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White matter structure in the uncinate fasciculus: Implications for socio-affective deficits in Autism Spectrum Disorder

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ABSTRACT

Individuals with Autism Spectrum Disorder (ASD) have social and communication deficits and difficulties regulating emotions. The brain bases of these socio-affective deficits are not yet clear, but one candidate is structural connectivity in the left uncinate fasciculus, which connects limbic temporal and frontal areas thought to be involved in socio-affective processing. In this study, we assessed white matter structure in the left and right uncinate fasciculus in 18 high-functioning individuals with ASD and 18 group-matched typically developing (TD) controls using Diffusion Tensor Imaging. To test specificity of the associations, we also examined the association between both uncinate fasciculi and restricted and repetitive behaviors. Compared to TD individuals, individuals with ASD had significantly lower fractional anisotropy (FA) in the left and right uncinate. Group status significantly moderated the association between left uncinate and socio-affective deficits, indicating that within the ASD group, FA was associated with socio-affective deficits: Individuals with ASD with lower FA in the left uncinate had significantly more social and emotion regulation deficits. There was no association with restricted and repetitive behaviors. This study provides evidence that the left uncinate may play a critical role in socio-affective skills in individuals with ASD.

1. Introduction

Individuals with Autism Spectrum Disorder (ASD) have social and communication deficits as well as increased restricted and repetitive behaviors (APA, 2013). It is now clear that ASD is also often associated with pronounced difficulties regulating emotions (Laurent and Rubin, 2004; Mazefsky et al., 2013, 2014; Samson et al., 2012, 2014, 2015a). At a neurobiological level, ASD has been associated with abnormal white matter tissue structure in several pathways in the brain, including the left uncinate fasciculus (see Aoki et al., 2013, for a review). This white matter pathway connects the anterior temporal lobe including amygdala and hippocampus with prefrontal areas and is of particular interest since it plays a crucial role in processing socio-affective information in typically developing (TD) participants as well as in individuals with psychopathology (e.g., Frey et al., 2000; Johnstone et al., 2007; Pehrs et al., 2015; Zuurbier et al., 2013). As a consequence, we sought to link difficulties in socio-affective domains in individuals with ASD to white matter tissue structure in the left uncinate fasciculus.

1.1. Socio-affective deficits in Autism Spectrum Disorder

Social deficits in individuals with ASD include failure to initiate reciprocal social interactions, verbal and non-verbal communication difficulties, decreased sensitivity to social and emotional cues, and poor performance on Theory of Mind tasks. Social withdrawal, indifference, even avoidance of affection or physical contact, reduced eye contact, and decreased joint attention and facial responsiveness are also common (Rutgers et al., 2004).

In addition to the well-documented deficits in the social domain, there is increasing awareness that individuals with ASD often experience considerable emotional disturbances. Not only do they exhibit more negative and less positive emotions in

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comparison to TD controls (e.g., Ben Shalom et al., 2006; Capps et al., 1993; Kasari and Sigman, 1997; Samson et al., 2012, 2014), they also experience more frequent symptoms of anxiety and depression, are more irritable, have more frequent meltdowns or tantrums, are more aggressive, and show increased self-injurious behavior (Dominick et al., 2007; Gotham et al., 2013; Mazefsky et al., 2013; Quek et al., 2012; Vasa et al., 2013; White et al., 2009).

Recent studies have corroborated the critical role of emotion dysregulation in affective functioning (Mazefsky et al., 2013; Samson et al., 2012, 2015b). Individuals with ASD, compared to TD participants, seem to have a dysfunctional pattern of emotion regulation, characterized by less frequent use of adaptive emotion regulation strategies (goal-directed behaviors, seeking social support, cognitive reappraisal; Jahromi et al., 2012; Rieffe et al., 2011; Samson et al., 2012, 2015ac) and more frequent use of maladaptive strategies (avoidance, venting, expressive suppression; Jahromi et al., 2012; Konstantareas and Stewart, 2006; Samson et al., 2012, 2015a; Mazefsky et al., 2014). Emotion dysregulation in ASD has been linked to increased psychopathology (Mazefsky et al., 2014), lower levels of prosocial peer engagement (Jahromi et al., 2013), and higher levels of maladaptive behavior (Samson et al., 2015b).

The current study focuses on both social deficits and emotion regulation deficits because these socio-affective deficits are (1) heavily linked and thought to influence one another (emotion regulation often takes place in social contexts and is acquired through social interactions, e.g. between child and caregiver in early stages of life, see English et al., 2012; Shefield Morris et al., 2007), (2) evident in ASD, and finally, (3) are thought to rely on heavily overlapping neural structures.

