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Research Report

Mirror movements and callosal dysgenesis in a family with a *DCC* mutation: Neuropsychological and neuroimaging outcomes

Jacquelyn L. Knight [a,1], *Megan S. Barker* [a,b,1], *Timothy J. Edwards* [b,c], *Joseph M. Barnby* [b,d], *Linda J. Richards* [b,e] *and Gail A. Robinson* [a,b,*]

[a] *Neuropsychology Research Unit, School of Psychology, The University of Queensland, St Lucia, Brisbane, QLD, 4072, Australia*

[b] *Queensland Brain Institute, The University of Queensland, St Lucia, Brisbane, Australia*

[c] *Metro South Addiction and Mental Health Services, Brisbane, QLD, 4102, Australia*

[d] *Social Computation and Cognitive Representation Lab, Department of Psychology, Royal Holloway, University of London, London, UK*

[e] *Department of Neuroscience, Washington University in St Louis School of Medicine, St Louis, MO, USA*

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ABSTRACT

Corpus callosum dysgenesis is a congenital abnormality whereby the corpus callosum fails to develop normally, and has been associated with a range of neuropsychological outcomes. One specific finding in some individuals with corpus callosum dysgenesis is "congenital mirror movement disorder", which is the presence of involuntary movements on one side of the body that mimic voluntary movements of the other side. Mirror movements have also been associated with mutations in the deleted in colorectal carcinoma (*DCC*) gene. The current study aims to comprehensively document the neuropsychological outcomes and neuroanatomical mapping of a family (a mother, daughter and son) with known *DCC* mutations. All three family members experience mirror movements, and the son additionally has partial agenesis of the corpus callosum (pACC). All family members underwent extensive neuropsychological testing, spanning general intellectual functioning, memory, language, literacy, numeracy, psychomotor speed, visuospatial perception, praxis and motor functioning, executive functioning, attention, verbal/nonverbal fluency, and social cognition. The mother and daughter had impaired memory for faces, and reduced spontaneous speech, and the daughter demonstrated scattered impairments in attention and executive functioning, but their neuropsychological abilities were largely within normal limits. By contrast, the son showed areas of significant impairment across multiple domains including reduced psychomotor speed, fine motor dexterity and general intellectual functioning, and he was profoundly impaired across areas of executive functioning and attention. Reductions in his verbal/non-verbal fluency, with relatively intact core language, resembled dynamic frontal aphasia. His relative strengths included aspects of memory and he demonstrated largely sound theory of mind.

* *Corresponding author*. Queensland Brain Institute & School of Psychology, University of Queensland, St Lucia QLD, 4072, Australia.
E-mail address: gail.robinson@uq.edu.au (G.A. Robinson).

[1] these authors contributed equally to this work.

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Neuroimaging revealed an asymmetric sigmoid bundle in the son, connecting, via the callosal remnant, the left frontal cortex with contralateral parieto-occipital cortex. Overall, this study documents a range of neuropsychological and neuroanatomical outcomes within one family with *DCC* mutations and mirror movements, including one with more severe consequences and pACC.

1. Introduction

The corpus callosum is the largest white matter connection in the human brain, comprising over 190 million axons that transfer information between the cerebral hemispheres (Edwards, Sherr, Barkovich, & Richards, 2014). Corpus callosum dysgenesis refers to a congenital abnormality in which the corpus callosum fails to develop properly; this may be a complete absence (agenesis), thinning (hypogenesis), or partial absence (or pACC) (Edwards et al., 2014). Prevalence of corpus callosum dysgenesis is estimated at 1 to 7 in 4000 live births, making callosal dysgenesis one of the most common congenital neurological malformations (Glass, Shaw, Chen, & Sherr, 2008; Wang, Huang, & Yeh, 2004). A range of genetic and environmental factors are involved in the aetiology of corpus callosum dysgenesis (Edwards et al., 2014). Single-gene Mendelian mutations, sporadic mutations, and complex genetics have been implicated (O'Driscoll, Black, Clayton-Smith, Sherr, & Dobyns, 2010; Schell-Apacik et al., 2008; Sherr et al., 2005). While the defining feature of corpus callosum dysgenesis is the absence or incomplete development of the corpus callosum, other subtle neuroanatomical changes are also commonly found in individuals with corpus callosum dysgenesis, which may affect functional outcomes (Edwards et al., 2014; Tovar-Moll et al., 2014).

