Discriminating Facial Emotion: Neural Pathways in Autism Spectrum Disorders

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Recent research has found aberrant neural connectivity between functionally connected areas in autism spectrum disorders. Diffusion Tensor Imaging offers a novel approach to studying functional connections by examining the integrity of structural connections—white matter tracts—between functionally connected regions. The research question of interest involves investigating the affective circuitry involved in atypical face processing in autism. Specifically, this study sought to corroborate the underconnectivity model by tracking major differences in the left and right uncinate fasciculus—a fiber bundle connecting the amygdala with the orbitofrontal cortex—in 13 autistic and 13 typically developing adolescents. There were no significant differences between the tracts or the groups, suggesting that aberrant functional activation may be intrinsic to the amygdala itself and does not extend to structural underconnectivity in regions surrounding it. The discussion addresses this study's limitations and provides future directions for the findings.

Keywords: Neuroimaging, uncinate fasciculus, face processing, DTI

Autism Spectrum Disorders refer to a cluster of behavioral abnormalities in three realms: social interaction, language acquisition, and interest in play as evidenced by the presence of repetitive stereotyped behaviors. According to the Center for Disease Control and Prevention (2010), an average of 1 in 110 children in the United States has an Autism Spectrum Disorder. Despite the high prevalence of this neurocognitive developmental disorder, little is known about its underlying etiology. Functional imaging has enabled neuroscientists to generate and test hypotheses linking neurological correlates to known interpersonal and communication deficits. Recently, there has been an emphasis on finding pathways, rather than specific brain regions, associated with pathological behavior. Researchers have found abnormalities in both white and gray matter in the brains of autistic individuals in functional (Alexander et al.,

2007) and resting states (Cherkassky, Kana, Keller, & Just, 2006). The advent of Diffusion Tensor Imaging (DTI) has enabled the investigation of structural connectivity between functionally related anatomical regions to gain a better grasp of the etiology underlying autism. We used DTI to explore the structural integrity of white matter tracts implicated in the emotion-processing pathways. Specifically, this investigation compared differences in the uncinate fasciculus, a major white matter tract connecting parts of the limbic system with the orbitofrontal cortex, for typically developing and autistic children.

For decades, the inability of autistic individuals to form fulfilling social bonds with others was poorly understood. Since optimal cognitive, emotional, and language abilities rely on integrating complex brain systems, some hypothesized that the deficits displayed by autistics in these realms reflect atypical connectivity between brain systems rather than deficiencies in individual brain regions (McAlonan et al., 2008). Indeed, brain-imaging studies demonstrate that autistic individuals do have reduced functional connectivity in brain areas implicated in social behavior, such as parts of the frontal lobe, temporal lobe, and the corpus callosum (Alexander et al., 2007). Morphologic studies show that the brain matures in a posterior-anterior pattern. Since it develops abnormally in autism, the late developing prefrontal areas used in higher-order executive functioning may show the most pronounced defects in adolescence (Carper, Moses, Tigue, and Courchesne, 2002).

DTI permits the researcher to characterize microstructural abnormalities in white matter tracts as it enables non-invasive in-vivo investigation of functional impairments of brain pathways. DTI is based on the premise that during random Brownian motion, displacement molecules probe tissue structure at a microscopic level (Bihan et al., 2001). Since diffusion is encoded via magnetic field gradient pulses, only molecular displacement that happens along the gradient is visible in a given image voxel. The observation of this displacement can provide clues to the structure and geometry of tissues, since diffusion is fastest along the longest vector of the 3-D tensor model of DTI. This directional property of diffusion is due to the fact that the rate of diffusion is fastest when it is parallel to the axon bundles within which it occurs. Based on the assumption that the fastest diffusion takes place parallel to the organization of axon bundles, a given alignment observed in a voxel should be able to indicate the overall orientation of the set of fiber bundles in question.

