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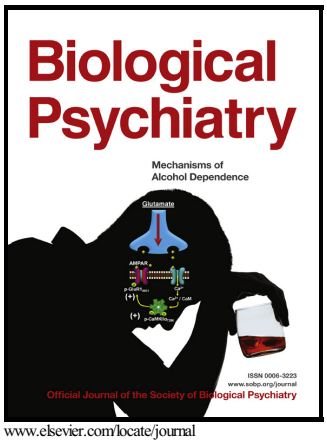

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Impaired communication between the motor and somatosensory homunculus is associated with poor manual dexterity in Autism Spectrum DisorderDexterity and fronto-parietal networks in Autism

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Title: Impaired communication between the motor and somatosensory homunculus is associated with poor manual dexterity in Autism Spectrum Disorder.

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Abstract

Background: Fine motor skill impairments are common in Autism Spectrum Disorder (ASD), significantly impacting quality of life. Sensory inputs reaching the primary motor cortex (M1) from the somatosensory cortex (S1) are likely involved in fine motor skill, and specifically motor learning. However, the role of these connections has not been directly investigated in humans. This study aimed to investigate, for the first time, the role of the S1-M1 connections in healthy controls *in vivo*, and whether microstructural alterations are associated with motor impairment in ASD.

Methods: 60 right-handed neurotypical adult males aged 18-45, and 60 right-handed age- and sex-matched subjects diagnosed with ASD underwent fine motor skill assessment and scanning with diffusion tensor imaging (DTI). The streamlines of the hand region connecting S1-M1 of the motor-sensory homunculus were virtually dissected using TrackVis, and diffusion properties extracted. The face/tongue region connections were used as control tracts.

Results: The ASD group displayed lower motor performances and altered DTI measurements of the hand-region connection. Behavioral performance correlated with hand-region DTI measures in both groups, but not with the face/tongue connections, indicating anatomical specificity. There was a left-hemisphere association of motor ability in the control group, and an atypical rightward shift in the ASD group.

Conclusions: These findings suggest that direct interaction between S1 and M1 may contribute to the human ability to precisely interact with and manipulate the environment. As electrophysiological evidence indicates these connections may underpin long-term potentiation in M1, our findings may lead to novel therapeutic treatments for motor skill disorders.

Text: Introduction

The development of fine motor skills for precision grasping has been crucial to achieving greater control of the environment throughout evolution. This is particularly true for humans that have acquired the finest ability to manipulate objects for a wide range of activities that are characteristic of our species, from tool making to writing and artistic expression. Skilful hand motor ability depends on precise movement of the thumb and forefingers, which is under the direct control of the primary motor cortex (M1) (1).

The neurons of M1 are arranged according to a topographical map of the opposite body half. A distinct feature of this map consists of the disproportionate representation of neurons controlling those muscles capable of finely controlled movements, generally referred to as the motor homunculus (2). For instance, the largest areas in M1 are occupied by neurons controlling finger movements, followed by neurons for lips and tongue movement. A similar topographical organization has been described for the primary somatosensory cortex (S1) in the parietal lobe (i.e. the somatosensory homunculus). Here, areas dedicated to the representation of tactile and proprioceptive information from the fingers and oral region are larger than other body parts.

We have recently demonstrated in humans that the motor and somatosensory homunculi are directly connected through short U-shaped fibres running beneath the central sulcus (3). The pattern of distribution of these fibres follows the topographical organization of M1 and S1. That is, greater connections exist between finger regions as compared to areas controlling other body parts. The existence of these connections in humans is consistent with previous reports supporting the role of somatosensory inputs in motor learning and precision grasping in animals (4-6). In monkeys, inactivation of S1 leads to altered finger co-ordination, such as the inability to oppose the thumb and forefinger and the inaccurate control of grip forces (4, 7). Furthermore, experimental studies in healthy humans have demonstrated that in conditions of digital anaesthesia, where tactile sensation is absent, co-ordination of thumb and finger

movements is impaired due to misalignment of fingers and an imbalance of the pressure applied (8). These studies suggest that direct connections between S1 and M1 may play a crucial role in precision grasping movements, although direct experimental evidence for this is lacking in humans (9, 10).

In the present study we therefore sought evidence of the role of S1-M1 connections in fine motor skill and precision grasping ability. To investigate this, first we combined behavioral measurements of fine motor skill performance with diffusion tensor tractography in a group of sixty healthy adults to understand the association between grasping performance and microstructural properties of U-shaped fibres connecting S1 to M1 of the hand region. As a control tract we also investigated the U-shaped connections of the face/tongue region, the microstructure of which would not be predicted to correlate with finger dexterity.

Second, we obtained diffusion tractography and grasping performance in a group of adults with a neurodevelopmental disorder in which precision grasping abnormalities are prevalent, namely Autism Spectrum Disorder (ASD). ASD affects approximately 1% of the population and is diagnosed on the basis of social-communication impairments, alongside repetitive and stereotypic behaviors (11). Motor abnormalities have been reported in up to 79% people with ASD (12). These include precision grasping impairments (13). Motor impairments are present across the spectrum of autism (14), and are reported to be some of the earliest signs of ASD to emerge in infancy (15). Motor difficulties can significantly reduce day-to-day quality of life because of altered peer-group interactions through sport and other social activities, and increased dependence on others (16). Furthermore, motor proficiency is a necessary prerequisite for interaction with the environment, which underpins the development of social and language skills (17), highlighting the importance of investigating motor deficits in ASD. ASD is also associated with the abnormal development of white matter connections. A large number of studies have found that children and adults with ASD display structural differences in white matter tracts, and across multiple brain regions (18). We therefore investigated, for the first time, whether abnormal structure of

the S1-M1 hand-region U-shaped fibres underpins precision grasping difficulties in sixty right-handed adult males with ASD.

Methods and Materials

Participants

Sixty neurotypical adult males aged 18-45, and 60 age- and sex-matched subjects with a diagnosis of ASD were recruited at the Institute of Psychiatry, Psychology and Neuroscience, King's College London or the Autism Research Centre, University of Cambridge, as part of the UK Medical Research Council Autism Imaging Multicentre Study. Approximately equal ratios of cases to controls were recruited at each site: Institute of Psychiatry, Psychology and Neuroscience, 34:32, University of Cambridge, 26:28. All participants were right-handed, as indicated by a score of +40 or higher on the Edinburgh Handedness Inventory (19).