Corpus callosum dysgenesis has been associated with an array of neuropsychological sequelae, from asymptomatic or mild disability to profound impairment (Brown and Paul, 2019; Paul et al., 2007). Small, heterogenous imaging studies make it difficult to identify structural and functional neuroanatomical changes that relate to cognitive impairments in those with corpus callosum dysgenesis. In one study that investigated children with corpus callosum dysgenesis compared to typically developing controls, interhemispheric structural connectivity was reduced, although no differences were found for interhemispheric functional connectivity (Siffredi et al., 2021). However, functional connectivity may become abnormal as task complexity increases (Hearne et al., 2019). Given this heterogeneity, it is difficult to provide a clear prognosis or to identify a specific cognitive and behavioural clinical phenotype; nevertheless, common areas of difficulty are recognised.

Individuals with corpus callosum dysgenesis often have difficulties with complex cognitive processes, such as executive functioning (Brown & Paul, 2019; Siffredi et al., 2013, 2018). Indeed, deficits in a range of executive functions, including tasks that tap inhibition, flexibility, decision-making and problem-solving, have been documented in individuals with corpus callosum dysgenesis (Brown, Anderson, Symington, & Paul, 2012; Brown & Paul, 2000; Marco et al., 2012). This may be coupled with a lack of insight into the severity of their impairment (Mangum et al., 2021). It has been suggested that these deficits might be accounted for by diminished interhemispheric transfer of complex information, or generally slowed processing speed in those with corpus callosum dysgenesis (Brown & Paul, 2000, 2019; Kosky et al., 2022).

Language and communication difficulties in individuals with corpus callosum dysgenesis have also been documented. While core expressive and receptive language abilities appear to be intact, including repetition, naming and comprehension, executive or "higher-order" language skills are commonly impaired. One manifestation of this is poor interpretation of second order meaning in language, for example understanding proverbs or narrative jokes (Brown, Paul, Symington & Dietrich, 2005; Rehmel, Brown, & Paul, 2016). Another manifestation is reduced spontaneous speech despite well-preserved core language abilities, a pattern resembling frontal dynamic aphasia (Luria & Tsvetkova, 1968), which has been documented in two case studies of individuals with corpus callosum dysgenesis (Barker et al., 2021; Stickles, Schilmoeller, & Schilmoeller, 2002).

Finally, social and emotional processing impairments, which are often captured under the umbrella term of "social cognition", have been reported in corpus callosum dysgenesis. These include deficits in social insight, social logic and self-perception (Barnby et al., 2022; Brown & Paul, 2000; Kosky et al., 2022; Symington et al., 2010), as well as first- and second-order beliefs inference (Melogno et al., 2021). Many clinical features of autism spectrum disorders (ASD) have been described in individuals with corpus callosum dysgenesis (Demopoulos et al., 2015) such as over adherence to social norms (Brown et al., 2021). Indeed, there is a very high incidence of ASD in children with corpus callosum dysgenesis, with estimates of incidence up to 43% (Lau et al., 2013). Further, those with corpus callosum dysgenesis have been found to demonstrate abnormal patterns of facial scanning, with reductions in the scanning of the eye region, which may also impact their interpretation of social information (Bridgman et al., 2014). Impairments in executive functions and higher-order language can also impact upon the ability of an individual to integrate socially.

One particular and specific observation in some individuals with corpus callosum dysgenesis is "congenital mirror movement disorder". Mirror movement disorder is characterised by involuntary movements on one side of the body that mimic voluntary movements of the other, usually most pronounced in finger movements (Depienne et al., 2011; Schott & Wyke, 1981). It can occur in isolation, as an inability to perform unilateral movements with the absence of other clinical features, or as part of a clinical disorder (e.g. Klippel-

Feil or X-linked Kallman syndrome; Bonnet et al., 2010). Congenital mirror movement disorder has been linked to mutations in the DCC netrin 1 receptor (*DCC*) gene (Depienne et al., 2011; Franz et al., 2015). *DCC* and its ligand Netrin-1 are implicated in the guidance of developing axons toward the midline, a crucial step in corpus callosum development (Depienne et al., 2011). *DCC* mutations in humans have more recently been associated with mirror movements and isolated agenesis/dysgenesis of the corpus callosum (Marsh et al., 2017, 2018). In this study we detail the cognitive, behavioural and neuroanatomical phenotypes resulting from *DCC* mutations in a single family.