Fractional Anisotropy (FA) is a scalar value between 0 and 1 where 0 denotes isotropy (equal diffusion in all directions) and 1 denotes anisotropy (diffusion occurs only along one axis). This measures the fraction of the magnitude of diffusion that can be ascribed to directional dependence (Bihan et al., 2001) and is a common metric used to quantify DTI imaging. Essentially, FA is one index used to measure coherence of directional diffusion, such that lower FA indicates lower white matter integrity (Schipul, Keller, & Just, 2011). FA is a good measure of white matter integrity since the water displacement present within an MRI image voxel informs the structure and geometry of tissues whose surface this diffusion is constantly probing at a microscopic level.

DTI is particularly applicable in a clinical setting as it is sensitive to developmental changes and pathological differences informed by axonal density, size, myelination, and the organization of fibers. Furthermore, from a neural maturation perspective, the degree of diffusion anisotropy increases in the white matter tracts of the brain during the myelination process. This knowledge can be used to assess brain maturation and compare connectivity of brain structures between typically developing individuals and those with neurocognitive developmental disorders such as autism.

Although brain-imaging technology has opened avenues to explore microstructural information, the evidence on what specific white matter differences underlie autism remain unclear. While Barnea-Goraly et al. (2004) reported lower FA in the ventromedial prefrontal cortex, anterior cingulate gyrus, and corpus callosum of autistic children (mean age 14.6), Ben Bashat et al. (2007) found that very young autistic children (mean age 1.8-3.3 years) tend to have accelerated white matter growth compared to normative controls. In attempting to reconcile contradictory findings, Cheung et al. (2009) suggested that since autism exists along a spectrum, investigating a distributed deficit is all the more challenging. They steered away from a group-difference comparison to test a symptoms-led approach in which they correlated neural information (FA values) in 28 autistic children between 6 and 14 years of age with behavioral data (Autism Diagnostic Interview-Revised algorithm scores). Firstly, FA in the autism group was significantly lower than in the control group in the right ventral temporal lobe adjacent to the fusiform gyrus and greater in the right inferior frontal gyrus and left occipital lobe. Further, there was a high correlation between lower FA and higher ADI-R scores across the white matter tracts extending from these regions of interest, indicating that overt symptoms of autism are indeed associated with a disruption in white matter development. The strength of this study lies in the fact that it incorporates a symptoms-led approach in redefining autism.

Longitudinal studies pose the most promising avenue in answering which specific affective processes link up with which neural pathways, since these allow a closer delineation of variables during different time points spanning the course of a developmental disorder. Experimental literature on face processing has documented that when autistic individuals are directly spoken to, they gaze at faces significantly less than typically developing individuals and tend to avoid eye contact, focusing on the mouth instead (Kirchner et al, 2011). Further, the neural speed with which autistic individuals process faces is also slower than controls (McPartland et al., 2004).

Dalton et al. (2005) collected eye-tracking data along with functional brain activity during face discrimination tasks from 30 autistic and 28 typically developing individuals. They found that the amount of time the autistic group spent fixating on faces was positively correlated with activation in the fusiform gyrus (an area important for recognizing facial expression) and amygdala (an area important for coding negative social information and threat). Dalton et al. (2005, p. 324) sum up their model by saying that “face-

processing deficits in autism arise from hyperactivation in the central circuitry of emotion that produces heightened sensitivity to social stimuli, leading to characteristic diminished gaze fixation, which in turn results in atypical activation of the fusiform gyrus." These data suggest that processing faces has a heightened—and possibly aversive—emotional valence for autistic individuals. Volumetric data on the amygdala also points to its central role in affective processing. In a longitudinal brain-imaging study of autism, Munson et al. (2006) found that larger right amygdalar volume at ages 3 and 4 was associated with severe social and communication impairments and was predictive of increased social and communication deficits at age 6.

These experiments illustrate face-processing deficits in autism by assessing functional activation in areas of the limbic system. It is worth noting that some researchers believe that while abnormal functional connectivity does not necessitate abnormal structural connectivity, abnormal structural connectivity commonly results in abnormal functional connectivity (Koch, Norris, & Hund-Georgiadis, 2002; Skudlarski, Jagannathan, Calhoun, et al., 2008). Thus, the value in using DTI lies in the fact that it offers a novel approach in corroborating the underconnectivity model of autism by assessing the structural linkages between functionally connected brain areas. The functional role of the amygdala in emotion processing has already been established, since the amygdala connects to the orbitofrontal cortex via the uncinate fasciculus. We used tractography to investigate the quality of this structure as it is implicated in social cognition.

