implicit memory in this previously neurotypical individual. Other studies have found autobiographical memory deficits (Hodges and McCarthy, 1993) and amnesia (Gentilini *et al.*, 1987) in individuals with paramedian thalamic injuries.

Dysarthria is also a common symptom possibly due to connections with motor loops associated with speech function, and is usually more severe with bilateral lesions

compared to unilateral ones (Ackermann *et al.*, 1983). Electrical stimulation studies on the median thalamus have found articulatory distortions resulting in prolongation of speech utterances (Mateer, 1978), as well as decreased voice volume and articulatory inaccuracies concurrent to speech acceleration (Guiot *et al.*, 1961). Ackermann et al. (1983) found that bilateral lesions may lead to articulatory impreciseness such as monotonous speech, high-pitched, breathy, and weak voice, and rough voice quality but normal speech rate. The median geniculate nucleus additionally relays information from the inferior colliculus to the auditory cortex, and lesions in this region are linked to hyperacousia, dichotic listening, or auditory agnosia (Fischer *et al.*, 1995).

Inferolateral thalamic regions include the ventrolateral nucleus, ventroposterior nuclei, and ventromedian nucleus (Carrera and Bogousslavsky, 2006). The ventrolateral nucleus has connections with the cerebellum and motor and prefrontal cortex; the ventroposterolateral nuclei receive afferents from the medial lemniscus and spinothalamic tracts; the ventromedian nucleus receives input from the trigeminothalamic pathway (Carrera and Bogousslavsky, 2006). Thalamic lesions in the inferolateral region comprise approximately 45% of all thalamic infarcts (Bogousslavsky *et al.*, 1988). Lesions in this region are usually associated with ataxia, hypesthesia, i.e., reduced physical sensation (Bogousslavsky *et al.*, 1988), reduced sensory sensitivity, chronic pain (Shintani *et al.*, 2000), and tremor pathophysiology (Marsden *et al.*, 2000). Executive dysfunction and affective changes may also occur with these lesions (Annoni *et al.*, 2003). The LGN falls within this region of the thalamus and the posterior half of the lateral side of this nucleus is the origin point of the optic radiation, which eventually connects to the primary visual cortex (Chandler *et al.*, 1992). Lesions in the LGN may result in homonymous quadrantanopia and homonymous hemianopia (Herrero *et al.*, 2002).

The pulvinar is the main region of the posterior nuclei, with the medial pulvinar projecting to the parieto-occipital cortex, prefrontal cortex, cingulate gyrus, and parahippocampal cortex, and the occipital and lateral pulvinar projecting to the parietal, occipital, and temporal cortex (Yeterian and Pandya, 1985; Yeterian and Pandya, 1988). Lesions to the pulvinar may result in difficulties with visual attention modulation. Thalamic lesions in the pulvinar constitute approximately 8% of all thalamic infarcts (Bogousslavsky *et al.*, 1988).Other commonly evidenced symptoms of posterior lesions are an array of visual problems including hypoesthesia, spatial neglect, and homonymous horizontal sectoranopsia, i.e., visual field loss (Karnath *et al.*, 2002).

Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a pervasive neurodevelopmental disorder with impairments in social and communicative functioning, along with stereotyped and repetitive behaviors (DSM-V, 2013). Abnormalities in motor and sensory perceptual domains are also fairly common. Individuals with ASD can display variable levels of cognitive skills, social functioning, and symptom severity. Genetic factors are considered predominant in the etiology of ASD, but the disorder is characterized by strong genetic heterogeneity (Eapen, 2011) and no comprehensive model of neuropathological development in autism is currently available. However, growing evidence indicates anomalies of early brain growth affecting basic mechanism of cortical organization and brain connectivity. This may lead to disruptions in functional properties of neural networks, and pose a deficit in the integration of information at neural and cognitive levels.

Functional connectivity findings in ASD

Studies using functional connectivity magnetic resonance imaging (iFC) have supported the existence of motor, sensorimotor, visual, and auditory neural networks

(Biswal *et al.*, 1995, Cordes *et al.*, 2000, Hampson *et al.*, 2002) (Hyde and Knudsen, 2000). The use of iFC to characterize connectivity patterns has recently been extended to clinical populations. IFC may be particularly useful in examining connectivity in developmental disorders, such as ASD, that show cognitive and behavioral changes throughout maturation. The research on functional connectivity in ASD has been partly conflicting due to methodological differences (Müller *et al.*, 2011). It has been proposed that there may be underconnectivity for long-range networks and overconnectivity for short-range or local networks within ASD (Thai *et al.*, 2009). The underconnectivity hypothesis was proposed initially by Just et al. (2004) who reported reduced functional connectivity in multiple regions of the in brain in ASD compared to TD groups during sentence comprehension tasks. The underconnectivity hypothesis has been supported in subsequent studies on executive function (Just *et al.*, 2007), sentence comprehension (Kana *et al.*, 2006), working memory (Koshino *et al.*, 2005), facial recognition (Kleinhans *et al.*, 2008), and theory of mind (Kana *et al.*, 2009). However, there have also been several studies reporting overconnectivity or mixed (both under- and over-connectivity) results in ASD (Koshino *et al.*, 2005, Mizuno *et al.*, 2006, Keehn *et al.*, 2012). In general, the aberrant connectivity seen may contribute differentially to the variety of social, sensorimotor, and cognitive deficits seen in ASD.

Alternative to task-related functional connectivity, resting state or intrinsic functional connectivity aims to measure the functional neurological connections at baseline or while the subject is "at rest". Pioneered by Biswal et al. (1995), resting state iFC detects slow, spontaneous, and synchronous fluctuations in cerebral blood flow using the BOLD signal. Although connectivity may vary depending on brain region, atypical connectivity is pervasive in ASD (Noonan *et al.*, 2009). Decreased connectivity during resting state iFC has been widely reported in ASD (e.g., Cherkassky *et al.*, 2006;

Assaf *et al.*, 2010; Wiggins *et al.*, 2011). However, increased and mixed connectivity

during resting state iFC have also been reported (Shih *et al.*, 2011). These

inconsistencies may be explained by several factors. For example, it has been

suggested that increases in connectivity could be a result of methodological choices

rather than reflective of intrinsic connectivity (Cordes et al., 2001). It is also possible that

the overconnectivity in some regions could be a compensatory mechanism for the

general, more widespread underconnectivity seen in the ASD brain. Although the exact

nature of these inconsistencies in resting state iFC is still unclear, interpretation of the

correlations between connectivity and symptomatology in ASD can vary greatly

depending on the direction (over- or under-connectivity) reported. For example,

decreased connectivity between the posterior cingulate cortex (PCC) and the medial

prefrontal regions have been correlated with symptoms such as social functioning

impairment, while increased connectivity between the PCC and parahippocampal gyrus

have been correlated with other characteristic symptoms such as repetitive behaviors

(Monk *et al.*, 2009).

Anatomical findings in ASD

Aberrant anatomical structures in ASD have been reported in postmortem and in

vivo MRI studies. Cellular abnormalities in many brain regions have been found with

some consistency in frontal and medial temporal regions as well as the cerebellum

(Amaral *et al.*, 2008; Zikopoulos and Barbas, 2010). Brain volume findings are less

consistent across studies as both reductions and increases have been found. In general,

no differences in whole brain volume between ASD and TD have been reported

(Aylward *et al.*, 2002). However, subsequent studies have found regional volumetric

increases in ASD (Palmen *et al.*, 2004). Also, one study reported region specific

volumetric reductions in the limbic system in adolescents with ASD (Aylward *et al.*, 2002)

which could correlate with social deficits. Evidence of atypical brain growth patterns has also been found in ASD. Despite normal head circumference at birth, after the first year of life, circumference enlargement occurs at an abnormal rate and continues to approximately age 12 at which point an abnormal slowing of growth rate seems to occur (Aylward *et al.*, 2002; Courchesne, 2001; Hazlett *et al.*, 2005).

Carper et al. (2002) reported early hyperplasia in frontal lobe white matter volume with significant deficit in the growth rate of ASD compared to TD individuals. Subsequent imaging studies have also reported similar abnormalities in white matter in ASD (Herbert *et al.*, 2004; Bonilha *et al.*, 2008). White matter abnormalities are generally examined using diffusion tensor imaging (DTI) techniques. DTI studies in ASD have allowed for the examination of microstructural regional differences in white matter properties. In particular, compared to more isotropic movement of water in grey matter, white matter is characterized by anisotropic water diffusion, due to the anatomical organization of axonal membranes and myelin sheaths (Beaulieu, 2002). Several measures can be extracted from DTI analyses, including fractional anisotropy (FA) and mean diffusivity (MD). FA is conventionally considered a measure of WM structural integrity, sensitive to anomalies in axonal density, myelination, and coherence of directional alignment of fibers within WM tracts (Basser and Pierpaoli, 1996; Pierpaoli and Basser, 1996). MD represents a measure of the average diffusivity (independent of directionality) that may reflect myelination, interstitial space, and axonal density (Norris, 2001).

In ASD, the DTI literature overall suggests an age-related pattern of white matter disturbances. Wolff et al. (2012) found that white matter development in infants with ASD was characterized by higher FA values at 6 months followed by slower growth rate over time relative to infants without ASD. In a study by Ben Bashat et al. (2007) looking at

toddlers with ASD (1.8-3.3 years), FA increase in several brain areas was reported, with particular involvement of the left and anterior regions. Weinstein et al. (2011) found increased FA as a result of decreased RD in ASD compared to TD toddlers in the corpus callosum and cingulum.

For school-aged children, increase in FA does not seem to be evident. Instead, reduced FA has been reported for this age range in various regions such as the uncinate fasciculus, inferior-occipital fasciculus, arcuate fasciculus, right cingulum, and corpus callosum (Ke *et al.*, 2009, Cheng *et al.*, 2010, Kumar *et al.*, 2010, Groen *et al.*, 2011). Reduced FA values were also found in the short association fibers of the frontal lobe of school-aged children with ASD (Sundaram *et al.*, 2008).

Studies of adolescents and adults with ASD have mostly reported reductions in FA values in regions such as the superior longitudinal fasciculus, inferior longitudinal fasciculus, internal capsule, corona radiate, corpus callosum, fronto-occipital fasciculus, corticospinal tract and, anterior thalamic radiation (Cheng *et al.*, 2010, Shukla *et al.*, 2010, Groen *et al.*, 2011). Mean diffusivity (MD) appears to be consistently higher in individuals with ASD across various age ranges, or no different from controls. Increased MD was reported in the corpus callosum, corona radiata, anterior and posterior limb of the internal capsule, middle cerebellar peduncle, thalamus and thalamic radiations, inferior and superior longitudinal and fronto-occipital fasciculus, corticospinal tract, external capsule, and uncinate fasciculus (Shukla *et al.*, 2010, Groen *et al.*, 2011). Several studies have also cited increased radial diffusivity (RD) in the corpus callosum, internal capsule, and prefrontal and temporal areas in ASD suggesting microstructural white matter aberrations (Keller *et al.*, 2007, Shukla *et al.*, 2010). The cerebellum has also shown abnormalities in white matter in ASD populations (e.g., Courchesne *et al.*, 2001; Akshoomoff *et al.*, 2002; Cheung *et al.*, 2009).