Individuals with mirror movements are documented to present with dyspraxia; specifically, difficulty with bimanual movements, stiffness, and clumsiness (Schott & Wyke, 1981). Few studies have investigated praxis or motor functioning in individuals with corpus callosum dysgenesis, but it is reasonable to hypothesise that cognitive control of motor movements may be impaired, especially for bimanual movements that rely on integration and coordination between the two cortical hemispheres. This notion is supported by one study that estimated gross and fine motor skills to be impaired in 11% of individuals with ACC (D'Antonio et al., 2016). In the current study, the presence of both mirror movements and corpus callosum dysgenesis in one individual, in contrast to mirror movements only in his sibling and mother, provides a unique opportunity to investigate this area further.

This study aims to provide comprehensive cognitive, behavioural and neuroanatomical phenotyping of a family with known *DCC* mutations and mirror movements. The family has previously been described in conjunction with other individuals with *DCC* mutations (Family 4—Marsh et al., 2017; 2018; Spencer-Smith et al., 2020); however, here we provide greater detail based on both standard and experimental neuropsychological and neuroimaging methods.

2. Materials & methods

2.1. Transparency and data availability statements

Here we report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. The sample size was determined to be all members of the family, described in Section 2.2 below, who had *DCC* mutations and the clinical phenomenon of mirror movements. There were no exclusion criteria defined. These criteria were established prior to the write up of this case report. No neuropsychological or neuroimaging data from any of the three participants was removed or excluded. This study reports on a subset of individuals who were part of a larger study of *DCC* mutations, mirror movements and corpus callosum dysgenesis, reported in Spencer-Smith et al. (2020). No part of the current study procedures or analysis plans was preregistered prior to the research being conducted.

Legal copyright restrictions prevent public archiving of the various neuropsychological tests used in this research. These materials can be obtained from the copyright holders in the cited references. The conditions of our ethics approval do not permit the public archiving of the clinical data, as the three participants in this study are highly identifiable as one of two families living with a rare genetic mutation and clinical phenotype in Australia. Qualified researchers seeking access to the data should contact the corresponding author (G.A.R.). Imaging data contained in the manuscript consists of a subset of raw images that have been visually analysed and characterised, rather than analysed with an additional program or code. Data will be shared with named individuals following completion of a data sharing agreement and approval of the local research ethics committee.

2.2. Family background

The family is comprised of the mother (II-1, aged 44 years), daughter (III-2, aged 12 years), and son (III-1, aged 10 years). All family members have *DCC* mutations and mirror movements, and the son has isolated partial ACC. As previously reported by Spencer-Smith et al. (2020), mirror movements were assessed via the Woods and Teuber classification (Woods & Teuber, 1978). Briefly, this classification system assigns a score from 0 (no clearly imitative movement) to 4 (movement equal to that expected for the intended hand) based on the observation of mirror movements in the contralateral limb. Total scores for the right (*R*) and left (*L*) sides were calculated by adding the individual 0–4 scores for finger flexion/extension, wrist flexion/extension, and forearm protonation/supination. The mother (II-1) scored R4 L0, the daughter (III-2) scored R6 L3, and the son (III-1) scored R7 L5 (Spencer-Smith et al., 2020).

The mother had 17 years of education. Her medical history included pituitary adenoma, which had been successfully treated pharmacologically. She had a history of depression and was medicated for this. Cognitively, she reported having subjective difficulty with memory for faces, and a lifelong difficulty with sustaining eye contact with people. Regarding mirror movements, she reported experiencing a sensation in the hand and fingers of the opposite hand to that which she is moving. She also reported that, although predominantly right-handed, she is able to use both hands for many tasks.