1.2. Potential neural correlates of socio-affective deficits in Autism Spectrum Disorder

In order to process and regulate socio-affective information, several brain regions need to work in concert. However, in ASD, neural connectivity between functionally connected regions seems to be altered (e.g., Aoki et al., 2013) which is in line with the aberrant connectivity hypothesis in ASD (Courchesne and Pierce, 2005). One particular promising candidate in explaining socio-affective deficits in ASD is the uncinate fasciculus.

The uncinate fasciculus connects polar temporal areas, including the amygdala and hippocampus, to cortical regions such as orbitofrontal cortex (OFC) (Kier et al., 2004; Olson et al., 2015; Von der Heide et al., 2013). It therefore connects basic emotion processing areas with regions involved in higher order processing, including emotion regulation. The uncinate has been linked to processing of emotional information in healthy populations (Frey et al., 2000), and has been reported to be related to impaired socio-emotional processing in disorders such as fronto-temporal dementia (Von der Heide et al., 2013), and also more generally with symptom severity in individuals with ASD (Poustka et al., 2012).

While multiple white matter structures have been found to be affected in ASD (for a review, see Aoki et al., 2013; Barnea-Golary et al., 2004; Barnea-Golary et al., 2010; Olson et al., 2015), the left uncinate may be particularly important in processing socio-affective information (Pehrs et al., 2015; Olson et al., 2015). There seems to be a relatively left dominant abnormality in the uncinate fasciculus in ASD. Brain asymmetry usually occurs in typical brain maturation, which seems to be essential for emotion processing and other functions including cognition, sensory and motor functions. Atypical brain maturation in ASD and possible pathophysiology of disturbances of these functions may specifically affect the left uncinate (see Aoki et al., 2013). In the same lines, there is recent evidence that white matter tissue structure specifically in the left uncinate fasciculus is related to emotion regulation in a healthy population (Zuurbier et al., 2013). Furthermore, there is evidence that neurotypicals engage the left prefrontal cortex to down-regulate amygdala responses to negative stimuli. In contrast, patients with major depression, who have more difficulties regulating their emotions, do not seem to engage the left lateral-ventromedial prefrontal circuitry important for the down-regulation of amygdala responses (Johnstone et al., 2007). These findings suggest the importance of the involvement of the left uncinate in socio-affective skills including emotion regulation.

1.3. The current study

The goal of this study was to examine the role of one white matter structure, the left uncinate, in socio-affective processing in individuals with ASD compared to TD participants. We focused on children and adolescents, since socio-affective skills mature during this important developmental stage (Riediger and Klipker, 2014). Parent reports were used to assess socio-affective skills and clinical symptomatology given difficulties of accessing own mental (including emotional) states in individuals with ASD (Fitzgerald and Bellgrove, 2006).

We used Diffusion Tensor Imaging (DTI) to examine the tissue structure of white matter tracts implicated in processing of socio-emotional information. DTI allows for in-vivo measurement of fiber tracts in the brain. Diffusion properties are affected by biological properties of the axons (e.g. myelination, axonal density, and diameter) that are driven by overall white matter maturation, as well as geometric configurations of the axons (tract curvature, directional coherence, crossing, branching and merging fiber bundles). Fractional anisotropy (FA) is one of several diffusion parameters quantifying directionality of water diffusion on a scale from zero (equal diffusion in all directions) to one (diffusion in one direction, see Ameis et al., 2011) and reflects myelination, white matter organization, and the density of white matter tracts (Olson et al., 2015). Abnormal development of white matter may result in atypical white matter structure, which in turn may affect behavior, including socio-affective deficits.

We expected individuals with ASD to have more socio-affective deficits than TD participants. Specifically, we expected individuals with ASD to have significantly more social deficits and lower control over their emotions compared to TD participants. Moreover, based on previous studies (Aoki et al., 2013, for a review), we hypothesized that individuals with ASD would have lower FA in the left uncinate. Furthermore, we expected group status to moderate the association between abnormal white matter structure in the left uncinate and socio-affective deficits. In particular, we expected white matter structure in the left uncinate to be linked to socio-affective skills in individuals with ASD, but not in TD individuals, since brain behavior associations are more frequently identified in individuals with neuropsychiatric disorders when compared to neurotypicals (Baur et al., 2011; Poustka et al., 2012; Thomason and Thompson, 2011). To test specificity of group effects as well as moderating effects, we also analyzed group differences in the right uncinate fasciculus and tested moderation effects of group status on the association between white matter tissue structure in the uncinate fasciculi and another core feature of ASD, namely restricted and repetitive behaviors. We did not expect group differences or moderation effects related to the right uncinate, or repetitive behaviors.

2. Methods

2.1. Participants

Eighteen individuals with ASD (2 female) and 18 TD individuals