Exclusion criteria for all subjects included any medical illness affecting brain function or history of epilepsy, intellectual disability, major psychiatric disorder such as psychosis and attention deficit hyperactivity disorder, head injury or genetic disorder associated with autism. Participants taking any current psychotropic medications including antipsychotic medication, mood stabilizers, benzodiazepines, stimulants and selective serotonin re-uptake inhibitors, or with a history of substance abuse, were excluded. ASD participants met the International Classification of Diseases, 10th Revision research criteria. This was confirmed with the Autism Diagnostic Interview-Revised (ADI-R) (20). All cases with ASD met ADI-R algorithm cut-off values in the three domains of impaired reciprocal social interaction, communication and repetitive behaviors, however one point below cut-off in one of the domains was permitted (Table 1).

Current symptoms were assessed using the Autism Diagnostic Observation Schedule (ADOS) (21), but not as inclusion criteria. All participants underwent a neuropsychological test battery (22). This included the Wechsler Abbreviated Scale of Intelligence (WASI) (23) as a measure of overall intellectual ability. All participants fell within the high-functioning range on the autism spectrum as defined by a full-scale

IQ of > 70. Written consent was acquired for all participants after a complete description of the study was given, in accordance with ethics approval by the National Research Ethics Committee, Suffolk, England.

Motor Assessment

The Purdue Pegboard Test (24) was selected to assess fine motor skill. The Purdue Pegboard is an established test of finger and hand dexterity and precision grasping ability with good test-retest reliability in both healthy subjects (25) and clinical populations (26). The participant is verbally instructed to place pins in one of two columns on a test board within a specified time period (Figure 1). There are five subtests giving five subscores: right hand (dominant hand), left hand (non-dominant hand), both hands alternatively and a bimanual 'Assembly' task (description in Supplementary Material). The fifth score is a composite of performance on the right + left hand + both hand (R + L + B) tasks.

DTI Data Acquisition and Pre-Processing

Participants were scanned at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London, and the Department of Radiology, University of Cambridge using two identical 3 T GE Signa System scanners (General-Electric, Milwaukee, WI, USA). A total of 60 contiguous slices were acquired using an acquisition sequence fully optimized for DTI, providing isotropic (2.4 x 2.4 x 2.4 mm^3) resolution and whole head coverage. There were 32 diffusion-weighted volume directions and 6 non-diffusion weighted volumes. The diffusion weighting was equal to a *b*-value of 1300 sec/mm^2. DTI processing was performed using Explore DTI (http://www.exploredti.com). The data were corrected for eddy current distortion and subject motion and the b-matrix was accordingly reoriented (27). The tensor model was fitted using a non-linear least square fitting procedure (28). DTI scalar maps including fractional anisotropy, mean diffusivity and perpendicular diffusivity were calculated and exported. Whole brain tractography was performed using a Euler-like streamline propagation algorithm with a step-size of 1 mm, FA threshold of .2 and an angle threshold of 35° (29). The whole brain tractography was imported into TrackVis for virtual dissections (30).

Tractography and Virtual Dissections

Virtual *in vivo* dissections of the tracts of interest for the left and right hemisphere were performed using TrackVis. The connections were dissected between the S1 and M1 in regions corresponding to the hand, face/tongue and foot regions of the motor-sensory homunculus (Figure 1). The foot and face/tongue region connections were dissected as control tracts (description in Supplementary Material).

The dissector was blinded to subject identity and diagnosis. Thirty-one data sets (25.8%) were reversed around the midline to ensure blindness to side. All dissections were completed after ensuring intra-rater reliability. This was tested with the use of 10 subjects from the current study, dissected twice by the same dissector. Reliability was tested using a two-way mixed intra-class correlation coefficient (ICC) (31). For the hand and face/tongue tracts, the ICC for single measures reached >.90 (32). We found the foot connections to consist of only one or two individual streamlines, and were not present in a number of participants. Diffusion properties for the foot streamlines did not reach >.90 on the ICC and were therefore excluded from all further analyses.

For each tract fractional anisotropy, perpendicular diffusivity and mean diffusivity were calculated. Alterations in these measures reflect microstructural differences which may include altered axonal integrity, compactness of fibre bundles, and myelination (33). Fractional anisotropy reflects the degree of directionality of water motion within a voxel. Although highly sensitive to microstructural differences, fractional anisotropy does not provide information on the contribution of axial or perpendicular diffusion to this process. Therefore, perpendicular diffusivity, a measure of water motion perpendicular to the fibre tract, was also included. Perpendicular diffusivity may be particularly sensitive to alterations in myelination (34). Mean diffusivity was also included.

Statistical Analysis

Statistical comparisons of the data were performed using SPSS software version 21 for PC (SPSS Inc., Chicago, IL). A student's t-test (two-tailed) for independent samples was used to investigate differences

between controls and individuals with ASD. A paired samples t-test was used to analyze behavioral lateralization of pegboard performance. For all t-test comparisons, Cohen's *d* effect sizes are reported (35). For the paired samples t-test this is corrected for dependence between means (36). To control for possible confounds, DTI tractography outcome measurements between groups were also compared using a general linear model (GLM), with age and center included as covariates. A two-tailed Pearson correlation analysis was calculated between DTI indices and pegboard measures for the control and ASD groups individually, controlling for age and center. The results of the correlation analysis were considered significant after Bonferroni correction for multiple comparisons. As both the sub-scales of the pegboard and tract-based DTI indices are highly inter-related, multiple comparison correction was calculated based on the number of tracts analyzed, leaving a threshold of $p < 0.025$. A Z-observation analysis was used to determine differences in Pearson's correlation coefficient 1) between hemispheres (within group), 2) between tracts (hand-region and face/tongue region tracts) (within group) and 3) between-groups.

Results

Relationship Between Manual Dexterity and Tract Properties in the Control Group.

Participants showed statistically significant faster performance when executing the task with their right hand as compared with the left hand (t=3.11, p = .003, *d*=.40). Tractography-based measurements of the hand-region U-shaped fibres in the left hemisphere correlated with performance on the pegboard test when subjects used their right or left hand (Table 2, Figure 1c). There were no significant correlations for the U-shaped fibres of the face/tongue region and pegboard performances (Supplementary Material). Also, no significant correlations were found between any right hemisphere diffusion measurement and pegboard performances.