The developmental history of the children was obtained from their mother's report. The daughter reportedly required resuscitation at birth. She met early developmental milestones within normal timeframes. She was noted to require strict routines and echolalia was observed when she was younger. At the time of assessment, she was in grade 7 at mainstream school. Although she had some difficulty with schoolwork (English and maths), she was achieving pass grades. She was reported to have difficulty in social situations and had received psychological treatment for anxiety. The daughter experienced subtle mirror movements, with her opposite hand twitching during movements of the other. She was also reported to have difficulty using cutlery and utensils.

No difficulties in pregnancy or birth were reported for the son. He was delayed in both language and motor early developmental milestones and received speech and language

as well as occupational therapy. He received a diagnosis of ASD due to speech and motor delay, echolalia, poor social skills, and the need for strict routines. At age 4, he began to experience tonic-clonic seizures approximately 6-monthly. He was commenced on anti-epileptic medications (sodium valproate and levetiracetam), which were eventually ceased. His last seizure was at 6-years-old. At the time of assessment, he was in grade 5 at mainstream school; however, he completed a differentiated curriculum with the support of a teacher aide. Cognitively, he was reported to have difficulty adapting to change and poor social skills. Mirror movements had been observed since birth and impacted his coordination and ability to complete bimanual tasks.

The mother reported a significant family history of neurodevelopmental conditions, including attention-deficit hyperactivity disorder (ADHD), auditory processing disorder, Pierre Robins syndrome, microcephaly, and global developmental delay.

2.3. *Neuroimaging*

Diffusion MRI data were acquired for each family member using a 7 T S Magnetom whole body MRI scanner fitted with a 32-channel head coil. The acquisition protocol and initial preprocessing steps using Mrtrix3 (www.mrtrix.org) were similar to that previously described (Hearne et al., 2019). Fiber orientation distribution (FOD) function maps for each individual were generated using the Tournier algorithm. For corpus callosum tractography, regions of interest (ROI)s were drawn in the coronal plane at the level of the forceps minor, and posteriorly at the level of the splenium. Frontal and sigmoid projections were generated using homotopic and heterotopic combinations of each ROI pair. For internal capsule tractography, ROIs were drawn at the levels of the midbrain and the basal ganglia, and streamlines were generated between each ipsilateral ROI pair. Tractography results were generated using the iFOD2 algorithm, number of streamlines = 20,000, FOD cut-off = .1, step size = 0.5 × voxel size, maximum angle = 45°. Fractional anisotropy (FA) maps were generated using *tensor2metric* in Mrtrix3. Tract-wise FA estimates were generated by averaging a sampling of the average FA values across all vertices of a subset of streamlines (n = 1000) from each tractography result.

2.4. *Neuropsychological assessment*

The cognitive baseline and experimental tests were completed on two consecutive days, with three training or qualified clinical neuropsychologists concurrently testing the family members, under the supervision of a senior clinical neuropsychologist. Tests were administered and scored according to their standardised procedures. Percentiles were calculated according to published normative data in the relevant test manuals, except where indicated. Scores below the 5th percentile were deemed to be severely impaired and are highlighted in bold, and scores below the 10th percentile were considered impaired. Testing batteries differed between the mother and the children, due to age-appropriate tests being included (see Tables 1–5).