The present study is part of a larger brain-imaging project exploring functional patterns of activation in facial emotion processing areas. The project as a whole uses imaging data from a group of adolescents who were diagnosed with autism between 12 and 24 months of age. It combines retrospective developmental data and treatment information regarding their current functional level with imaging data to evaluate which structural and functional differences in emotion-processing pathways are contributing to these differential outcomes. The present study is a subset of this project and uses DTI and tractography to compare the uncinate fasciculus—a tract connecting the amygdala (an area important for encoding social threat and fear conditioning) to the orbitofrontal cortex (an area implicated in decision-making and reward systems)—in autistic and typically developing adolescents.

A study by Jou et al. (2011) helped anchor our hypotheses regarding structural differences between autistic and typically developing adolescents. They used voxel-wise comparison of FA and tractography to examine the integrity of major fiber tracts connecting key structures involved in social information processing. Ten autistic males were compared with ten typically developing ones (mean age 13.5 years). They found that there was lower FA in the inferior longitudinal fasciculus, superior longitudinal fasciculus, and the corpus callosum. These findings provide preliminary support for aberrant neural connectivity between the amygdala, fusiform face area, and superior temporal sulcus—areas critical for social perception and cognition.

Other imaging studies have replicated the finding that autistic children have lower fractional anisotropy in the left and right inferior and superior longitudinal fasciculus (Shukla et al., 2010; Groen et al., 2010). The inferior longitudinal fasciculus is adjacent to the uncinate fasciculus, and since areas proximal to seed regions of interest also tend to have similar FA values, and because FA is a measure of structural integrity and is negatively correlated with social deficits in behavior (Cheung et al., 2009), we expect FA values in the left and right uncinate fasciculi to be significantly lower in autistic subjects compared to controls. We also chose to explore group differences in the left and right uncinate fasciculi to gauge if there were structural differences between these tracts and if these differences are mediated by the diagnosis. It is worth noting that the lateralization of the fasciculi denote specialized functions, such that the integrity of the left tract is implicated in verbal memory and general intelligence while the integrity of the right tract is associated with social anxiety and other social deficits. In keeping with this knowledge, we expected that the FA values in the left uncinate fasciculus would correlate positively with IQ measures.

Method

Participants

Participants in the autism group were recruited in cooperation with the Wisconsin Early Autism Program (WEAP) from a sub-sample of children treated at their clinics. In the previous study conducted by WEAP (2005), 35 children were randomly assigned to a clinic-directed group or to a parent-directed group that received intensive hours but less supervision by well-trained supervisors. Four years after treatment, at age seven, 48% of the children showed rapid learning, achieved average post-treatment scores, and were succeeding in regular education classrooms (fast responders), while the remaining 52% were not (slow responders), although no differences were found between treatment types.

Participants who met the following criteria from the WEAP sample of respondents were included in our study: chronological age between 10 and 18 years of age, minimum mental age of 5 as assessed by the Wide Range Intelligence Test (Glutting, Adams, & Sheslow, 2000), willingness to participate and provide informed consent/assent, and MRI compatibility (as gauged by the MRI pre-screening form).

We recruited the typically developing group from the Madison area through newspaper advertisements. They were matched for age and handedness to the autism group. Typically developing participants were excluded if they had any cognitive impairments or psychological diagnoses or contraindications to MRI scanning with a standard MRI pre-screen.

The final sample of participants encompassed 13 autistic and 13 typically developing males averaging 13.6 years of age. Two autistic participants from the WEAP referrals withdrew from the study due to discomfort with the scanner environment (noise, claustrophobia, and boredom). One typically de-

veloping participant withdrew after the first scan sequence due to the noise in the scanner.