The developmental mechanisms underlying early brain overgrowth and other anatomical anomalies in white and gray matter in ASD, however, remain poorly understood (Bailey *et al.*, 1998; Casanova *et al.*, 2006). Despite some inconsistencies, it is apparent that atypical anatomical development in ASD is present and these potential abnormalities may impact interregional connectivity and information processing and could play an important role in the cognitive and social impairments seen in ASD.

The thalamus in ASD

Various lines of evidence have implicated abnormal thalamic development in ASD. Foremost of these are findings of reduced thalamic volume (Tsatsanis *et al.*, 2003; Tamura *et al.*, 2010). Additionally, Hardan et al. (2006) found that there was an absence of the normal linear relationship between thalamic volume and brain size. While some studies have found laterality effects for observed differences in thalamic volume between ASD and TD groups (Creasey *et al.*, 1986), other studies did not find such laterality differences (Tsatsanis *et al.*, 2003). Asymmetries in serotonin synthesis have also been reported, with a pattern of decreased serotonin synthesis observed in the left frontal cortex and thalamus versus elevated levels in thalamus and contralateral dentate nucleus of the cerebellum (Chugani *et al.*, 1997). Abnormalities of white matter structures related to the thalamus have also been reported in the ASD literature such as reduced white matter integrity in the dentato-rubro-thalamic pathway (Jeong *et al.*, 2012), which the authors suggested may be related to motor and communicative deficits observed in ASD. Additionally, reduced white matter integrity has also been found for ASD groups in anterior thalamic radiation (Cheon *et al.*, 2011). Other thalamic abnormalities reported in ASD include impacted neuronal integrity (Friedman *et al.*, 2003), perfusion (Ryu *et al.*, 1999, Starkstein *et al.*, 2000), and glucose metabolism (Haznedar *et al.*, 2006) within the thalamus.

Some of the above-mentioned findings are suggestive of abnormal TC connectivity (Chugani *et al.*, 1997, Cheon *et al.*, 2011). The thalamus has been suggested as a structure facilitating communication between collaborative networks implicated in important cognitive functions (Just *et al.*, 2004). Abnormal activation of TC networks involved in language processing has also been reported for ASD adults (Müller *et al.*, 1998). Reduced thalamic input in face processing (Kleinhans *et al.*, 2008), and increased functional connectivity between thalamus and fronto-parietal networks (Mizuno *et al.*, 2006) have additionally been reported for ASD groups compared to TD groups.

In view of these existent findings and the known fundamental importance of TC connectivity for the development of regional functional specialization in cerebral cortex, it is surprising how little firm knowledge is available about the thalamus and its connections with cortex in ASD. The present dissertation project used functional connectivity MRI, and probabilistic diffusion tensor tractography to examine functional and anatomical connectivity between cerebral cortex and thalamus as well as thalamic metabolite concentration levels to provide a more comprehensive understanding of the role of the thalamus in ASD.

Specific aims and hypotheses

Aim 1: Examine functional (intrinsic functional connectivity MRI - iFC) and anatomical (diffusion tensor imaging - DTI) connectivity between five broad cortical regions of interests (ROIs: prefrontal, temporal, motor, somatosensory, and parietal-occipital) and the thalamus in a sample of children and adolescents with ASD compared to TD controls.

Hypothesis 1. iFC indices will show underconnectivity in the ASD group compared to the TD group for all five ROIs, indicating impacted TC network synchronicity.

Hypothesis 2. DTI indices of fractional anisotropy (FA) will be reduced in the ASD group compared to the TD for all five ROIs, and mean diffusivity (MD), and radial diffusivity (RD) will be increased in the ASD group compared to the TD group for all five ROIs indicating aberrant structural development of TC pathways in the ASD group.

Exploratory Aim 1: To relate functional and anatomical connectivity, to diagnostic and neuropsychological measures specifically looking at socio-communicative abilities, motor skills and cognitive functioning.

Aim 2: The first aim uses large cortical ROIs, encompassing many smaller functional regions. The second aim will delve deeper into the specificity of connections between more narrowly specialized regions (e.g., inferior frontal cortex or anterior temporal pole) and the thalamus. The Harvard-Oxford cortical and subcortical structural atlases (FSL; **(Smith *et al.*, 2004)** will be used to derive probabilistic maps for 68 ipsilateral cortical structural areas and the thalamus. Functional (iFC) and anatomical (DTI) connectivity between these smaller, more specialized cortical ROIs and the thalamus will be examined for a sample of children and adolescents with ASD compared to TD controls.

Hypothesis 1. iFC indices in specific ROIs in the temporal and prefrontal regions will be especially disrupted for the ASD group compared to the TD group. For instance, connections between superior temporal regions (involved in auditory processing) and thalamus may be atypically increased based on previous literature (Shih *et al.*, 2011). Comparatively, connections between orbitofrontal cortex and thalamus may be reduced provided the role the former plays in inhibition and emotional control – both areas of difficulty for several individuals with ASD.

Hypothesis 2. DTI indices of fractional anisotropy (FA) will be reduced in the ASD group compared to the TD for the ROIs showing atypical iFC findings, and mean diffusivity (MD), and radial diffusivity (RD) will be increased in the ASD group compared to the TD group for these ROIs indicating aberrant structural development of TC pathways in the ASD group.

Exploratory Aim 2: To relate functional and anatomical connectivity, to diagnostic and neuropsychological measures specifically looking at socio-communicative abilities, motor skills and cognitive functioning.

METHODS

Participants

For the first study, twenty-nine children with ASD (4 female) and thirty-four typically developing (TD) children (5 female) participated in the study. Three ASD and seven TD participants were excluded from DTI analyses due to head motion. In view of the extreme sensitivity of iFC to even small amounts of head motion (see below), an additional four ASD and four TD participants were excluded from iFC analyses. In the second study, one hundred and five children participated in the study, including 60 children with ASD (eight female) and 45 typically developing (TD) children (ten female). For the iFC analyses, 23 ASD and 7 TD participants were excluded due to excessive head motion (as defined below), resulting in a final sample of 37 ASD and 38 TD children. These included 19 ASD and 21 TD participants from the first study. For DTI analyses, 26 participants with ASD and 12 TD participants were excluded because of missing field-maps (8 ASD, 2 TD) or failed quality assessment (e.g. motion artifact; 18 ASD, 10 TD). The final DTI sample included 34 participants with ASD and 33 TD participants. The sample with combined usable data in both modalities consisted of 27 ASD and 30 TD participants. For both analyses, groups were matched for age, handedness, verbal IQ, and nonverbal IQ (Tables 1A and 1B).

Clinical diagnoses were confirmed using the Autism Diagnostic Interview – Revised (ADI-R; Rutter, 2003), the Autism Diagnostic Observation Schedule (ADOS; Lord, 1999), and expert clinical judgment according to DSM-V criteria. Children with ASD-related medical conditions (e.g., Fragile-X syndrome, tuberous sclerosis), and other neurological conditions (e.g., epilepsy, Tourette's Syndrome) were excluded following phone screening and parent interview. Participants in the ASD group were not excluded

based on commonly occurring comorbidities with ASD such as attention-deficit hyperactivity disorder, anxiety disorder, and obsessive compulsive disorder. Participants in the TD group had no reported personal or family history of ASD, nor any reported history of other neurological or psychiatric conditions. Informed assent and consent was obtained from all participants and their caregivers in accordance with the University of California, San Diego, and San Diego State University Institutional Review Boards.

Data acquisition

Imaging data for both studies were acquired on a GE 3T MR750 scanner with an 8-channel head coil. Head movement was minimized with foam pillows around participants' heads. High-resolution structural images were acquired with a standard FSPGR T1-weighted sequence (TR: 11.08ms; TE: 4.3ms; flip angle: 45°; FOV: 256mm; 256 x 256 matrix; 180 slices; $1mm^3$ resolution). Functional T2-weighted images were obtained using a single-shot gradient-recalled, echo-planar pulse sequence. One 6:10 minute resting-state scan was acquired consisting of 180 whole-brain volumes (TR: 2000ms; TE: 30ms; 3.4mm slice thickness; in-plane resolution: $3.4mm^2$). Physiological measures of respiration and heart rate were also acquired during the scan using a BIOPAC system. Diffusion weighted images were collected with an echo planar imaging (EPI) pulse sequence with full head coverage and encoded for 61 non-collinear diffusion directions at b=1000 s/mm2, and one at b=0 s/mm2 (2D EPI; TR=8500ms; TE=84.9ms; flip angle=90°; NEX=1; FOV=24cm; resolution=1.875 x 1.875 x 2mm3). Field maps were collected for functional and diffusion weighted sequence to correct for field inhomogeneities (TR=1097ms; TE=9.5ms; flip angle=45°; 2 averages).

Neuropsychological data were obtained for both groups of participants on the Wechsler Abbreviated Scale of Intelligence (WASI/WASI-2; Wechsler, 1999), the Developmental Test of Visual-Motor Integration - Sixth Edition (VMI; Beery, 2010), and

the Clinical Evaluation of Language Fundamentals – Fourth Edition (CELF-4; Semel, 2003). For the sociocommunicative domain, additional data beyond ADI-R and ADOS (which were available only for ASD participants) were acquired using the Social Communication Questionnaire (SCQ; Rutter, 2003), the Social Responsiveness Scale (SRS; Constantino, 2005), and the parent report versions of the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, 2000) and Sensory Profile (SP; Dunn, 1994). For the second study, an additional measure of repetitive behaviors was also acquired using the parent report Repetitive Behaviors Scale-Revised (RBS-R; Lam and Aman, 2007).

Cortical and thalamic regions of interest

For the first study, five cortical regions of interest (ROIs) were selected consistent with TC parcellation established in the non-imaging literature (Jones, 2007) and in previous imaging studies reporting thalamic parcellation based on differential connectivity with cerebral cortical regions (Behrens *et al.*, 2003, Zhang *et al.*, 2008, Fair *et al.*, 2010, Zhang *et al.*, 2010). Seeds were created based on Brodmann areas (BAs) as identified using the Talairach-Tournoux Stereotaxic Atlas (TT-Daemon) in the software suite Analyses of Functional NeuroImages (AFNI; http://afni.nimh.nih.gov/afni) (Cox, 1996). Cortical ROIs were: prefrontal, parietal-occipital, motor, somatosensory, and temporal (see Figure 2C for details). A thalamic mask was further obtained using TT-Daemon atlas in AFNI (Figure 2D). For both DTI and iFC, analyses were performed separately for each hemisphere, i.e., only ipsilateral TC connectivity was considered. This methodological simplification is in agreement with the predominantly unilateral organization of thalamic efferents to striatum and cerebral cortex (although a few thalamic nuclei have been shown to receive some afferents from contralateral cerebral cortex; Jones, 2007, p.142-6).