2.4.1. *Cognitive and language baseline*

Overall intellectual functioning of the mother was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), while the son and daughter completed the WASI second edition (WASI-II) (Wechsler, 2011). The mother additionally completed Raven's Advanced Progressive Matrices (Raven, 1976) to measure nonverbal reasoning abilities. Memory skills of the son and daughter were assessed with the NEPSY-II (A Developmental **NE**uro**PSY**chological Assessment, second edition) (Korkman, Kirk, & Kemp, 2007) Memory for Faces and Names and Narrative Memory subtests. The mother completed the Recognition Memory Test for words, faces, and topography (Clegg & Warrington, 1994; Warrington, 1984). All three family members completed the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1941) as a verbal list learning task, and the Rey–Osterrieth Complex Figure Test (RCFT) (Osterrieth, 1944) as a measure of nonverbal memory. Language skills of the son and daughter were assessed with the NEPSY-II Speeded Naming and Comprehension of Instructions subtests. The mother's language skills were assessed with the Graded Naming Test (McKenna & Warrington, 1980) and the Sydney Language Battery (SYDBAT) (Savage et al., 2013), and word and sentence repetition. In all three family members, spontaneous speech output was assessed using picture description tasks, including the Cookie Theft Scene (Goodglass & Kaplan, 1983) and the Beach Scene (Warrington, 1989), where they were additionally prompted to speak continuously for the duration of the task. To assess literacy and numeracy, the son and daughter completed the Wechsler Individual Achievement Test, second edition (WIAT-II) (Wechsler, 2005), and the mother completed the National Adult Reading Test, second edition (NART) (Nelson & Willison, 1991), the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) (Kay, Lesser, & Coltheart, 1996), the Oral Graded-Difficulty Spelling Test (Baxter & Warrington, 1994), and the Oral Graded Arithmetic Test (Jackson & Warrington, 1986). Visuospatial skills were assessed with the NEPSY-II Arrows subtest in the son and daughter, while the mother completed the Incomplete Letters subtest from the Visual Object and Space Perception Battery (Warrington & James, 1991) and the Bells Cancellation Task (Gauthier, Dehaut, & Joanette, 1989). All three family members completed the Benton Facial Recognition Test (Benton, Sivan, Hamsher, Varney, & Spreen, 1994). The mother's speed of processing/psychomotor speed was measured using the Symbol-Digit Modalities Test (Smith, 1982) and Trail Making Test A (Reitan & Wolfson, 1985).

2.4.2. *Praxis and motor functions*

Praxis and motor functions were assessed via gesture production (copy, transitive, intransitive), the Grooved Pegboard (Matthews & Klove, 1964), and the Tapping Test (Reitan, 1969). The son and daughter additionally completed the NEPSY-II Visuomotor Precision and Manual Motor Sequences.

2.4.3. *Executive functions and attention*

To assess attention skills, the mother completed subtests from the Test of Everyday attention (TEA) (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994), and the son and daughter

Table 1 – Cognitive and language baseline test scores.

Cognitive Domain/Test	Standard Score/Percentile		
	Children		Adult
	III-1 (10)	III-2 (12)	II-1 (44)
INTELLECTUAL FUNCTIONING			
Wechsler Abbreviated Scale of Intelligence[a]			
FSIQ	**67 (Impaired)**	95 (Average)	108 (Average)
VIQ	**65 (Impaired)**	93 (Average)	97 (Average)
PIQ	**75 (Impaired)**	99 (Average)	119 (High Average)
Raven's Advanced Progressive Matrices	-	–	12/12 (≥97th %ile)
MEMORY FUNCTIONING			
Recognition Memory Test – Words	–	–	>90th %ile
Recognition Memory Test - Topography	–	–	95th %ile
Recognition Memory Test – Faces	–	–	< **5th %ile**
NEPSY-II Memory for Faces – Delayed	25th %ile	**0.1st %ile**	–
NEPSY-II Memory for Names – Delayed	**2nd %ile**	63rd %ile	–
NEPSY-II Narrative Memory – Free Recall	25th %ile	50th %ile	–
Rey Auditory Verbal Learning Test – Total	< **1st %ile**	12th %ile	93rd %ile
Rey Complex Figure Test - Delayed	< **10th %ile**	40–50th %ile	70–80th % ile
LANGUAGE BASELINE			
Spontaneous Speech (Cookie Scene)[b]	**80 wpm (< 1st %ile)**	**101 wpm (< 1st %ile)**	**85 wpm (< 1st %ile)**
Spontaneous Speech (Beach Scene)[b] – Goal version	**94 wpm (2nd %ile)**	**100 wpm (4th %ile)**	167 wpm (96th %ile)
NEPSY-II Speeded Naming (Combined)	**0.4th %ile**	37th %ile	–
NEPSY-II Comprehension of Instructions	9th %ile	50th %ile	–
Repetition (3-Syllable Word/Sentence)	–	–	Pass
Graded Naming Test	–	–	25–50th %ile
SYDBAT Naming, Repetition, Semantic Association	–	–	Normal
LITERACY AND NUMERACY			
WIAT-II Word Reading	73 (Borderline)	99 (Average)	–
WIAT-II Pseudoword Decoding	75 (Borderline)	99 (Average)	–
WIAT-II Spelling	73 (Borderline)	94 (Average)	–
WIAT-II Numerical Operations	**41 (Impaired)**	100 (Average)	–
NART Estimated IQ	–	–	107 (Average)
PALPA Non-Word Reading	–	–	Pass
Oral Graded Spelling Test	–	–	51–75th %ile
Oral Graded Arithmetic Test	–	–	71st %ile
VISUAL/SPACE PERCEPTION			
Incomplete Letters	–	–	Normal
Benton Facial Recognition[c]	**Impaired**	Normal	Normal
Bell's Cancellation (Neglect)	–	–	Normal
NEPSY-II Arrows	16th %ile	25th %ile	–
SPEED OF PROCESSING			
Symbol-Digit Modalities Test[d]	–	–	50th %ile
Trail Making Test A[e]	–	–	86th %ile