Z-observation analysis revealed that Pearson's correlation between pegboard performance of the right hand and mean diffusivity of the hand-region tracts in the left hemisphere were higher compared to the correlation between right hand performance and right hemisphere hand-region tracts (z = -1.64, p = .05). Correlations between the fractional anisotropy of the hand-region tracts in the left hemisphere and pegboard performance with the left hand were significantly higher than the correlations for the face/tongue tract (z = 2.04, p = .021), and the correlation between left hand performance and the hand-region tracts in the right hemisphere (z = 2.27, p = .012). There were also significantly higher correlations between the left-hemisphere hand-region perpendicular (z = -2.37, p = .009) and mean diffusivity (z = -2.15, p = .016) and left hand pegboard performance, when compared to correlations with the hand-region tract of the right hemisphere and the left hand pegboard performance.

Comparison of Manual Dexterity Performance Between the Control and ASD Group.

Behavioural asymmetry in participants with ASD was lower compared to controls, and differences between right and left hand performances were not statistically significant (t=1.96, p = .055). Statistically significant between-group differences in Pegboard performance between the ASD and control group were evident for a number of measurements and included: lower performance of the ASD group (1) when using

their right hand (t=2.08, p = .040, *d*=.38), (2) on the bimanual 'Assembly' task (t=3.98, p = .001, *d*=.74), and (3) on a composite score of right, left and both hands (t=2.01, p = .047, *d*=.37) (Table 3). Performances with the left hand were not significantly different to those of healthy controls.

Comparison of Tract Properties Between the Control and ASD Group.

The tractography analysis showed that in comparison to the healthy control group, in the ASD group there was significantly decreased fractional anisotropy (t=3.55, p = .001, *d*=.65), and significantly increased perpendicular diffusivity (t=-3.51, p = .001, *d*=.65) and mean diffusivity (t=-3.24, p = .002, *d*=.59) of the U-shaped fibres of the hand-region in the left hemisphere (Figure 2a). In the right hemisphere, there was significantly decreased fractional anisotropy (t=2.29, p = .024, *d*=.43) and significantly increased perpendicular diffusivity (t=-2.48, p = .015, *d*=.46) and mean diffusivity (t=-2.46, p = .015, *d*=.46) of the U-shaped fibres of the hand-region, however this did not remain significant when controlling for age and centre. When controlling for age and centre, only the left-hemisphere differences remained significant.

There were no significant between-group differences of the face/tongue tracts in both hemispheres (Figure 2b).

Relationship Between Manual Dexterity and Tract Properties in the ASD Group.

Unlike the healthy control group, in the ASD group there were no significant correlations between pegboard performances and diffusion measurements in the left hemisphere hand-region tract; conversely there were a number of significant correlations between pegboard performances and diffusion measurements in the right hemisphere hand-region tract (Table 4, Figure 3). There were no significant correlations between manual dexterity scores and DTI measures of the face/tongue tract (Supplementary Material).

Z-observation analysis revealed that the correlation between pegboard performance with 'both hands' and perpendicular diffusivity was significantly higher for the right hemisphere hand-region tract in

comparison to the right face/tongue tract ($z = -2.29$, $p = .011$). There were also significantly higher correlations between the right hemisphere hand-region tract mean diffusivity and both pegboard performance with 'both hands' ($z = -2.46$, $p = .007$) and performance in the composite score of right + left + both hands ($z = -1.92$, $p = .027$), compared to the correlations with the mean diffusivity of the face/tongue tract.

Finally, there was a significant difference in strength of correlation between the right hemisphere hand-region tract mean diffusivity and assembly scores ($z = -2.19$, $p = .014$) when comparing the ASD and control groups.

Discussion

The present study provides the first direct support of the role of connections between the M1 and S1 in fine motor skill performance. This finding was specific to the S1-M1 connections of the hand-region of the motor-sensory homunculus, and was not present for the S1-M1 connections of the face/tongue region, demonstrating that the U-shaped white matter fibres connecting either side of the central sulcus display functional topographical organization (2). Disruption of the S1-M1 connections was associated with precision grasping impairments in a group of individuals with ASD. In comparison to healthy controls, participants with ASD showed a slower performance on the pegboard test and showed decreased fractional anisotropy, and increased perpendicular diffusivity and mean diffusivity in the left hemisphere. These differences in diffusion measurements have previously been associated with alterations to tract structure such as reduced tract coherence and organization, and reduced myelination (37) and may be associated with reduced conduction speed (38). These processes may contribute to ASD pathology (39, 40), as studies report lower myelin content in areas of the frontal lobes (41), and increased transmission times of brainstem auditory-evoked potentials in ASD (42). Additionally, lower tract coherence may be linked to abnormally low signal to noise, which has been proposed to underpin ASD symptoms (43). Such pathology might reasonably be expected to degrade performance in the pegboard test in the ASD group. This is consistent with the existence of significant correlations between slower performances in the pegboard test and tractography measurements in the ASD group.

The association between the S1-M1 connections and precision grasping is asymmetrical and only present in the left hemisphere in the control group. The finding of asymmetry is in line with previous clinical studies on patients with acquired apraxia, in which a loss of grasping abilities in the left or right hand is invariably associated with left hemisphere lesions (44, 45). Unlike the healthy control group, in the ASD group there were no significant correlations with the left hemisphere tract, but there were a number of significant correlations with the right hemisphere tract. Together these data suggest that the left hemisphere is dominant for precision grasping in healthy individuals and that the loss of this typical left

dominance is associated with reduced fine motor skills in individuals with ASD. Loss of hemispheric dominance in the ASD group is in accordance with studies that suggest an atypical right hemispheric shift of lateralization may be a fundamental feature of brain organization in ASD (46). Atypical rightward lateralization in ASD has most frequently been linked to language abnormality (47-49), but studies that report a rightward shift of lateralization across widespread brain areas (46, 50), suggest atypical lateralization in ASD may result from a generalized maturational disturbance.

A number of factors must be taken into consideration when interpreting the present findings. Whilst the pegboard task measures motor speed, cognitive factors such as motivation or comprehension of task instructions, may also impact on the speed of pegboard completion. Although there were no significant differences in IQ between the ASD and control groups in the present study, we cannot rule out the possibility that other cognitive factors, such as attention, may have played a role in the difference in pegboard scores observed. Additionally, our sample is restricted to a high-functioning ASD group, with relatively low ADOS scores. Our findings may not, therefore, be generalizable to low-functioning individuals with ASD. We also excluded participants with comorbid ADHD. Whilst this may be considered a strength of the sample, it also limits the generalisability of our findings to individuals with ASD and comorbid ADHD. ADHD may be present in up to 78% of individuals with ASD (51, 52), and studies suggest the nature of motor impairments may be distinct in individuals with ASD with and without ADHD (53). Future studies should therefore aim to investigate this.