Both autistic and typically developing participants were compensated for completing the full experiment ($140 and $80 respectively). Additionally, all autistic participants and their families who came in from more than 1.5 hours of travel distance outside of Madison, Wisconsin, were reimbursed for mileage and were offered the option of housing and meals.

Materials

The following retrospective assessments were obtained from WEAP on the autistic participants enrolled in this study: Bayley Scales of Infant Development-II (Bayley, 1993); Wechsler Preschool Primary Scales of Intelligence-III (Wechsler, 1991); Reynell Developmental Language Scales (Reynell & Gruber, 1990); Clinical Evaluation of Language Fundamentals (Semel, Wiig, & Secord, 1995); Vineland Adaptive Behaviors Scales (Sparrow, Balla, & Cicchetti, 1984); Social Communication Questionnaire (Rutter, Bailey & Lord, 2003); Wide Range Intelligence Test (Glutting & Sheslow, 2000); the Early Learning Measure (Smith, Buch, & Gamby, 2000); and the hours and types of treatment received by each participant. On behalf of WEAP, psychologists made these assessments at two times - when the participants were ages 2 and 12. A clinical psychologist at the Waisman center who is certified as research reliable on the Autism Diagnostic Observation Schedule-Generic (ADOS) (Lord et al., 1994), was engaged to obtain a current measure of social and verbal functioning and autism severity.

Brain MRI images were acquired with a GE Signa 3-T scanner equipped with high-speed gradients and a whole-head transmit-receive quadrature birdcage headcoil (GE Medical Systems). We acquired structural brain images for anatomical localization of functional activity. After the anatomical images were collected, functional data were collected using whole-brain echo-planar imaging (EPI). Sagittal acquisition was used to acquire 30 slices per functional volume, with an image thickness of 4 mm and gap of 1 mm. Four hundred and nine functional images were acquired (TE 1⁄4 30 ms, TR 1⁄4 2 s, FOV 1⁄4 240 x 240mm, 64 x 64 matrix). The resulting voxel size was 3.75 x 3.65 x 5 mm. High angular DTI data were obtained in 48 directions along with 8 B0 acquisitions and a voxel matrix of 256 x 256 x 74., with a resulting pixel dimension of 1mm x 1mm x 2mm. Forty eight standard black and white Eckman faces—24 neutral and 24 fearful expressions—were utilized to show subjects in the scanner.

Procedure

Participants read and signed all consent and assent forms regarding the experimental procedure, MRI scanning, and standardized testing involved in the study. Parents provided consent for participants under 18, and adoles-

cents between 14 and 18 years of age signed the minor portion of the standard consent form, while those less than 14 years of age signed an assent form.

All participants first underwent a simulation to acclimatize to the environment of the MRI scanner. The participants were shown the mock scanner and the procedure was described to them. During the practice scan, each participant was given earplugs and head phones to protect their hearing and allow them to communicate with researchers. We utilized an unrelated practice task during the mock scanning session that resembled the experimental facial emotion discrimination task in timing and required response. Participants pressed a button corresponding to either a blue or a yellow colored square shown on a screen while in the scanner. The mock scan took approximately 45 minutes.

Once the participant felt comfortable with the mock scan, he or she was led to the real MRI machine. Participants were fitted with an elastic belt for respiration data collection and a small clip on their left index finger for the collection of pulse oxygenation data. All scans started with approximately 20 minutes of anatomical scans followed by the 7-minute functional scan during which the participants performed the facial emotion discrimination task.

We used a total of 48 standard black and white Eckman faces (24 male, 24 female) conveying either fearful or neutral expressions. Each face was presented for 2.5 seconds, separated by a pseudo randomized interstimulus interval of 1.5 to 3.5 seconds. The participant was instructed to press a fuzzy button for the fearful face and a smooth one for the neutral face. This task was followed by a 7-minute resting state scan in which the participant was told to close his or her eyes and try to relax. We counter-balanced the resting state and facial emotion discrimination tasks to balance potential order effects. We also collected standard structural scans and DTI scans providing data on white matter fiber strength, location, and directionality. Additionally, eye movements, fixations, and pupil diameters were acquired using an iView system with a remote eye-tracking device (SensoMotoric Instruments, 2001), although these data were not included for this research project. The full scanning session lasted approximately 45 minutes and participants were shown a DVD of their choice for the duration of the scan time, except during the 15 minutes when they were engaged in facial emotion discrimination and the resting state scans.