In the second study, the Harvard-Oxford cortical and subcortical structural atlases were used to derive seed masks for 34 cerebral cortical areas in each hemisphere (68 total; Table 2) and the thalamus (Makris *et al.*, 2006). Analyses were performed separately for each hemisphere, i.e., only ipsilateral TC connectivity was considered. Thalamic masks were identified using the CA_MNI_N27 atlas in Analysis of Functional NeuroImages (AFNI; (Cox, 1996).

iFC data processing

Functional images were processed using the AFNI (Cox, 1996) and FMRIB Software Library (FSL) suites (Smith *et al.*, 2004). Functional images were slice-time and head motion corrected registering each functional volume to the middle time point of the scan. Field map correction was applied on each participant using in-house software for correcting magnetic resonance image distortion due to field inhomogeneity. Functional images were registered to the anatomical images via FSL's FLIRT (Jenkinson *et al.*, 2002). Both images were resampled (3mm isotropic) and standardized to the atlas space of the MNI152 template via FSL's nonlinear registration tool (FNIRT) for group comparisons. In order to isolate spontaneous low-frequency BOLD fluctuations (Cordes *et al.*, 2001), fMRI time series were bandpass filtered (.008 < f < .08 Hz), using a second-order Butterworth filter, which was also applied to all nuisance regressors described below. Images were spatially smoothed to a Gaussian full width at half-maximum (FWHM) of 6mm, using AFNI's 3dBlurToFWHM.

Linear effects attributable to scanner drift were removed during regression. In order to remove signal from cerebral white matter and lateral ventricles, masks were created at the participant level, using FSL's FAST automated segmentation. Masks were trimmed to avoid partial-volume effects, and an average time series for each segment was extracted and removed via regression. Derivatives for white matter and ventricular

time series were also removed. Physiological measures of heart rate and respiration were further modeled as nuisance regressors (usable data not available for 12 ASD and 11 TD participants). Analyses were performed without global signal regression (GSR) to avoid the creation of spurious anti-correlations (Murphy *et al.*, 2009), which may substantially distort group difference (Saad *et al.*, 2012, Gotts *et al.*, 2013).

In view of the known impact of head motion on BOLD correlations (Power *et al.*, 2012) several steps beyond conventional motion correction were taken to reduce the effect of motion. Six rigid-body motion parameters and their derivatives estimated from motion correction of functional volumes were modeled as nuisance variables and removed with regression from all analysis. Additionally, motion for each time point, defined as root mean square of the sum displacement of all six translational and rotational axes (RMSD), was determined for each participant and used as a covariate in all group-level analyses. For any instance of RMSD >0.5mm, considered excessive motion, the time point as well as the preceding and following time points were censored, or "scrubbed". If two censored time points occurred within ten time points of each other, all time points between them were censored. Additionally, a two-way analysis of variance (ANOVA) tested the effects of group and type of motion (three translational and three rotational), as well as their interaction. The main effect of group was not significant nor was the interaction of group and motion type significant for both studies. This suggests that group differences in iFC were unlikely to be driven by motion or related to differences in type of motion.

Partial correlation analyses were undertaken to accentuate the specificity of TC connections. The average BOLD time course was extracted from each cortical ROI. Partial correlations were then computed between each cortical seed and each voxel within ipsilateral thalamus, eliminating the shared variance by partialling out the

averaged time series from entire cerebral cortex except the given ROI (Zhang *et al.*,

2008). These partial correlation coefficients were then converted to a normal distribution

using Fisher's r-to-z transform. To test for correlations between ROIs and ipsilateral

thalamus within each group, we performed one-sample, two-tailed t-tests (*p*<.05) on

these Fisher r-to-z transformed values. For direct group comparisons, we performed

two-sample, two-tailed t-tests (assuming unequal variance; *p*<.05). Statistical maps were

adjusted for multiple comparisons (c. 685 voxels within ipsilateral thalamus), using

Monte Carlo simulation (Forman *et al.*, 1995), to a corrected *p*<.05. TC connectivities

demonstrating significant positive t-values for the contrast ASD-TD were considered to

be "overconnected", those with significant negative t-values "underconnected". For each

cortical seed with significant group differences, the mean z' was obtained from the

cluster of between-group effects in ipsilateral thalamus in each participant, which was

then entered into Pearson correlation analyses with scores obtained from diagnostic and

neuropsychological measures.

As mentioned previously, the thalamus is functionally highly differentiated into

numerous specialized nuclei and regions. We therefore also examined the functional

differentiation within thalamus in the first study, following the procedure from Shih et al.

(2011). A differentiation index (DI) was calculated separately for each hemisphere after

extracting time courses for each participant from each thalamic parcel (using group-

specific parcellation shown in Figure 1G-H), as follows: $DI = \sqrt{1-\alpha^2}$

Alpha, based on Cronbach (1951), is given by: $\alpha = \dfrac{k\overline{r_{ij}}}{1+(k-1)\overline{r_{ij}}}$,

where i, j = (1, …, k }, k is the number of ROI (parcel) pairs and rij is the average

correlation between all ROI pairs. To test for age-related changes, Pearson correlations

between age and DI were performed, partialling out six motion regressors (3 translations and 3 rotation) detected during motion correction (AFNI's 3dvolreg).

Additionally, in the second study the Euclidean distance between each ROI with significant between-group effects and the centroid of ipsilateral thalamus was calculated (Alexander-Bloch *et al.*, 2012), using the formula: $d = \sqrt{(x_1 - x_2)^2 + (y_1 - y_2)^2 + (z_1 - z_2)^2}$ wherein x, y, z are the MNI coordinates for the centroid of each ROI.

DTI: Probabilistic tractography

Diffusion weighted data were preprocessed using the FSL Diffusion Toolbox (FDT; (Smith *et al.*, 2004). Preprocessing included field-map correction of field inhomogeneities, removal of skull and non-brain tissue (FSL BET), and eddy current correction (FSL eddy correct). For the second study only, to reduce motion effects on diffusion measures (Yendiki *et al.*, 2013), we thoroughly assessed all scans for subject motion both through visual inspection for (i) signal dropout (ii) image noise and (iii) shifts of head placement, and through quantification of artifacts, excluding any scans with more than minor motion. Motion quantification was performed as suggested by Yendiki et al. (2013): Mean image translation and rotation applied during eddy correction were recorded as were the severity and frequency of signal drop-outs across all slices. These four quantities were combined into a total motion index (TMI) and this measure was used as a covariate in all analyses. The diffusion tensor was calculated at each voxel and maps of axial and radial diffusivity (AD and RD), mean diffusivity (MD), and fractional anisotropy (FA) were generated. The FA map was registered to MNI standard space using non-linear registration (FSL FNIRT) and the FMRIB58 FA template. Transformation matrices were saved to facilitate fiber tracking in native space.

Fiber tracking was performed using the probabilistic tractography algorithms in FSL. The probability distribution of principal diffusion direction was calculated at each

voxel in the brain. Multiple streamlines were generated from each voxel in the target

region (thalamus ipsilateral to cortical ROI), using repetitive sampling from the probability

distribution, and the resulting output was limited to streamlines reaching the designated

target regions (cortical areas). In the first study, for each participant, 5000 tract-following

samples were initiated for each target region resulting in a probability map of

connectivity. For the second study, due to the CPU-intensive nature of probabilistic

tractography, the target regions for these analyses were restricted to ROIs with

significant group difference in iFC.1000 streamlines were then initiated from each seed

voxel generating a probability map of the tract location for each target. Voxels found to

be above a threshold probability (minimum of 50 streamlines per voxel) formed a binary

mask to define the subject-specific location of the tract, and the mean MD, RD, AD, and

FA were calculated for each tract. These means were used for between-group

comparisons as well as for correlations with scores obtained from neuropsychological

and diagnostic measures.

'Winner-take-all' parcellation

For the first study only, iFC-based parcellation of the thalami was carried out

using z- transformed partial correlation maps averaged across all participants in each

group and a 'winner' was determined for each thalamic voxel and was color-coded

based on maximum correlation with a cortical seed (Figure 2G-H). Similarly, for

connectivity-based parcellation of the thalami using DTI data, the total number of

samples that reached each cortical region was obtained for each thalamic voxel. Each

thalamic voxel was then color-coded according to the target cortical region with the

maximum proportion of samples from averaged map across all participants in each

group (Figure 2E-F). DTI indices were extracted for each of the resulting thalamic

parcellation.

RESULTS

Functional connectivity

In the first study, partial correlation maps between cortical seeds and thalamus

for TD participants were largely consistent with previous studies in healthy adults (Zhang

et al., 2008, Zhang *et al.*, 2010), as well as in adolescents of similar age as in the

present study (Fair *et al.*, 2010). Specifically, the prefrontal seed showed strongest

correlation with anterior dorsomedial regions of the thalamus, the parietal-occipital seed

with posterior regions including the pulvinar, the motor seed with anterior ventrolateral

regions, the somatosensory seed with more posterior ventrolateral regions, and the

temporal seed with ventromedial and posterior regions. In the ASD group, partial

correlation maps were overall similar in location, but smaller in extent for all seeds

except the temporal seed, for which extensive functional connectivity was detected

bilaterally. These patterns of within-group results were corroborated by between-group

findings, which showed several clusters of underconnectivity in the ASD group for all

seeds except the temporal seed, for which extensive clusters of atypically increased

connectivity were found in the right thalamus.

In view of the possibility of global (non-region specific) connectivity differences

between groups, we also performed a group comparison for total correlations between

each cortical seed and the thalamus. We found clusters of underconnectivity in the ASD

group for the prefrontal, parietal-occipital, and somatosensory seeds, compared to the

TD group (Figure 2B, bottom row). For the motor and temporal seeds findings were

mixed, with both clusters of under- and overconnectivity in the ASD group. Additionally,

iFC based thalamic parcellation revealed that parieto-occipital connectivity was larger

that DTI based thalamic parcellation, mostly at the expense of the temporo-thalamic

parcel (Figure 2G). In the ASD group, the thalamic parcel obtained from the prefrontal seed was also greatly reduced, whereas the temporo-thalamic parcel was expanded into anterior thalamic regions occupied by the prefrontal parcel in TD participants (Figure 2H). Results for the differentiation index (examining the specialization of thalamic parcels with respect to their BOLD time series) indicated no significant differences between TD and ASD groups for either right (t= -1.33, p=.19) or left (t=1.56, p=.12) hemispheres. We further examined the asymmetry of functional differentiation, using the formula ($DI_{left} - DI_{right}$)/($DI_{left} + DI_{right}$), and found significant group differences in asymmetry (t= -5.17, p<.001), reflecting leftward asymmetry in the TD group (M= .099, SD= .08), but slight rightward asymmetry (M= -.028, SD= .08) in the ASD group.

In the second study delving deeper into specificity of TC connectivity, of the 68 total ROIs iFC was found to be reduced for 15 and increased for 9 ROIs. While TC underconnectivity effects in the ASD group predominated for frontal, parietal, and occipital ROIs, effects for temporal ROIs were mixed. For fronto-thalamic iFC, we found underconnectivity in the ASD group for left middle frontal gyrus (LMFG) and superior frontal gyri (LSFG & RSFG) and supplementary motor area (LSMA & RSMA) bilaterally (Figure 3A). Conversely, overconnectivity was observed for precentral gyri bilaterally (LPCG & RPCG) and right anterior cingulate cortex (RACC).

Among temporal ROIs, bilateral superior temporal gyri (LSTG & RSTG) and transverse temporal gyri (LTG & RTG) as well as right parahippocampal gyrus (RPHG) were overconnected with thalamus in the ASD group. Conversely, TC underconnectivity was seen in bilateral amygdala (Lamyg & Ramyg), right fusiform gyrus (RFF), and left temporal pole (Ltempol). Given that the most robust overconnectivity finding was detected for STG, which extends from anterior pole to most posterior temporal regions, we conducted a reverse iFC analysis. Within thalamus (left and right separately),

clusters of significance from partial correlation analysis for superior temporal ROIs were used as seed for iFC analyses with unilateral temporal lobes. Thalamic overconnectivity was found mainly in posterior sections of Brodmann area 22 in the vicinity of primary auditory cortex (Figure 3B).