Furthermore, the motor impairments we report in the ASD group may relate to abnormalities in other brain regions, in addition to the S1-M1 connections. Cerebellar (54) and thalamic (55) abnormalities have been reported in ASD, including altered white matter connectivity of these regions (56, 57). Abnormality of these regions may have a distinct influence on motor impairments in ASD. For example, whilst the S1-M1 connections likely play a role in sensory feedback after contact with an object, anterior

cerebellar abnormalities may be associated with deficits in the feedforward planning, which occurs prior to object contact (58). A more comprehensive assessment of the tracts involved in motor planning and execution, which may also include, for example, the superior cerebellar peduncle and the superior longitudinal fasciculus (SLF) system, will be necessary to understand the specific role of each tract to fine motor skills in ASD. Due to the characteristics of our dataset we were unable to perform dissections of the SLF for which HARDI models, that necessitate higher number of directions and higher B-values, are required (59).

Several theories of 'disconnection' in ASD propose a dual mechanism of increased connectivity in short-range connections and reduced connectivity in long-range connections (43). The present study reports alterations in U-shaped fibres between frontal and parietal lobes, which are anatomically considered to be short tracts compared to other association pathways. However, the concept of 'short' and 'long' range connectivity in ASD is not well defined (51), and indeed other studies have previously reported reductions in 'short-range' white matter connectivity in ASD (52, 53). Future studies will be required to determine whether the 'short' vs 'long' range dichotomy defined at the anatomical and functional level accurately reflects underlying biology in ASD. Such studies will require advanced methods to quantify connectivity of intracortical fibres, U-shaped fibres and long interlobar fibres.

The S1-M1 connections are thought to be the terminal component of an indirect route for thalamic sensory information to reach M1, as opposed to a direct thalamo-M1 pathway (3). Electrophysiological studies in cats indicate that this indirect route may play a role in motor learning. For example, tetanic stimulation of S1 leads to long-term potentiation (LTP) in M1 (5), an effect that does not occur with tetanic stimulation of the thalamus alone (6). Further evidence in support of the role of the S1-M1 connections in motor learning comes from the finding that ablation of S1 in macaque monkeys prevents the ability to learn novel motor sequences (60). Our study is restricted to an adult cohort and it is not

possible to establish whether the microstructural abnormalities reported are due to processes occurring early or late in development. However, white matter differences have been reported across the lifespan in ASD, including early childhood (61). Due to the involvement of the S1-M1 connections in LTP and motor learning, as suggested by the above studies in non-human animal models, the findings of the present study may lead to novel therapeutic approaches targeting motor learning in young children with ASD and in children with developmental dyspraxia in general. Navigated trans-cranial magnetic stimulation (nTMS) of the S1 cortex, for example, could be used to elicit LTP in M1 and facilitate consolidation of behaviorally-induced motor learning. As motor disturbance is one of the earliest signs of abnormality in infants with ASD, and underpins later abnormal development of language and social abilities (15, 17), the development of a therapeutic approach for motor impairments in ASD would be of great importance.

In conclusion we reported significant correlations between pegboard performance skill and the microstructural properties of white matter connections between S1 and M1 of the left hand region in a group of healthy adults. We also found that poor pegboard performance was associated with structural abnormality of this tract in a clinical population of individuals with ASD. Our findings represent the first empirical evidence in humans that development of normal S1-M1 connections play an important role in fine motor control. In addition, as S1 input to M1 underpins long-term potentiation in M1, these findings may lead to novel therapeutic approaches for motor rehabilitation in people affected by ASD, and in individuals with specific motor learning disability.

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References:

1. Porter R, Lemon RN (1993): Corticospinal Function and Voluntary Movement. Clarendon Press.
2. Penfield W, Boldrey E (1937): Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain: A journal of neurology., pp 389-443.
3. Catani M, Dell'acqua F, Vergani F, Malik F, Hodge H, Roy P, et al. (2012): Short frontal lobe connections of the human brain. *Cortex*. 48:273-291.
4. Hikosaka O, Tanaka M, Sakamoto M, Iwamura Y (1985): Deficits in manipulative behaviors induced by local injections of muscimol in the first somatosensory cortex of the conscious monkey. *Brain Res*. 325:375-380.
5. Sakamoto T, Porter LL, Asanuma H (1987): Long-lasting potentiation of synaptic potentials in the motor cortex produced by stimulation of the sensory cortex in the cat: a basis of motor learning. *Brain Res*. 413:360-364.
6. Iriki A, Pavlides C, Keller A, Asanuma H (1991): Long-term potentiation of thalamic input to the motor cortex induced by coactivation of thalamocortical and corticocortical afferents. *J Neurophysiol*. 65:1435-1441.
7. Brochier T, Boudreau MJ, Paré M, Smith AM (1999): The effects of muscimol inactivation of small regions of motor and somatosensory cortex on independent finger movements and force control in the precision grip. *Exp Brain Res*. 128:31-40.
8. Monzée J, Lamarre Y, Smith AM (2003): The effects of digital anesthesia on force control using a precision grip. *J Neurophysiol*. 89:672-683.
9. Davare M, Kraskov A, Rothwell JC, Lemon RN (2011): Interactions between areas of the cortical grasping network. *Curr Opin Neurobiol*. 21:565-570.
10. Grafton ST (2010): The cognitive neuroscience of prehension: recent developments. *Exp Brain Res*. 204:475-491.
11. Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, et al. (2006): Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet*. 368:210-215.
12. Lai MC, Lombardo MV, Baron-Cohen S (2014): Autism. *Lancet*. 383:896-910.
13. Hardan AY, Kilpatrick M, Keshavan MS, Minshew NJ (2003): Motor performance and anatomic magnetic resonance imaging (MRI) of the basal ganglia in autism. *J Child Neurol*. 18:317-324.
14. Fournier KA, Hass CJ, Naik SK, Lodha N, Cauraugh JH (2010): Motor coordination in autism spectrum disorders: a synthesis and meta-analysis. *J Autism Dev Disord*. 40:1227-1240.
15. Baranek GT (1999): Autism during infancy: a retrospective video analysis of sensory-motor and social behaviors at 9-12 months of age. *J Autism Dev Disord*. 29:213-224.