[a] FSIQ = Full Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient.
[b] Narrative speech scored according to QPA criteria (Saffran, Berndt, & Schwartz, 1989); control group $n = 5$, $M = 132.4$, $SD = 19.0$.
[c] Normative data from Paquier et al. (1999) for son (III-1) and daughter (III-2) as reported in Strauss, Spreen and Sherman (2006).
[d] Normative data from Nielsen et al. (1989) as reported in Strauss, Spreen and Sherman (2006).
[e] Normative data from Tombaugh (2004) as reported in Strauss, Spreen and Sherman (2006).

completed the Test of Everyday Attention for Children (TEA-Ch) (Manly, Robertson, Anderson, & Nimmo-Smith, 1999). Additional measures of attention and executive functioning completed only by the son and daughter included the NESPY-II Auditory Attention, Response Set, Inhibition, and Animal Sorting subtests. The mother's executive functioning skills were assessed with the Trail Making Test B (Reitan & Wolfson, 1985), the Brixton Spatial Anticipation Test and the Hayling Sentence Completion Test (Burgess & Shallice, 1996), the Stroop Neuropsychological Screening Test (Trennery, Crosson, DeBoe, & Leber, 1989), the Proverbs Test (Gorham, 1956a, 1956b), anagrams (Rees & Israel, 1935) and Remote Association Test (Mednick, 1962). Auditory attention was assessed with the Digit Span subtest from either the Wechsler Intelligence Scale for Children, fourth edition (WISC–V) (Wechsler, 2004) (son/daughter) or the Wechsler Adult Intelligence Scale, third edition (WAIS-III) (Wechsler, 1997) (mother).

2.4.4. *Generation and fluency*

Verbal fluency was assessed with a phonemic cue (letter–F, A, S for the mother; F & S for son and daughter), and a semantic cue (category–animals) (Battery, 1944). All family members also completed Design Fluency tasks (free and fixed

Table 2 – Summary of scores for praxis and motor functions.

Cognitive Domain/Test	Score/Percentile		
	Children		Adult
	III-1 (10)	III-2 (12)	II-1 (44)
PRAXIS AND MOTOR FUNCTIONS			
Gesture Production – Right Hand	Pass	Pass	Pass
Gesture Production – Left Hand	Pass	Pass	Pass
Transitive Gesture Production	Pass	Pass	Pass
Intransitive Gesture Production	Pass	Pass	Pass
Grooved Pegboard Right (seconds)[a]	< 1st %ile	8th %ile	69th %ile
Grooved Pegboard Left (seconds)[a]	2nd %ile	8th %ile	86th %ile
Tapping Test Right (seconds)[b]	4th %ile	99th %ile	42nd %ile
Tapping Test Left (seconds)[b]	2nd %ile	99th %ile	12th %ile
NEPSY-II Visuomotor Precision (Combined)	1st %ile	25th %ile	–
NEPSY-II Manual Motor Sequences (seconds)	3–10th%ile	11–25th %ile	–

[a] Normative data from Ruff and Parker (1993) for mother (II-1), Rosselli et al. (2001) for son (III-1) and Paniak, Miller and Murphy (personal communication, April 2004, per Lafayette Instrument Grooved Pegboard Test User's Manual) for daughter (III-2) as reported by Strauss, Spreen and Sherman (2006).