For parietal lobe, underconnectivity with thalamus was observed for superior parietal lobule (LSPL & RSPL) and supramarginal gyri (LSMG & RSMG), whereas right posterior cingulate gyrus (RPCC) showed increased iFC. For occipito-thalamic iFC, underconnectivity effects were observed for left supracalcarine gyrus (Lcalc) and right occipital pole (Roccpol) (Figure 3A).

We created a Pearson's correlation matrix including only ROIs with significant iFC group differences to test for possible links between region-specific overconnectivity and underconnectivity findings (Figure 4). ROIs were sorted according to between-group effects (underconnectivity [indicated by blue font] vs. overconnectivity [red font]). The question of interest was whether thalamic overconnectivity in the ASD group for some ROIs may have come at the expense of ROIs with reduced thalamic iFC; i.e., whether mean z' for one ROI was negatively correlated with mean z' for the other. This question could be answered by focus on one quadrant of the matrix (outlined by dashed black line at top right of Figure 4), which shows mean z' correlations between underconnected and overconnected ROIs in the ASD group. For every ROI pair (outlined with white box) within this quadrant that showed significant negative correlations, the correlation coefficients were converted to a normal distribution using Fisher's r-to-z transform. Two-sample, two-tailed t-tests (assuming unequal variance; $p<.05$) were performed to determine significant group differences in any of the z-transformed values for these ROI pairs. LMFG pairings with LPCG and RACC, and between RPHG pairings with RSMG and Roccpol showed significant group differences (with the ASD group demonstrating

significantly greater negative correlations than the TD group). For each of these ROI

pairs, this indicates that underconnectivity in one was linked to overconnectivity in the

other in the ASD (but not the TD) group.

Correlations were run between mean *z*' scores and Euclidean distance between

ROIs and ipsilateral thalamus, co-varied for motion and age, averaged across

participants within each group. Results showed that functional connectivity indices were

negatively correlated with distance in the ASD (*r*=-.59, *p*=.002), but not the TD group (*r*=-

.28, *p*=.19). To further test for group differences, Pearson's correlation coefficients were

computed for each participant between individual ROI iFC *z*' score and corresponding

Euclidean distance with thalamus. The correlation coefficients were converted to a

normal distribution using Fisher's r-to-z transform. Two-sample, two-tailed t-tests

(assuming unequal variance; *p*<.05) were performed to determine group differences. No

significant group differences were found for the relation between Euclidean distance and

iFC *z*' scores, *t*(73)=.61, *p*=.55.

Anatomical connectivity

In the first study, DTI analyses (Figure 5) showed significantly increased MD in

the ASD group compared to the TD group for tracts connecting thalamus with motor and

somatosensory cortices bilaterally and with prefrontal, parietal-occipital and temporal

ROIs in the right hemisphere. Marginally significant increased MD in the ASD group was

also found for prefrontal and parietal-occipital thalamic tracts in the left hemisphere.

Radial diffusivity was significantly increased in the ASD group in both hemispheres for

tracts between thalamus and motor and somatosensory cortices and for tracts between

thalamus and prefrontal cortex in the right hemisphere, with further marginal increases in

parietal-occipital and temporal thalamic tracts in the right hemisphere. No between-

group differences were found for FA. Volume of tracts between thalamus and motor cortices in the left hemisphere was marginally lower in the ASD group.

Between group comparisons of connection probabilities for each cortical ROI showed reduced probability of connections in the ASD group between thalamus and parietal-occipital, somatosensory, and temporal ROIs in both hemispheres and prefrontal and motor ROIs in the left hemisphere (Figure 2A). Furthermore, connectivity-based thalamic parcellation for our sample of TD adolescents using a 'winner-take-all' approach was largely consistent with results from previous DTI studies in adults (Behrens *et al.*, 2003, Zhang *et al.*, 2010) (Figure 2E). Parcellation for the ASD group was overall similar (Figure 2F).

In the second study, due to the computationally demanding nature of probabilistic tractography, the target regions for anatomical connectivity analyses were restricted to the 24 ROIs with significant group difference in iFC (as shown in Figure 3A). Between group *t*-tests of average DTI indices (FA, MD, RD, AD; Table 3) for each tract showed significantly decreased FA (grossly considered a positive index of 'tract integrity') in the ASD group compared to the TD group for tracts connecting right thalamus with RACC and RSMA. Significant increases in the ASD group were observed for MD in tracts connecting thalamus with SFG and SMA bilaterally and with LPCG, Ltempol, and RSPL; and for RD in those connecting with PCG and SMA bilaterally, as well as RSMA, RACC, RSFG, Ltempol, and RSPL (both MD and RD are often described as negative indices of 'tract integrity'). Finally, significantly increased AD in the ASD group was observed for tracts connecting thalamus with LSFG, RSFG, and RSPL. No significant group differences in DTI findings were observed for occipital ROIs.

We again performed Pearson correlation analyses (partialling out motion) between Euclidean distance (from each ROI with significant group difference to the

centroid of the ipsilateral thalamus) and mean FA, MD, RD, and AD, each averaged

across participants within each group. MD, RD, and AD were all negatively correlated

with distance in both groups (all $p<.01$).

We also tested for correlations between DTI indices and iFC z' scores for each

region to explore the relationship between anatomical and functional measures, using

false discovery rate (FDR) correction for multiple comparisons at $p<.05$ (Benjamini *et al.*,

2001), which is preferable in neuroimaging to the overly conservative Bonferrroni

approach (Genovese *et al.*, 2002). Results indicated that for LSTG iFC z' scores were

positively correlated with AD ($r=.37$, p<.02), and MD ($r=.37$, $p=.04$), for LTG iFC z'

scores were positively correlated with MD ($r=.33$, $p=.04$) and RD ($r=.28$, $p=.05$), and for

RACC iFC z' scores were positively correlated with AD ($r=.32$, $p=.04$), MD ($r=.31$, $p=.04$),

RD ($r=.29$, $p=.04$), and tract volume ($r=.33$, $p=.04$).

Diagnostic and neuropsychological correlates

In the first study, to explore how anatomical and functional connectivity results

related to diagnostic and neuropsychological scores, we performed a series of Pearson

correlation analyses, partialling out head motion (root mean square of displacement, as

described above). Firstly, significant positive correlations between age and differentiation

indices for both right ($r=.47$, $p=.05$) and left ($r=.50$, $p=.03$) hemisphere for TD group were

found after partialling out the effects of motion. Corresponding correlations with age

were slightly weaker in the ASD group and did not reach significance (Figure 6A-B).

In the first study, correlation results for mean iFC z' values after partialling out

motion effects were extracted from each thalamic parcel. These results indicated

significant negative correlations for motor thalamic connectivity with ADOS

communication scores ($r = -.35$, $p =.\ 03$) and the ADI social interaction index ($r = -.32$, p

$=\ .05$) in the ASD group for the right hemisphere (Figures 6G-H). Furthermore, right

hemisphere temporo-thalamic connectivity was correlated with the Autistic Mannerisms (r = .34, p =. 03) subdomain on the SRS in both groups. For the left hemisphere, negative correlations were seen for parietal-occipital thalamic connectivity and the Metacognition index of the BRIEF (r = -.43, p =. 02) in both groups (Figures 6I-J). Note that based on our directional hypotheses (of impaired connectivity being associated with diagnostic severity and functional impairment), no Bonferroni correction was applied to these correlation analyses. In the second study, Pearson correlation analyses were undertaken for the ASD group, partialling out age and head motion (RMSD for iFC and TMI for DTI). All results were then FDR-corrected for multiple comparisons. Among iFC measures, we found positive correlations for ADOS and ADI-R with right cingulate ROIs (reflecting increased symptom severity with greater iFC), but inverse effects for right superior frontal and superior parietal ROIs. Robust positive correlations were detected between iFC z' scores from RFF with CELF-4 Total Score, indicating improved language skills with greater connectivity between thalamus and these temporal and parietal ROIs. Robust negative correlations were also detected between iFC z' scores for RFF and planning/organizing, working memory, metacognition, and global executive composite of the BRIEF (Table 4), indicating reduced executive impairment associated with increased iFC.

In the first study, correlations between FA and diagnostic scores (Figures 6C-D) in the ASD group yielded significant negative correlations for bilateral fronto-thalamic tracts and ADOS social score (r=-.56, p=.02 in the left hemisphere; r=-.52 p=.03 in the right hemisphere) and ADOS total score (r=-.54, p=.04 in the left hemisphere; r=-.49, p=.03 in the right hemisphere; Figure 5C-D). Negative correlations with ADOS social (r=-.55, p=.02) and ADOS total scores (r=-.55, p=.02) were also significant for temporo-thalamic connections in the left hemisphere. For the ASD group, there was also a

significant negative correlation between bilateral temporo-thalamic FA and CELF total

scores (r=-.93, p=.01 in the left hemisphere; r=-.89, p=.01 in the right hemisphere;

Figures 6E-F). In the second study, to minimize multiple comparisons testing for links

between DTI indices and diagnostic and neuropsychological measures, we only tested

correlations of FA (the most commonly used DTI measure; Table 5) and RD (the index

yielding most robust between-group effects; Table 6) for ROIs with significant group

differences in the ASD group. Results showed negative correlations between FA in right

frontal TC tracts and SRS, and BRIEF, indicating associations between reduced FA and

greater impairment with respect to social interaction, and executive functions. For SP,

we found positive correlations with FA in right frontal tracts, indicating links between

sensory behaviors and TC tract structure. Additionally, we found positive correlations

between RD in both right and left frontal tracts and SRS and BRIEF, further indicating

impairment with respect to social interaction and executive functions. These correlations

are in the direction of impairment for the ASD group. Therefore, more severe social and

executive function scores were associated with compromised anatomical connectivity.

Additionally, we also found positive correlations between ADI-R social scores and RD for

superior frontal and superior parietal tracts, suggesting increased symptom severity with

higher diffusivity.

DISCUSSION

This dissertation project is the first to investigate TC connectivity in ASD using combined measures from iFC and DTI tractography. Our findings suggest that, looking more globally across brain regions (lobes), TC connectivity is predominantly reduced in the ASD group. However when examining more specialized brain regions within the lobes differential patterns of connectivity emerges, with findings of both under- and overconnectivity for each lobe (except the occipital). While atypical TC connectivity in ASD was overall highly region-specific, some general principles emerged. Overconnectivity was mostly found for limbic (cingulate, parahippocampal) and sensorimotor regions (auditory, motor), although there were exceptions (underconnectivity for amygdala and occipital ROIs). Conversely, regions involved in multimodal and social cognition, such as executive functions, face processing, and language, were underconnected with thalamus. This pattern partly resembles findings from a large-sample multi-site study (Di Martino *et al.*, 2014), which reported overconnectivity in children and adults with ASD between sensorimotor cortices and subcortical regions (including thalamus). However, this study did not detect predominant underconnectivity for multimodal regions, as observed in the present investigation.