16. Jasmin E, Couture M, McKinley P, Reid G, Fombonne E, Gisel E (2009): Sensori-motor and daily living skills of preschool children with autism spectrum disorders. *J Autism Dev Disord*. 39:231-241.
17. Iverson JM (2010): Developing language in a developing body: the relationship between motor development and language development. *J Child Lang*. 37:229-261.
18. Ameis SH, Catani M (2015): Altered white matter connectivity as a neural substrate for social impairment in Autism Spectrum Disorder. *Cortex*. 62:158-181.
19. Oldfield RC (1971): The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 9:97-113.
20. Lord C, Rutter M, Le Couteur A (1994): Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 24:659-685.
21. Lord C, Rutter M, Goode S, Heemsbergen J, Jordan H, Mawhood L, et al. (1989): Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J Autism Dev Disord*. 19:185-212.
22. Wilson CE, Happé F, Wheelwright SJ, Ecker C, Lombardo MV, Johnston P, et al. (2014): The neuropsychology of male adults with high-functioning autism or asperger syndrome. *Autism Res*. 7:568-581.
23. Wechsler D (1999): Wechsler Abbreviated Scale of Intelligence (WASI). San Antonio, TX: Harcourt Assessment.
24. Tiffin J, Asher EJ (1948): The Purdue pegboard; norms and studies of reliability and validity. *J Appl Psychol*. 32:234-247.
25. Desrosiers J, Hébert R, Bravo G, Dutil E (1995): The Purdue Pegboard Test: normative data for people aged 60 and over. *Disabil Rehabil*. 17:217-224.
26. Gallus J, Mathiowetz V (2003): Test-retest reliability of the Purdue Pegboard for persons with multiple sclerosis. *Am J Occup Ther*. 57:108-111.
27. Leemans A, Jones D (2009): The B-matrix must be rotated when correcting for subject motion in DTI data. Magnetic Resonance in Medicine, pp 1336-1349.
28. Jones DK, Basser PJ (2004): "Squashing peanuts and smashing pumpkins": how noise distorts diffusion-weighted MR data. *Magn Reson Med*. 52:979-993.
29. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A (2000): In vivo fiber tractography using DT-MRI data. *Magn Reson Med*. 44:625-632.
30. Wang R, Wedeen V (2007): Diffusion Toolkit and TrackVis. Berlin: Proceedings of the International Society for Magnetic Resonance in Medicine.
31. Bartko JJ (1966): The intraclass correlation coefficient as a measure of reliability. *Psychol Rep*. 19:3-11.
32. Landis JR, Koch GG (1977): The measurement of observer agreement for categorical data. *Biometrics*. 33:159-174.
33. Beaulieu C (2002): The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed*. 15:435-455.
34. Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH (2002): Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage*. 17:1429-1436.
35. Cohen J (1992): A power primer. *Psychol Bull*. 112:155-159.
36. Morris SB, DeShon RP (2002): Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychol Methods*. 7:105-125.

37. Beaulieu C (2011): What makes diffusion anisotropic in the nervous system? In: Jones, D, editor of Diffusion MRI.: Oxford: Oxford University Press, pp 92-109.
38. Hartline DK, Colman DR (2007): Rapid conduction and the evolution of giant axons and myelinated fibers. *Curr Biol*. 17:R29-35.
39. Catani M, Dell'Acqua F, Budisavljevic S, Howells H, Thiebaut de Schotten M, Froudist-Walsh S, et al. (2016): Frontal networks in adults with autism spectrum disorder. *Brain*. 139:616-630.
40. Pugliese L, Catani M, Ameis S, Dell'Acqua F, Thiebaut de Schotten M, Murphy C, et al. (2009): The anatomy of extended limbic pathways in Asperger syndrome: a preliminary diffusion tensor imaging tractography study. *Neuroimage*. 47:427-434.
41. Zikopoulos B, Barbas H (2010): Changes in prefrontal axons may disrupt the network in autism. *J Neurosci*. 30:14595-14609.
42. Wong V, Wong SN (1991): Brainstem auditory evoked potential study in children with autistic disorder. *J Autism Dev Disord*. 21:329-340.
43. Belmonte MK, Allen G, Beckel-Mitchener A, Boulanger LM, Carper RA, Webb SJ (2004): Autism and abnormal development of brain connectivity. *J Neurosci*. 24:9228-9231.
44. Geschwind N (1975): The apraxias: neural mechanisms of disorders of learned movement. *Am Sci*. 63:188-195.
45. Catani M, Dell'acqua F, Bizzi A, Forkel SJ, Williams SC, Simmons A, et al. (2012): Beyond cortical localization in clinico-anatomical correlation. *Cortex*. 48:1262-1287.
46. Cardinale RC, Shih P, Fishman I, Ford LM, Müller RA (2013): Pervasive rightward asymmetry shifts of functional networks in autism spectrum disorder. *JAMA Psychiatry*. 70:975-982.
47. Flagg EJ, Cardy JE, Roberts W, Roberts TP (2005): Language lateralization development in children with autism: insights from the late field magnetoencephalogram. *Neurosci Lett*. 386:82-87.
48. Gage NM, Juranek J, Filipek PA, Osann K, Flodman P, Isenberg AL, et al. (2009): Rightward hemispheric asymmetries in auditory language cortex in children with autistic disorder: an MRI investigation. *J Neurodev Disord*. 1:205-214.
49. Kleinhans NM, Müller RA, Cohen DN, Courchesne E (2008): Atypical functional lateralization of language in autism spectrum disorders. *Brain Res*. 1221:115-125.
50. Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Kennedy DN, Filipek PA, et al. (2005): Brain asymmetries in autism and developmental language disorder: a nested whole-brain analysis. *Brain*. 128:213-226.
51. Hanson E, Cerban BM, Slater CM, Caccamo LM, Bacic J, Chan E (2013): Brief report: prevalence of attention deficit/hyperactivity disorder among individuals with an autism spectrum disorder. *J Autism Dev Disord*. 43:1459-1464.
52. Murray MJ (2010): Attention-deficit/Hyperactivity Disorder in the context of Autism spectrum disorders. *Curr Psychiatry Rep*. 12:382-388.
53. Mahajan R, Dirlikov B, Crocetti D, Mostofsky SH (2016): Motor Circuit Anatomy in Children with Autism Spectrum Disorder With or Without Attention Deficit Hyperactivity Disorder. *Autism Res*. 9:67-81.
54. Carper RA, Courchesne E (2000): Inverse correlation between frontal lobe and cerebellum sizes in children with autism. *Brain*. 123 (Pt 4):836-844.