Dependent Measures

The primary variable of interest for this study was the DTI measure of FA to explore between-group differences in the uncinate fasciculus. In addtion, we explored differences between the left and right tracts and correlated IQ and SCQ scores with the FA values we generated.

Results

We used TrackVis, a software tool used in visualizing and analyzing fiber tracts in the brain acquired from DTI imaging, to analyze each individual subject's uncinate fasciculus. The FA values generated upon manual tractography of each subject's fiber tracts were then imported into SPSS. A 2x2 mixed design ANOVA was conducted on the FA values of the left and right uncinate fasciculi in the autism and typically developing groups. There were no significant differences in FA values between the typically developing and autistic participants (M = .449, SD = .006; M = .456, SD = .006) or between the left and right tracts (M = .457, SD = .006; M = .447, SD = .004). The interaction between the group and tract was also nonsignificant, indicating that the FA values for each tract did not vary as a function of group membership. IQ scores differed significantly between groups ($p < .01$), with the typically developing adolescents scoring higher than the autistic subjects. Similar trends occurred in the SCQ scoring ($p < .01$) with typically developing adolescents scoring significantly lower than the autistic subjects, indicating higher social functioning. IQ was significantly and negatively correlated with SCQ scores (r = -.78, $p < .01$), indicating that the participants with higher IQs had lower social dysfunction as measured by the SCQ. Neither IQ nor SCQ scores significantly moderated the relationship between diagnosis and FA values, suggesting that these variables of intellectual and social function level are not predictive of the structural integrity of the emotion-processing pathway in question.

Discussion

Neither a significant main effect nor an interaction was found in our data, suggesting that aberrant functional activation may be intrinsic to the amygdala itself and does not extend to abnormalities in structural connectivity in surrounding regions. On the other hand, since the uncinate fasciculus is the last white matter tract to mature in the human brain (Lebel et al., 2008)—sometimes even developing into a person's 30s—it is possible that our conservative methods did not detect subtle developmental differences between groups that may polarize more over time.

Consistent with previous literature, IQ scores were significantly different between autistic and typically developing groups, but this did not mediate the relationship between diagnosis and FA values between groups. Our nonsignificant findings are surprising in light of the fact that IQ and SCQ scores are strongly and negatively correlated—the overlapping intellectual and social deficits in this low-functioning group should predict stronger differences in the structural integrity of the uncinate fasciculi against controls.

That said, our nonsignificant findings can be explained by taking many factors into consideration. First of all, our sample size was limited to 13 participants in each group, and having a larger sample size would have improved the power and statistical reliability of our study and increased the generalizability of these findings. Secondly, it is possible that the film that partici-

pants were allowed to watch for the duration of their scanning procedure potentially confounded our results; since each participant was allowed to choose his or her own DVD, self-selection in choice of stimuli may have spurred some changes in functional activity of regions such as the amygdala and canceled out variance between groups. Since the uncinate fasciculus is a fiber bundle connecting areas of the limbic system with frontal regions, we do not expect this self-selection to affect its long-standing structural integrity, but caution is due in interpreting functional findings of amygdala activation, given this potential confound.

Future directions in analyzing tractography results can be improved if researchers take the number of fibers in the left and right uncinate fasciculi into account, since it offers a more nuanced picture than just looking at FA values. Additionally, this analysis is part of a much larger study that involves voxel-based morphometry to investigate several regions of interest associated with affective mechanisms in face processing in the frontal and temporal lobes. Contextualizing these findings in line with analyses on other major white matter tracts will provide further clues to whether there are structural deficits in face-processing pathways in autism. On a final note, since DTI data is informative of structural connections between functionally connected areas, a valuable future direction may be towards combining functional information with structural information into holistic explanatory models of face processing in autism instead of studying DTI findings in isolation.

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