Functional and anatomical connectivity of cortex with thalamus

Functional connectivity results suggested that overall prefrontal functional connectivity was underrepresented especially in the right thalamus. Specifically, TC-iFC was predominantly reduced for bilateral superior frontal and left middle frontal gyri, known for their roles in executive control, working memory, and attention (Haxby *et al.*, 2000). Reduced iFC within executive control networks has been reported in ASD (Kana

et al., 2007), associated with increased symptom severity (Agam *et al.*, 2010).
Supplementary motor area, for which reduced TC-iFC was also found bilaterally, is
important for high-order initiation and planning of internally guided movements (see
review; (Nachev *et al.*, 2008). Conversely, primary motor cortex, crucial for voluntary
motor execution, showed TC overconnectivity. For precentral gyri, overconnected
clusters fell within the anterior and medial dorsal nuclei – thalamic subdivisions typically
connected with prefrontal cortex (Jones, 2007). There was an inverse correlation of TC-
iFC between left middle frontal gyrus and bilateral primary motor cortex. This further
highlights the possibility of a 'functional invasion' by overconnected motor cortex into
thalamic territory typically connected to prefrontal cortex. This pattern may relate to
earlier fMRI findings of motor-related activation expanding into prefrontal association
areas in adults with ASD (Müller *et al.*, 2003). Overconnectivity clusters also detected for
right ACC fell within right ventral posterolateral nucleus, which typically has
somatosensory function (Jones, 2007). DTI findings suggested reduction in white matter
integrity for prefrontal and motor regions. DTI findings further suggested atypical white
matter structure in fronto-thalamic connections for bilateral primary motor cortex,
supplementary motor areas, superior frontal gyrus, and right cingulate regions.
Anatomical compromise of right anterior cingulate connectivity was also correlated with
aberrant iFC for that region. For fronto-thalamic anatomical tract integrity, diagnostic
correlations were particularly robust bilaterally, with reduced FA and increased RD being
associated with increased symptom severity. Anatomical compromise in fronto-thalamic
tracts was also associated with executive functioning difficulties in ASD.

　　　　Although no group differences in white matter integrity in temporo-thalamic tracts
emerged in our DTI findings, direct group comparison for iFC indicated temporo-thalamic
overconnectivity in the ASD group, especially in the right hemisphere. Diagnostic

correlations were hemisphere-specific (beneficial on the left, but unexpectedly detrimental on the right). However, temporo-thalamic overconnectivity was not pronounced on group comparisons for total correlation, suggesting that such overconnectivity is relative (with respect to connectivity with other cortical regions) and occurs in a context of predominant TC underconnectivity overall. More specifically for the temporal lobe, we found several subregions with increased iFC in the ASD group, including superior temporal gyri and transverse gyri bilaterally, as well as right parahippocampal gyrus. The overconnectivity clusters for both superior temporal and transverse gyri spilled into the ventral anterior and medial dorsal nuclei – thalamic subdivisions predominantly connecting with prefrontal cortex in the TD brain (Jones, 2007). A reverse connectivity analysis pinpointed bilateral hotspots of temporo-thalamic overconnectivity in primary auditory cortex and immediate vicinity (Figure 2B). This finding may relate to heightened auditory sensitivity (Matsuzaki *et al.*, 2012), and atypical language development (Herbert *et al.*, 2002), which are common in ASD. Thalamic iFC of superior temporal and transverse gyri was correlated with autistic mannerisms, and impaired social interaction and planning abilities. TC-iFC of transverse gyri (bilaterally) was also inversely correlated with age in the TD group, whereas in the ASD group both overconnectivity and absence of this age-related effect suggest a lack of typical maturational progression in TC connectivity. The overconnectivity cluster for right parahippocampal gyrus, a region involved in visual encoding and memory (Maguire *et al.*, 1998), was mainly seen in right pulvinar, which is typically connected with medial temporal and parieto-occipital cortices (Jones, 2007) and may relate to strengths in non-social visual processing in ASD (Samson *et al.*, 2012).

Conversely, bilateral amygdala, left temporal pole, and right fusiform gyrus showed TC underconnectivity. DTI findings also revealed white matter compromise in

tracts connecting left temporal pole and thalamus. Both amygdala and fusiform gyrus play a role in face processing (Kanwisher *et al.*, 1999), and aberrant functioning of these regions is associated with impaired face processing in ASD (Schultz *et al.*, 2003). Reduced TC-iFC of right fusiform gyrus was associated with poor language skills and executive functions. This may reflect links between social and executive processing, as suggested by a meta-analysis of visual processing studies revealing atypically reduced frontal activity during face processing in ASD (Samson *et al.*, 2012). Weak fusiform-thalamic response to faces may thus be exacerbated by executive deficits in ASD. In contrast, TC-iFC of right transverse and left superior temporal gyri was positively correlated with planning and organization skills. TC overconnectivity of auditory cortex furthermore spilled into typically thalamic-prefrontal networks. Studies have suggested strong connections between dorsolateral prefrontal cortex (DLPFC) and auditory cortex, and involvement of DLPFC in goal-directed auditory tasks (Procyk and Goldman-Rakic, 2006). Our current findings may highlight heightened DLPFC involvement in auditory processing networks in ASD.

The relative strength of temporo-thalamic connectivity was again apparent in the parcellation, with temporal parcels impinging on thalamic regions occupied by other ROIs (especially frontal) in the TD group. This strong representation of temporal connections in anterior and dorsal thalamus, accompanied by reduced parcels for motor-thalamic connectivity, resembled the iFC parcellation patterns observed in pre-teen children (but not adolescents or adults) by Fair and colleagues (2010). These findings may collectively relate to reduced differentiation in gene expression between frontal and temporal lobes in ASD reported by Voineagu et al. (2011). Related findings in macaque monkeys show that thalamic connectivity of some temporal regions (TE in anterior and TEO in posterior inferior temporal cortex) found in infants is lost or reduced in adults

(Webster *et al.*, 1995). However, the functional relevance of the relative temporo-thalamic overconnectivity in ASD remains unclear. Two fMRI studies have reported increased temporal activity in the context of reduced frontal activity in response to language tasks (Just *et al.*, 2004), potentially consistent with our findings.

For parietal regions, we found mostly reduced iFC, namely with superior parietal lobules and supramarginal gyri bilaterally. Superior parietal lobules play important roles in working memory (Koenigs *et al.*, 2009) and spatial orientation (Karnath, 1997), while supramarginal gyri are involved in language functions (Stoeckel *et al.*, 2009) and empathy (Silani *et al.*, 2013). For both regions volumetric abnormalities have been reported in ASD (Ke *et al.*, 2008). DTI findings also showed compromised thalamic white matter tracts for right SPL. Both iFC and white matter indices were correlated with diagnostic severity. In contrast, right posterior cingulate cortex showed functional overconnectivity with thalamus, associated with repetitive behavior symptom severity. PCC is part of the default mode network, which is poorly modulated in ASD (Assaf *et al.*, 2010). The overconnectivity clusters for right posterior cingulate region fell mostly within the ventral anterior and ventral lateral nuclei – thalamic subdivisions typically connected with prefrontal and motor cortices (Jones, 2007). Connectivity-based parcellation of the thalamus derived from DTI results also showed comparatively extensive representation of parieto-occipital connectivity in posterolateral thalamus in the ASD group. However, this difference was only seen qualitatively on parcellation results, whereas direct group comparison of probabilistic tractography maps actually showed bilaterally reduced parieto-occipital connectivity for the ASD group in posterior thalamus (primarily in the pulvinar). The pulvinar and its parietal connections are functionally important for spatial attention (Shipp, 2004) and abnormalities of anatomical connectivity detected in our

study may relate to impaired attention in ASD (Townsend and Courchesne, 1994; Allen and Courchesne, 2001).

The occipital lobe was the only subdivision with exclusively reduced iFC in the ASD group. DTI findings did not indicate significant group differences in white matter integrity for the occipital lobe. Among the underconnected thalamic regions were anterior dorsal nuclei, lateral geniculate nucleus and inferior pulvinar, the latter two typically connecting to occipital cortex. Several studies have indicated increased functional connectivity of visual cortex in ASD associated with socio-communicative deficits (Samson *et al.*, 2012). Our findings suggest that while the occipital lobe may be hyperconnected with itself (Keown *et al.*, 2013), it has reduced connectivity with subcortical visual structures. Reduced thalamic iFC for right occipital pole along with right supramarginal gyrus – both involved in visual/visuospatial processing – was linked with overconnectivity for right parahippocampal gyrus, suggesting enhanced mediotemporal TC connectivity at the expense of parieto-occipital connectivity in pulvinar (Jones, 2007).

In addition, Euclidian distance of cortical ROI from thalamus was associated with reduced TC-iFC in the ASD group, possibly consistent with a hypothesis by (Lewis *et al.*, 2013) according to which early brain overgrowth in ASD may affect long-distance connectivity due to greater conduction delays. However, no group differences in correlational patterns with Euclidean distance were noted for DTI indices. Additionally, the relation between distance and TC-iFC did not significantly differ between groups and any interpretation along those lines therefore requires great caution. Rather than distance per se, the overall pattern of our findings may instead reflect maturational timelines, suggesting that in the context of early brain overgrowth in ASD (Courchesne *et al.*, 2001). TC connectivity for early-maturing sensorimotor and limbic regions may be

atypically robust, at the expense of TC connectivity for late-maturing association cortices. These abnormalities are particularly relevant given the importance of TC afferents in the emergence of regional functional specializations in cerebral cortex during early brain development (O'Leary and Nakagawa, 2002).

Comparison between iFC and DTI findings

Comparing iFC with DTI findings, it was remarkable that relative temporal overconnectivity was not observed at all in probabilistic tractography. Although the iFC and DTI findings may thus appear divergent, they are in fact overall consistent with the literature. Previous DTI studies have reported reduced FA in anterior thalamic radiation (Cheon *et al.*, 2011) and in the anterior limb of the internal capsule, which incorporates TC fibers (Jou *et al.*, 2011; Shukla *et al.*, 2011). Cheung et al. (2009) found no group differences for the anterior thalamic radiation, but reported correlation between FA in this tract and ADI reciprocal social interaction scores in children with ASD. Differences in iFC and DTI findings for temporo-thalamic connectivity can again be attributed to the very different signal sources mentioned above, which make them sensitive to different aspects of connectivity. For example, whereas DTI tractography will probe the integrity of direct axonal connections between temporal lobe and thalamus, iFC may detect effects of indirect polysynaptic connectivity via other brain regions, such as the basal ganglia (cf.Di Martino *et al.*, 2011).

Thalamic parcellation based on iFC also did not fully match the DTI-based parcellation. Similar inconsistencies between these modalities have been reported for healthy adults (Zhang *et al.*, 2010). Notably, the pattern of iFC-based parcellations in our study of TD children and adolescents was quite similar to results in adults (Fair *et al.*, 2010) and resembled the pattern reported for adolescents in Fair et al. (2010).

Differences between connectivity techniques are expected given the very different signal sources (blood oxygenation in cortex vs. water diffusion in white matter) of iFC and DTI.