55. Tsatsanis KD, Rourke BP, Klin A, Volkmar FR, Cicchetti D, Schultz RT (2003): Reduced thalamic volume in high-functioning individuals with autism. *Biol Psychiatry*. 53:121-129.
56. Catani M, Jones DK, Daly E, Embiricos N, Deeley Q, Pugliese L, et al. (2008): Altered cerebellar feedback projections in Asperger syndrome. *Neuroimage*. 41:1184-1191.
57. Nair A, Carper RA, Abbott AE, Chen CP, Solders S, Nakutin S, et al. (2015): Regional specificity of aberrant thalamocortical connectivity in autism. *Hum Brain Mapp*. 36:4497-4511.
58. Mosconi MW, Mohanty S, Greene RK, Cook EH, Vaillancourt DE, Sweeney JA (2015): Feedforward and feedback motor control abnormalities implicate cerebellar dysfunctions in autism spectrum disorder. *J Neurosci*. 35:2015-2025.
59. Thiebaut de Schotten M, Dell'Acqua F, Forkel SJ, Simmons A, Vergani F, Murphy DG, et al. (2011): A lateralized brain network for visuospatial attention. *Nat Neurosci*. 14:1245-1246.
60. Pavlides C, Miyashita E, Asanuma H (1993): Projection from the sensory to the motor cortex is important in learning motor skills in the monkey. *J Neurophysiol*. 70:733-741.
61. Ben Bashat D, Kronfeld-Duenias V, Zachor DA, Ekstein PM, Hendler T, Tarrasch R, et al. (2007): Accelerated maturation of white matter in young children with autism: a high b value DWI study. *Neuroimage*. 37:40-47.

Table Legends:

Table 1: Subject demographic characteristics.

Table 2: Correlations between Pegboard performance and tract-specific measurements for the control group (controlling for age and center).

Table 3: Comparison of Purdue Pegboard Test scores between control and Autism groups.

Table 4: Correlations between Pegboard performance and tract-specific measurements for the Autism group (controlling for age and center).

Figure Legends:

Figure 1: The fronto-parietal U shaped connections of the foot, hand and face/tongue regions (a), and the relation between diffusion measures of the hand-region tract and performance on the Purdue Pegboard Test (b) in healthy controls (c). *statistically significant at $p < 0.025$.

Figure 2: Between-group differences in fractional anisotropy, mean diffusivity and perpendicular diffusivity. These were significant for the hand-region connection (a) but not for the face/tongue tract (b). Mean and standard deviation are displayed. Statistically significant at * $p < 0.025$, ** $p < 0.01$, *** $p < 0.001$.

Figure 3: Pearson's R correlations between left and right hemisphere hand-region tract mean diffusivity and Pegboard performance in the control and Autism groups. Statistically significant at * $p < 0.025$, ** $p < 0.01$.

Table 1: Subject Demographic Characteristics

Characteristic	Mean (SD) [Range]	
	Healthy Controls (N = 60)	Subjects with autism (N = 60)
Age, y[a]	29 (7) [18-45]	26 (7) [18-43]
WASI IQ score[a]		
Full scale	111 (12) [88-133]	115 (12) [77-137]
Verbal	108 (13) [84-139]	112 (13) [71-137]
Performance	111 (13) [88-133]	115 (13) [75-137]
ADI-R score		
Total	N/A	39 (10) [21-62]
Social	N/A	18 (5) [9-28]
Communication	N/A	14 (4) [8-24]
Repetitive	N/A	5 (2) [2-10]
ADOS score[b]		
Total	N/A	11 (5) [1-23]
Social	N/A	6 (3) [1-14]
Communication	N/A	3 (2) [0-7]
Repetitive	N/A	1 (1) [0-6]

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; WASI, Wechsler Abbreviated Scale of Intelligence.

[a]There were no significant between-group differences in age, full-scale IQ, Verbal IQ or Performance IQ (all $P > .05$, 2-tailed).

[b]Information was available for 58 subjects with AS

Table 2: Correlations between Pegboard performance and hand-region tract-specific measurements for the control group (controlling for age and center).

	Diffusion Tensor Measures of Hand-Region Fronto-Parietal U Tract					
	Left Hemisphere			Right Hemisphere		
	Fractional Anisotropy	Perpendicular Diffusivity	Mean Diffusivity	Fractional Anisotropy	Perpendicular Diffusivity	Mean Diffusivity
Pegboard						
Right	.074	-.213	-.305*	-.140	.030	-.008
Left	.352**	-.376**	-.315*	-.057	.049	.077
Both	.199	-.157	-.051	.169	-.192	-.212
R+L+Both	.244	-.316*	-.287*	.021	-.095	-.116
Assembly	.183	-.157	-.090	.002	.005	.009

Values are Pearson's r. Significance is * $p < 0.025$, ** $p < 0.01$, *** $p < 0.001$.
Abbreviation: R+L+Both; Right hand + left hand + both composite score.

Table 3: Comparison of Purdue Pegboard Test scores between control and Autism groups.