On the other hand, there was some convergence of functional and anatomical connectivity findings, with functional underconnectivity for several ROIs (SMA, SFG, left temporal pole, right SPL) accompanied by DTI evidence of white matter compromise. Yet, there were also notable differences. For temporal regions, group differences in TC-iFC were robust for STG and TG, without corresponding DTI findings. Notably though, iFC overconnectivity effects were found to be positively correlated with anatomical indices of mean and radial diffusivity for left STG and TG, possibly signs of myelin loss or compromise. For other (especially frontal) regions, both iFC and DTI analyses yielded evidence of aberrant connectivity. For right ACC and bilateral PCG, iFC overconnectivity was associated with increased RD. Right ACC iFC was associated with reduced FA and was significantly correlated with increased MD and RD, again suggesting a link between functional overconnectivity and anatomical white matter compromise. The described findings for temporal and frontal ROIs appear contradictory only at first glance and probably reflect limitations of tensor-based approaches in DTI (Jones *et al.*, 2013). Generally, the two modalities (iFC, DTI) examine very different parameters of 'connectivity' and may therefore not correspond in simple ways. More specifically, reduced FA and increased RD may reflect presence of multiple fiber orientations (Johnson *et al.*, 2013). Such DTI findings thus do not necessarily imply reduced or impaired connectivity and may, in fact, be consistent with observed functional overconnectivity.

Limitations

Our ASD cohort was high-functioning, as only participants able to hold extremely still during MRI scans could be included. Findings may not apply to lower-functioning

children. Second, the inclusionary age range was relatively large. Although, this allowed

us to test for age-related changes, the cross-sectional nature of our study prevented firm

conclusions with respect to maturational changes in TC connectivity between ages 8 and

17 years. Third, our study was more comprehensive for functional connectivity, whereas

anatomical analyses (probabilistic tractography) could not be performed for all ROIs due

to their computationally demanding nature. Restricting ROIs for these analyses to those

with significant iFC group differences, we may have missed some additional group

differences in anatomical connectivity. A further simplification in our study was the focus

on ipsilateral TC connections. While these are vastly predominant in the TD brain, any

possible abnormalities in this hemispheric organization in ASD may have gone

undetected in our study. Additionally, atypical thalamocortical connectivity in ASD likely

relates to iFC with other subcortical structures (such as basal ganglia) and cerebellum

(Khan, 2015). The complex circuits linking these could not be examined in the present

study.

Conclusions

Few previous studies have presented results relevant to TC connectivity in ASD.

Abnormal activation of TC networks involved in language processing has also been

reported for ASD adults (Müller *et al.*, 1998). Reduced thalamic input in face processing

(Kleinhans *et al.*, 2008), and increased functional connectivity between thalamus and

fronto-parietal networks (Mizuno *et al.*, 2006) have additionally been reported for ASD

groups compared to TD groups. Mizuno et al. (2006) also reported overconnectivity

between thalamus and anterior superior temporal lobe in the left hemisphere,

accompanied by thalamic underconnectivity with medial temporal regions bilaterally.

Shih et al. (2011) detected robust overconnectivity between thalamus and posterior

superior temporal sulcus in a larger sample of children and adolescents with ASD.

Methodological differences may account for divergent findings. Mizuno et al. (2006) studied adults (rather than children) and used thalamic (rather than cortical) seeds. Shih et al. (2011) tested for thalamic connectivity only in a small region of lateral temporal cortex. Both studies used task-activated (rather than resting state) data, although task effects were regressed out. This dissertation study is the first to provide comprehensive evidence of bilateral impairment of functional and anatomical connectivity between cerebral cortex and thalamus in ASD. Our findings provide evidence of regionally specific aberrations of thalamic connectivity in frontal and temporal lobes, with additional involvement of some parieto-occipital ROIs. While these findings were relatively consistent for five large cortical seeds, some regional differences were also found with relatively robust impairment of fronto-thalamic connections, but relative sparing and partial functional overconnectivity for temporo-thalamic connections especially in the right hemisphere. They suggest – albeit with some exceptions – a gross pattern of functional overconnectivity for earlier-maturing limbic and sensorimotor regions, but underconnectivity for later maturing supramodal regions. Correlations with diagnostic and neuropsychological measures suggest a role of TC connectivity in social interaction, executive difficulties, and repetitive and restricted behaviors in ASD. In a broader context, our findings of impaired TC connectivity are consistent with previous studies indicating functional (Ryu *et al.*, 1999, Starkstein *et al.*, 2000, Friedman *et al.*, 2003, Haznedar *et al.*, 2006) and anatomical (Tsatsanis *et al.*, 2003, Tamura *et al.*, 2010) impairment of thalamus in ASD. They are also consistent with the very first functional connectivity study that explored TC correlations using glucose positron emission tomography (Horwitz *et al.*, 1988).

Table 1A: Demographic data for autism spectrum disorders (ASD) and typically developing (TD) groups for first study.

	iFC sample			DTI sample		
	ASD (*n=22*)	TD (*n=23*)	*p*	ASD (*n=26*)	TD (*n=27*)	*p*
Age	14.2 (1.5) 12-17	14.3 (1.5) 12-17	.89	14.1 (2.5) 9-17	14.2 (2.2) 9-17	.82
Nonverbal IQ	111.1 (13.1) 70-140	108.0 (12.0) 86-129	.56	112.4 (14.9) 70-140	107.4 (13.1) 77-129	.43
Sex (Male:Female)	21:1	19:4		22:4	23:4	
Handedness (Right:Left)	18:4	20:3		24:2	24:3	

Table 1B: Demographic data for autism spectrum disorders (ASD) and typically developing (TD) groups for second study.

	iFC sample			DTI sample		
	ASD (*n=37*)	TD (*n=38*)	*p*	ASD (*n=34*)	TD (*n=33*)	*p*
Age	13.9 (2.6) 9-17	13.0 (2.6) 8-17	.43	13.7 (2.8) 7-17	12.9 (2.6) 8-17	.24
Nonverbal IQ	104.4 (16.9) 62-140	107.5 (12.5) 83-137	.37	105.2 (16.8) 69-140	107.5 (12.8) 83-137	.54
Sex (Male:Female)	32:5	30:8	.39	31:3	27:8	.10
Handedness (Right:Left)	32:5	31:7	.56	30:4	27:6	.47
Motion (RMSD/TMI)	.081 (.048) .021-.246	.082 (.041) .019-.166	.92	2.12 (3.9) -1.5-11.6	.70 (2.4) -2.1-7.8	.07

Table 2: List of all Harvard-Oxford Stereotaxic atlas ROIs used in iFC analysis (R: right, L: left).

Frontal Lobe	Temporal lobe	Parietal lobe	Occipital Lobe
R frontal pole	R temporal pole	R posterior cingulate	R lingual
R orbitofrontal	R inferior temporal	R central operculum	R cuneal
R medial frontal	R middle temporal	R parietal operculum	R supracalcarine
R frontal operculum	R superior temporal	R postcentral	R intracalcarine
R anterior cingulate	R transverse	R superior parietal lob.	R lateral occipital
R subcallosal	R fusiform	R precuneous	R occipital pole
R inferior frontal	R parahippocampal	R supramarginal	L lingual
R middle frontal	R hippocampus	R angular	L cuneal
R superior frontal	R amygdala	L posterior cingulate	L supracalcarine
R suppl. motor	L temporal pole	L central operculum	L intracalcarine
R precentral	L inferior temporal	L parietal operculum	L lateral occipital
L frontal pole	L middle temporal	L postcentral	L occipital pole
L orbitofrontal	L superior temporal	L superior parietal lob.	
L medial frontal	L transverse	L precuneus	
L frontal operculum	L fusiform	L supramarginal	
L anterior cingulate	L parahippocampal	L angular	
L subcallosal	L hippocampus		
L inferior frontal	L amygdala		
L middle frontal			
L superior frontal			
L suppl. motor			
L precentral			

Table 3: Significant DTI tractography results (all *p*-values FDR corrected). For all ROIs listed, TC-iFC underconnectivity was also found, except those marked **†**, for which iFC overconnectivity was detected.

Lobe	DTI index and region
	Fractional Anisotropy (FA; TD > ASD)
Frontal	RSMA; p=.006
	RACC; p=.006 †
	Mean Diffusivity (MD; ASD > TD)
Frontal	LSFG; p=.03
	RSFG; p=.008
	LSMA; p=.05
	RSMA; p=.03
	LPCG; p=.03 †
Temporal	Ltempol; p=.04
Parietal	RSPL; p=.04
	Radial Diffusivity (RD; ASD > TD)
Frontal	RSFG; p=.006
	LSMA; p=.05
	RSMA; p=.01
	LPCG; p=.03 †
	RPCG; p=.04 †
	RACC; p=.05 †
Temporal	Ltempol; p=.04
Parietal	RSPL; p=.04
	Axial Diffusivity (AD; ASD > TD)
Frontal	LSFG; p=.03
	RSFG; p=.05
Parietal	RSPL; p=.04

Table 4: Significant correlations between iFC z' scores for ASD group and behavioral/diagnostic measures (all *p*-values FDR corrected). BRIEF data were only available for 25 ASD participants.

Measure	RACC		RSFG		RFF		RSPL		RPCC	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
ADOS Total	.39	.01								
ADOS RRB									.35	.03
ADI-R Social			-.37	.02						
ADI-R Comm.							-.38	.02		
ADI-R RB	.42	.01								
CELF-Total					.45	.02				
BRIEF Plan/Orgn.					-.37	.02				
BRIEF WM					-.53	.01				
BRIEF MET					-.52	.01				
BRIEF GEC					-.42	.04				

Table 5: Significant correlations between FA and behavioral/diagnostic measures (all *p*-values FDR corrected) for ASD group. SP data were only available for 29 ASD participants, and BRIEF data for 25 ASD participants. For all measures except SP, higher scores indicate more severe symptoms.

| | FA | | | |
| | RACC | | RSMA | |
Measure	*r*	*p*	*r*	*p*
SCQ Total			-.45	.01
SRS Social Aware.	-.47	.01	-.48	.01
SRS Autistic Mann.			-.48	.01
SRS Social Cog.	-.49	.005	-.56	.001
SRS Total			-.51	.005
SP Sens. Seek.	.48	.01	.49	.005
SP Sens. Avoid.			.47	.01
BRIEF Inhibition	-.46	.01		
BRIEF Emotion. Reg.	-.48	.01	-.50	.005
BRIEF Shifting	-.53	.001	-.48	.01
BRIEF Monitor.	-.45	.01	-.50	.005
BRIEF BRI	-.49	.005	-.46	.01
BRIEF MET	-.47	.01	-.46	.01
BRIEF GEC	-.49	.005	-.46	.01

Table 6: Correlations between RD for ROIs showing significant group differences and behavioral/diagnostic measures (all *p*-values FDR corrected) in the ASD group. * *p*<.05. BRIEF data was only available for 25 ASD participants.