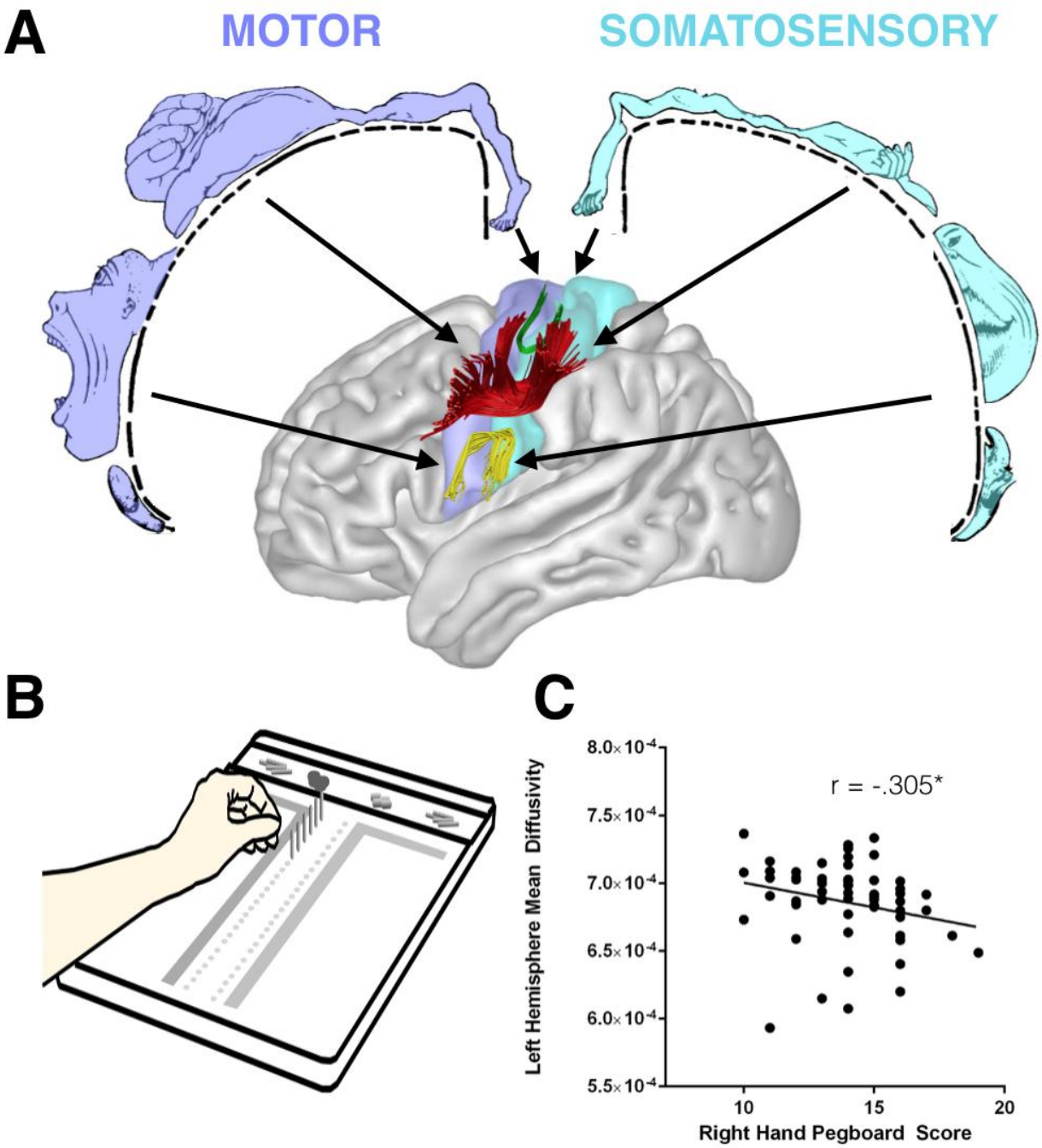
Purdue Pegboard Test	Mean (SD)		
	Control	Autism	t
Right Hand	14 (2)	13.1 (2.4)	2.08*
Left Hand	13.3 (2)	12.6 (2.8)	1.57
Both	13.6 (2.9)	12.6 (4.3)	1.39
RH+LH+Both	40.7 (4.8)	38.3 (7.8)	2.01*
Assembly	34.6 (8.2)	28.3 (8.9)	3.97***

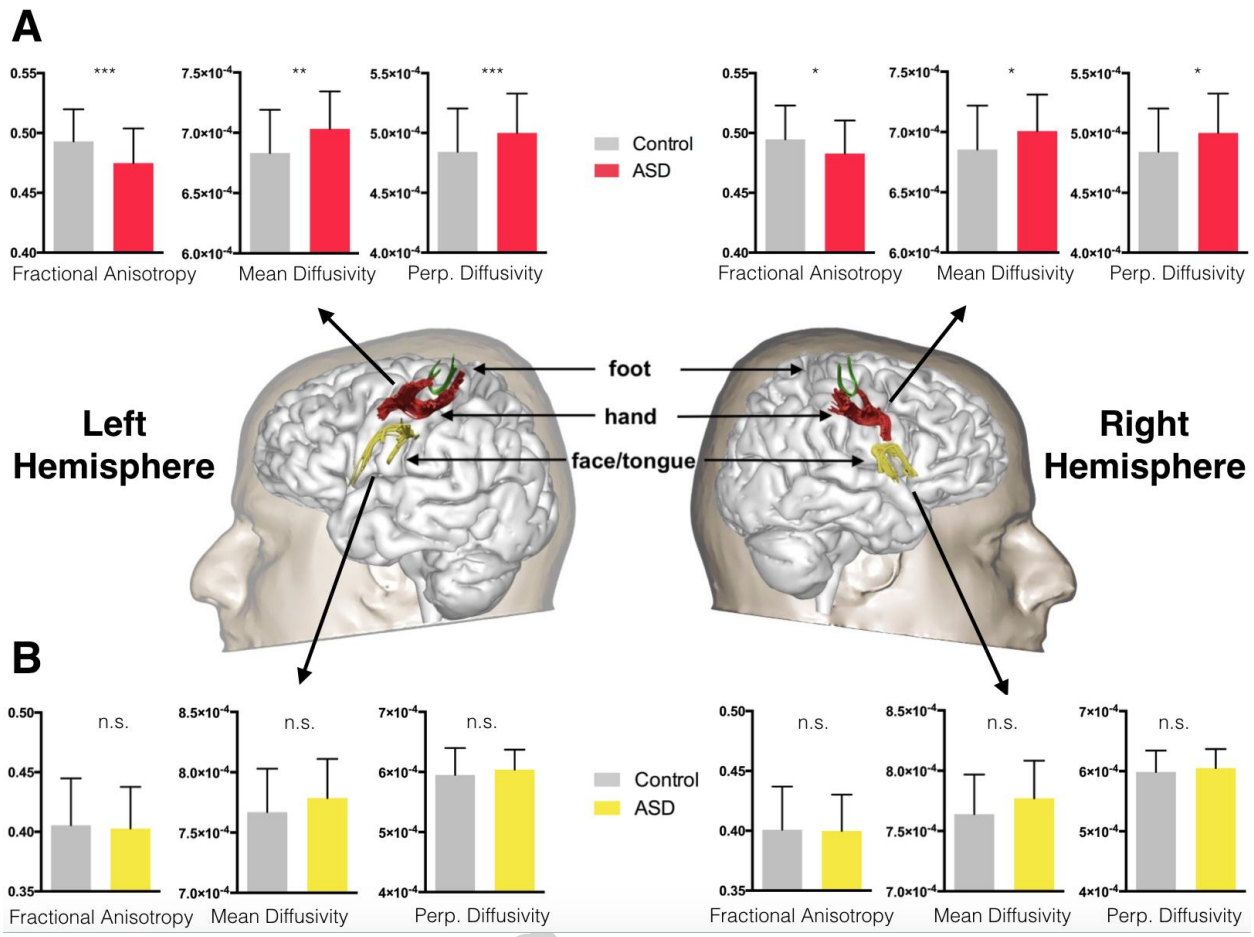
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 4: Correlations between Pegboard performance and hand-region tract-specific measurements for the ASD group (controlling for age and center).