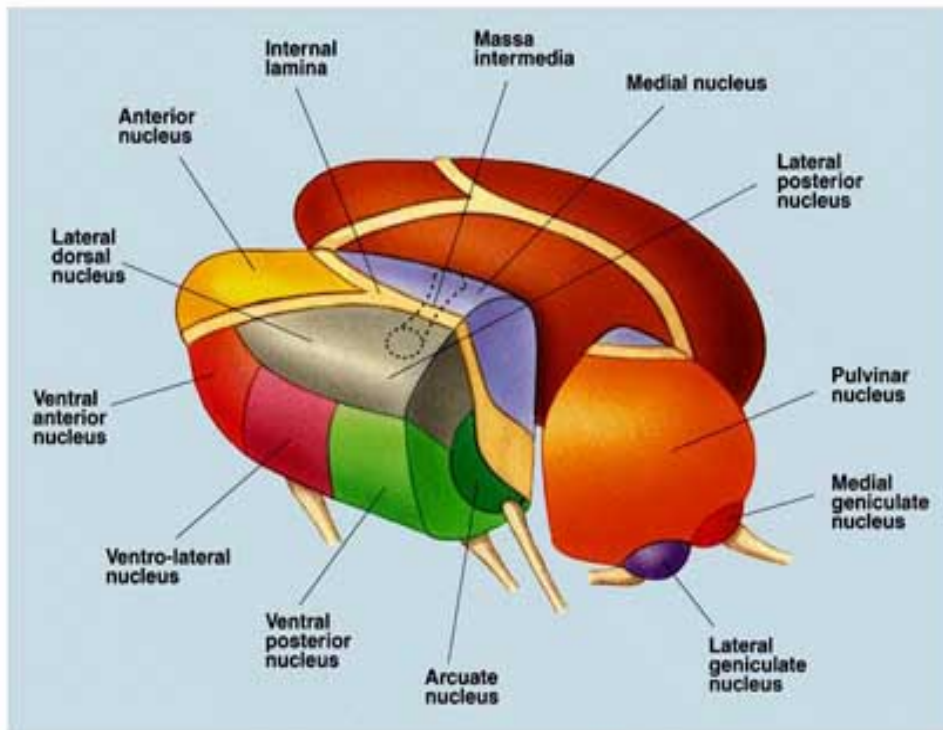| Measure	RACC *r*	RACC *p*	LPCG *r*	LPCG *p*	LSMA *r*	LSMA *p*	RSMA *r*	RSMA *p*	RSFG *r*	RSFG *p*	RSPL *r*	RSPL *p*
ADI-R Social			.45	.01			.46	.01	.42	.02	.46	.01
ADI-R Comm.					.42	.02						
SRS Soc. Aware.			.41	.01					.43	.01		
SRS Aut. Mann.			.40	.01	.31	.04	.33	.05				
SRS Soc. Comm.			.38	.02								
SRS Total			.49	.00	.39	.02	.39	.02				
BRIEF Shifting									.46	.01		
BRIEF WM	.42	.01										
BRIEF Monitor.									.38	.02		
BRIEF MET									.40	.01		
BRIEF GEC									.41	.01		

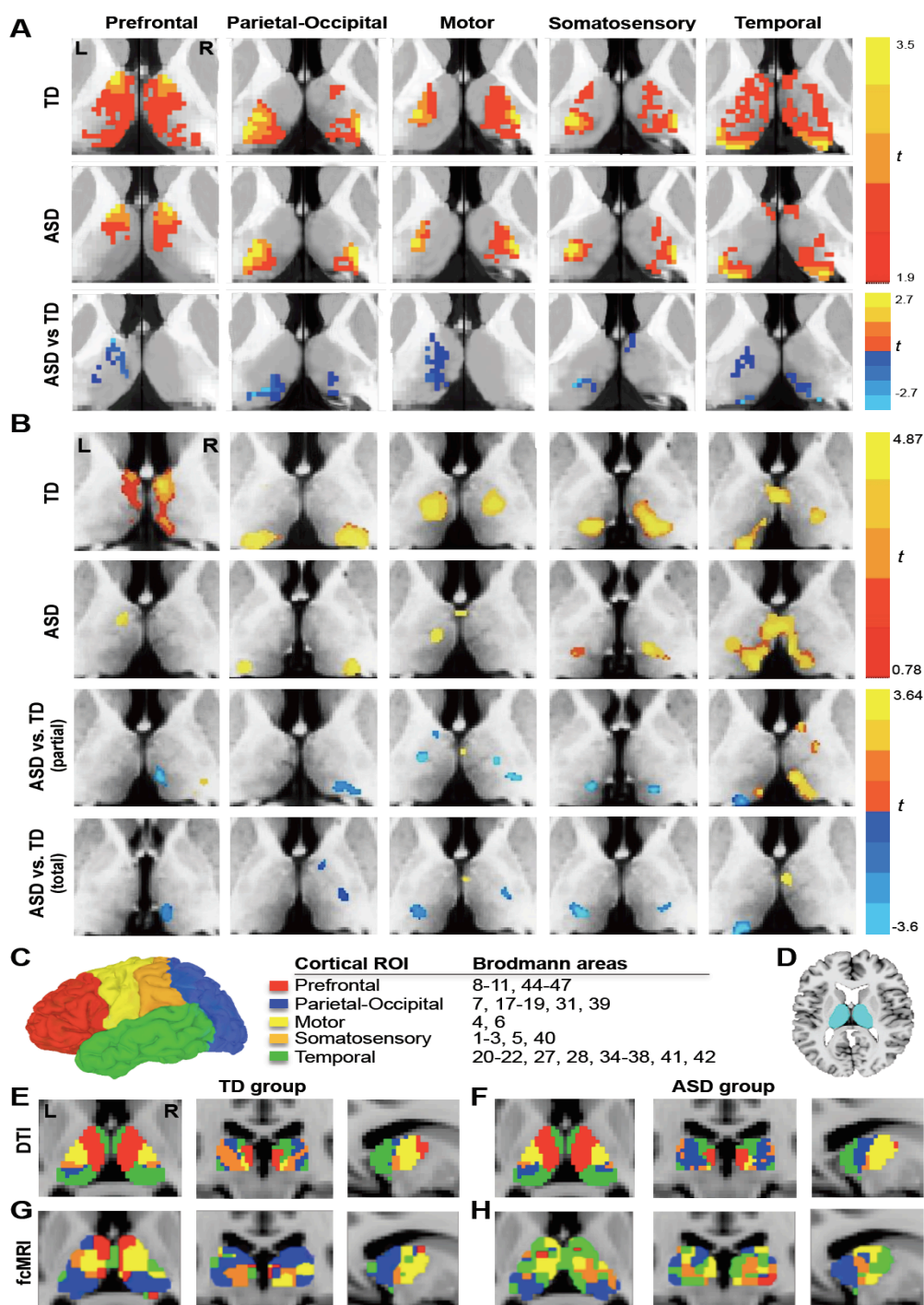Figure 1: Subdivisions of nuclei of the thalamus.

Figure 2: (A) DTI probabilistic tractography results; (B) iFC results from partial correlation analysis; total correlation analysis results are shown additionally in the bottom row; (C) Surface rendering of cortical ROIs (only left hemisphere shown) with color code used in parcellation and tabulation of Brodmann areas included in each cortical ROI; (D) thalamic mask. Thalamic parcellation for TD and ASD groups based on DTI (E-F), and iFC (G-H).
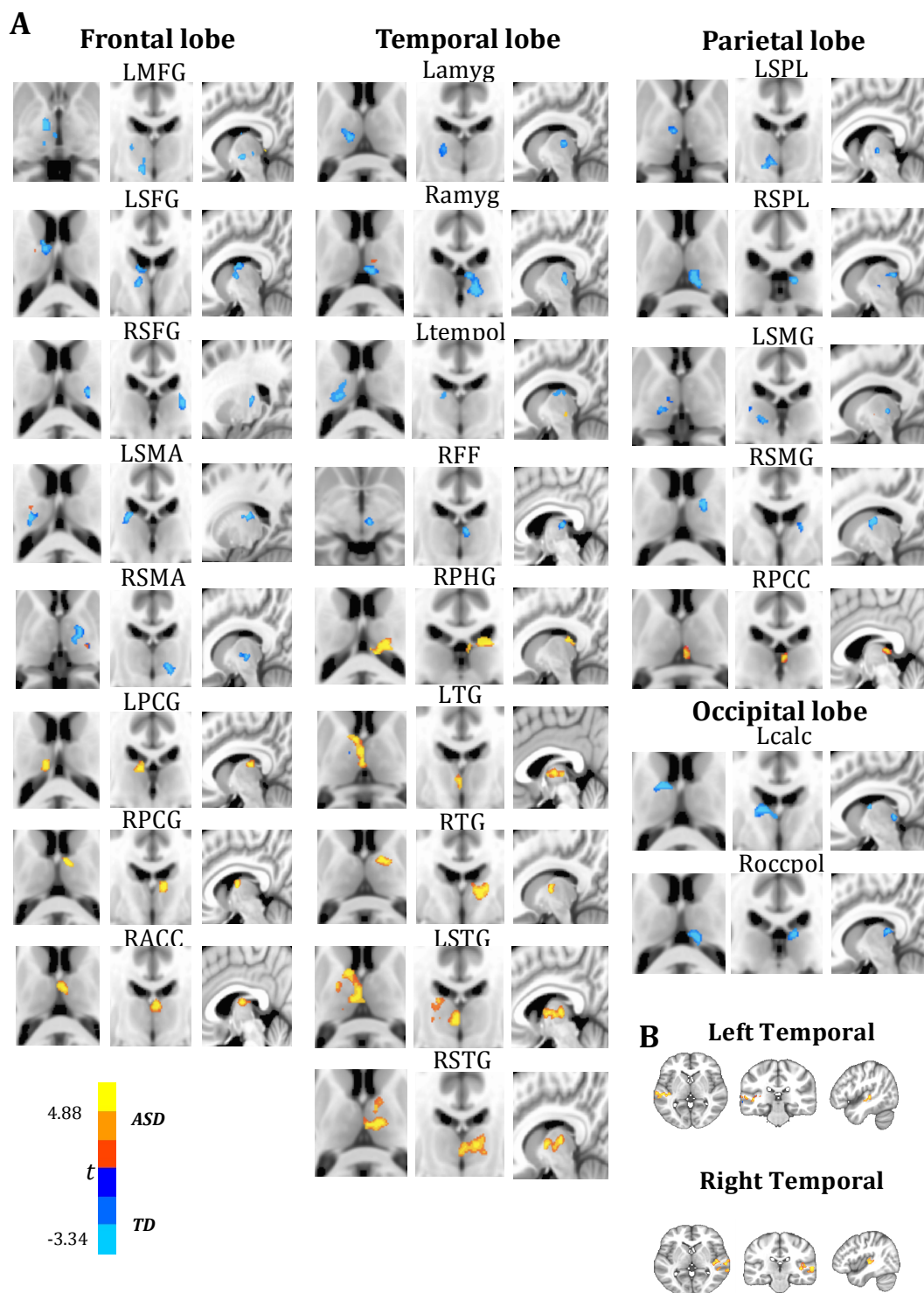
Figure 3: [A] iFC between frontal, temporal, parietal, and occipital ROIs from the Harvard-Oxford cortical atlas and ipsilateral thalamus. Only ROIs with significant between-group findings are shown. [B] Reverse connectivity analysis, using thalamic clusters of overconnectivity with superior temporal gyri (as shown in [A]) as seeds, indicates regions in and around auditory cortex driving these overconnectivity effects.
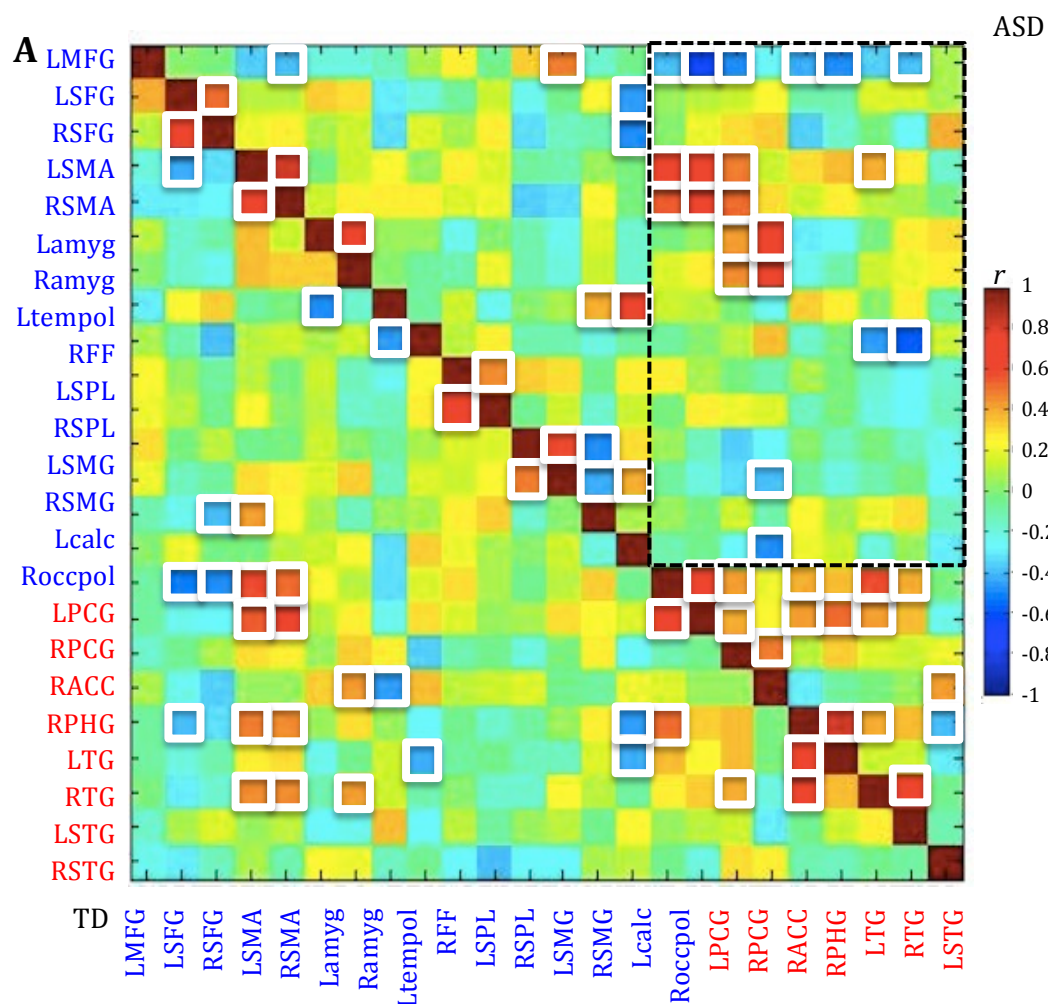
Figure 4: Correlation matrix for ROIs with significant iFC group differences. White squares indicate correlations $r > .39$ or $r < -.39$ ($p < .05$; FDR corrected). Font color indicates ROIs that were underconnected (blue labels) or overconnected (red labels) with thalamus in the ASD group (abbreviations as in main text). Dashed black line highlights the upper right quadrant of specific interest that shows correlations between underconnected and overconnected ROIs in the ASD group. For example, negative correlation ($r=-.63$) for LMFG-RPCG in the ASD group shows that low iFC with thalamus for LMFG was associated with high iFC for RPCG, indicating possible linkage between the two findings.
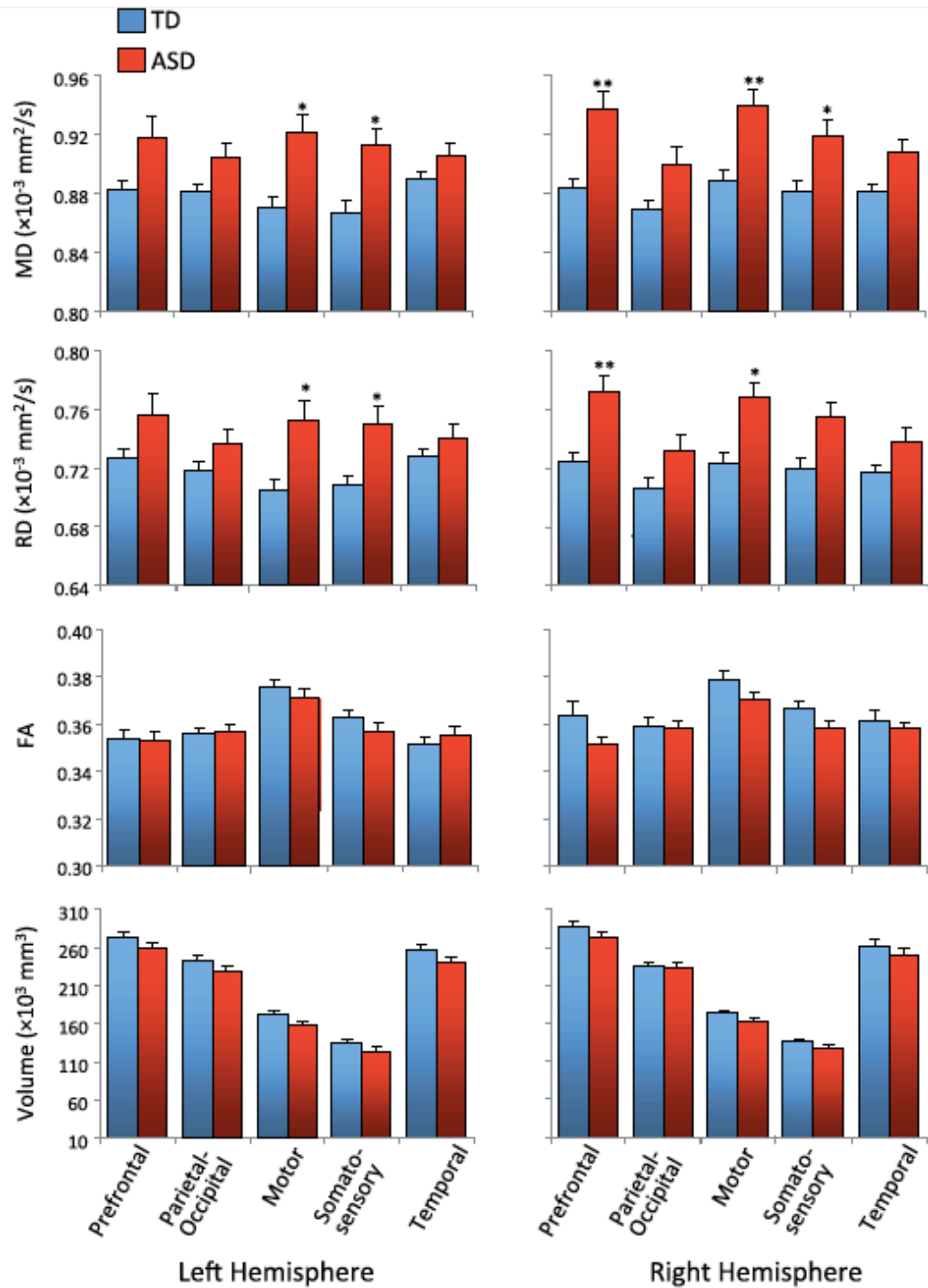
Figure 5: Mean diffusivity (MD), radial diffusivity (RD), fractional anisotropy (FA) and volume of thalamic connections with prefrontal, parietal-occipital, motor, somatosensory and temporal cortices in ASD and TD groups (** $p<0.001$; * $p<0.05$; corr.; error bars represent SEM).
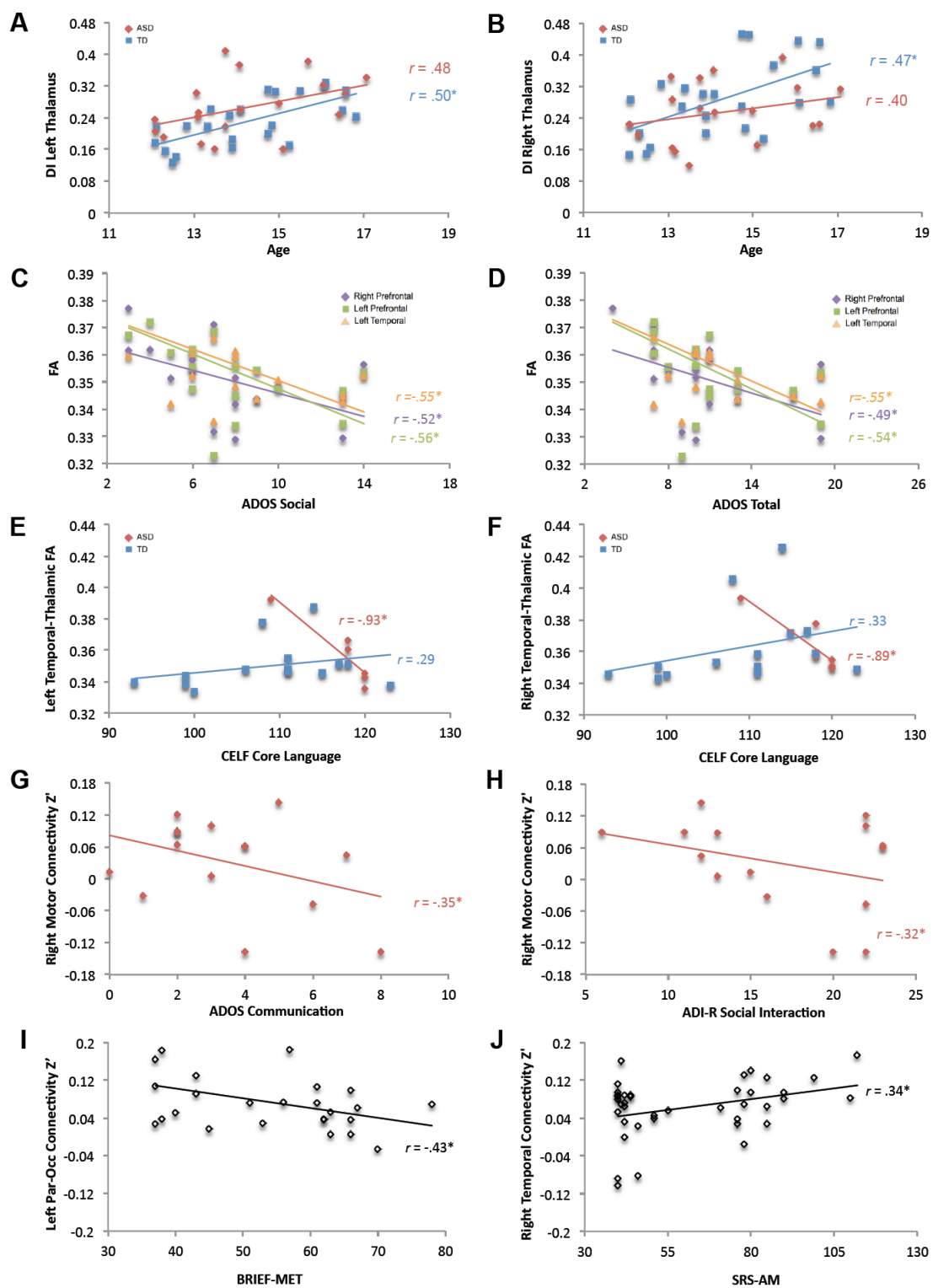
Figure 6: Correlations of connectivity measures as well as differentiation indices with age and diagnostic and neuropsychological scores for first study,

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