	Diffusion Tensor Measures of Hand-Region Fronto-Parietal U Tract					
	Left Hemisphere			Right Hemisphere		
	Fractional Anisotropy	Perpendicular Diffusivity	Mean Diffusivity	Fractional Anisotropy	Perpendicular Diffusivity	Mean Diffusivity
Pegboard						
Right	-.029	-.053	-.112	.080	-.175	-.158
Left	.175	-.135	-.121	.116	-.214	-.221
Both	.256	-.253	-.223	.280*	-.413**	-.413**
R+L+Both	.176	-.186	-.187	.201	-.331*	-.328*
Assembly	.136	-.182	-.196	.050	-.289	-.382**

Values are Pearson's r. Significance is * $p < 0.025$, ** $p < 0.01$, *** $p < 0.001$.
Abbreviation: R+L+Both; Right hand + left hand + both composite score.


A
MOTOR
SOMATOSENSORY
B
C
8.0×10-4
7.5×10-4
7.0×10-4
6.5×10-4
6.0×10-4
5.5×10-4
r = -.305*
Left Hemisphere Mean Diffusivity
10
15
20
Right Hand Pegboard Score


A
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Control
ASD
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Fractional Anisotropy
Mean Diffusivity
Perp. Diffusivity
Left Hemisphere
foot
hand
face/tongue
Right Hemisphere
B
n.s.
n.s.
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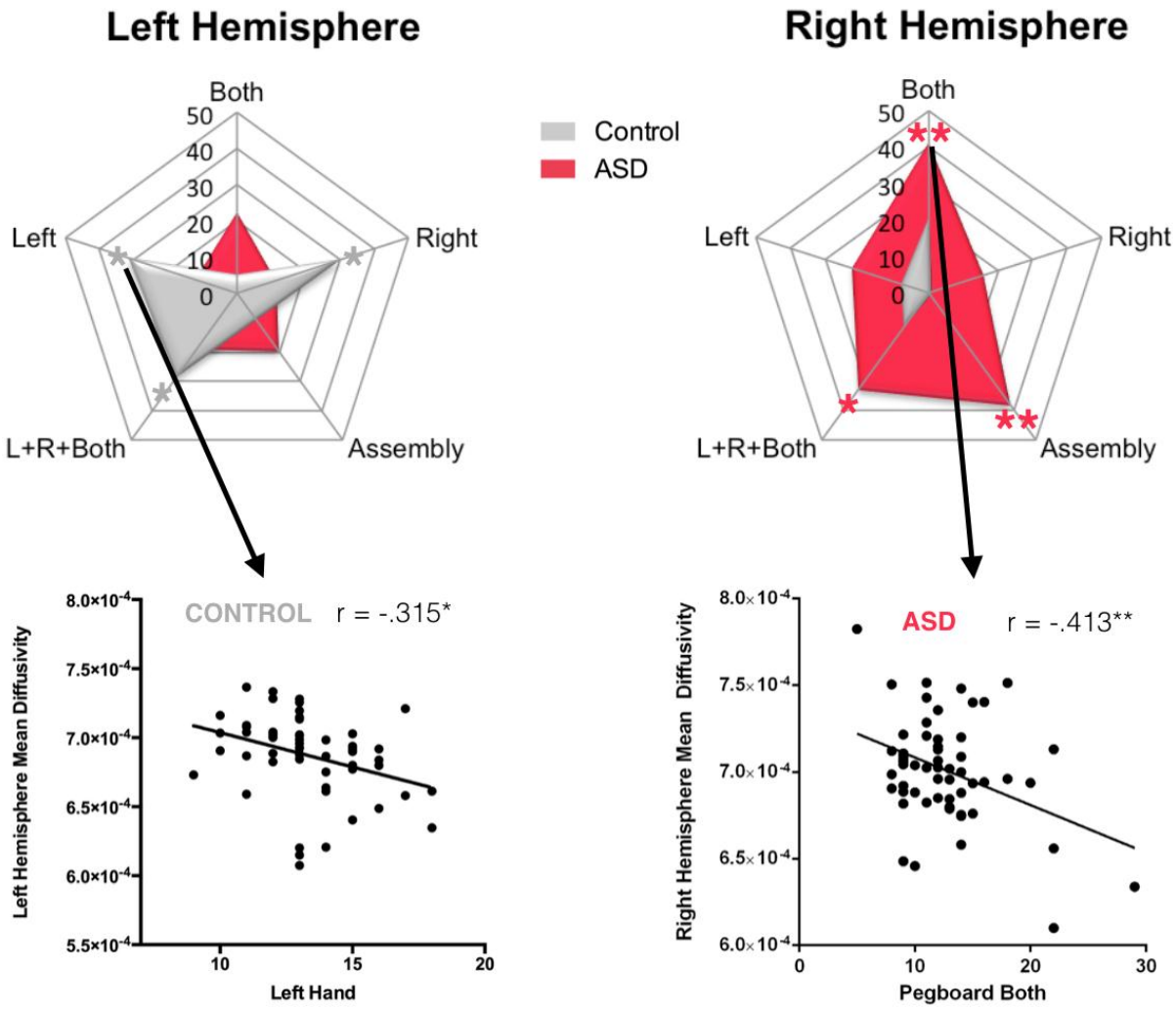
Control
ASD
n.s.
n.s.
n.s.
Fractional Anisotropy
Mean Diffusivity
Perp. Diffusivity


Left Hemisphere
Right Hemisphere
Control
ASD
Both
Left
Right
L+R+Both
Assembly
50
40
30
20
10
0
CONTROL r = -.315*
ASD r = -.413**
Left Hemisphere Mean Diffusivity
Right Hemisphere Mean Diffusivity
Left Hand
Pegboard Both