[b] Normative data from Ruff and Parker (1993) for mother (II-1) and Findeis and Weight (1994) for son (III-1) and daughter (III-2) as reported by Strauss, Spreen and Sherman (2006).

Table 3 – Summary of scores for attention/executive functions.

Cognitive Domain/Test	Scaled score/Percentile		
	Children		Adult
	III-1 (10)	III-2 (12)	II-1 (44)
ATTENTION/EXECUTIVE FUNCTIONS			
TEA-Ch Sky Search/TEA Telephone Search	0.1st %ile	25th %ile	84th %ile
TEA-Ch Sky Search/TEA Telephone Search Dual Task	0.1st %ile	16th %ile	75th %ile
TEA-Ch Score!/TEA Elevator Counting	1st %ile	1st %ile	16th %ile
TEA-Ch Score/TEA Elevator Counting with Distraction	0.1st %ile	63rd %ile	25th %ile
NEPSY-II Auditory Attention (Combined)	0.1st %ile	75th %ile	–
NEPSY-II Response Set (Combined)	50th %ile	25th %ile	–
NEPSY-II Inhibition – Inhibition	5th %ile	5th %ile	–
NEPSY-II Inhibition – Switching	2nd %ile	1st %ile	–
NEPSY-II Animal Sorting	1st %ile	34th %ile	–
WISC-IV/WAIS-III Digit Span	0.1st %ile	25th %ile	50th %ile
Stroop Colour-Word (seconds/accuracy)	–	–	89/69th %ile
Trail Making Test B[a]	–	–	69th %ile
Hayling Sentence Completion Test (Section 1/Section 2/Errors/Overall)	–	–	50th/50th/10th/25th %ile
Brixton	–	–	50th %ile
Proverbs	–	–	Pass
Remote Association Test	–	–	Pass
Anagrams	–	–	Pass

[a] Normative data from Tombaugh (2004) as reported in Strauss, Spreen and Sherman (2006).

Table 4 – Summary of scores on fluency tasks.

Cognitive Domain/Test	Score/Percentile			
	Children		Adults	
	III-1 (10)	III-2 (12)	II-1 (44)	Healthy Controls[b]
FLUENCY TASKS				(*n* = 150)
Verbal Fluency (Phonemic - FAS)[a]	5th %ile	5th %ile	34 (27th %ile)	40.5 (10.7)
(Semantic - Animals)[a]	37th %ile	50th %ile	24 (77th %ile)	20.4 (4.9)
Design Fluency (Fixed)[a]	7 (6-8th %ile)	10 (11–25th %ile)	27 (63rd %ile)	23.3 (11.3)
(Free)[a]	12 (9–10th %ile)	15 (26–75th %ile)	26 (58th %ile)	23.0 (15.7)
Gesture Fluency (Meaningful)	3 (1st %ile)	6 (4th %ile)	17 (51st %ile)	16.9 (6.3)
(Meaningless)	8 (14th %ile)	12 (20th %ile)	23 (42nd %ile)	26.6 (17.3)

[a] Son (III-1) and daughter's (III-2) scores from Word Generation and Design Fluency tasks from the NEPSY-II. Normative data from NEPSY-II.

[b] Normative data from Robinson et al., 2021 used for the mother's (II-1) fluency scores (except phonemic fluency), and son (III-1) & daughter's (III-2) gesture fluency. Mother's phonemic fluency scores were derived from Tombaugh, Kozak, & Rees (1999).

Table 5 – Summary of scores on social cognition tasks.

Cognitive Domain/Test	Score/Percentile		
	Children		Adult
	III-1 (10)	III-2 (12)	II-1 (44)
SOCIAL COGNITION			
Emotion Attribution Task	–	–	Normal
Reading the Mind in the Eyes[a]	18th %ile	21st %ile	58th %ile
TASIT A Emotion Attribution	–	–	92nd %ile
NEPSY-II Affect Recognition	**1st %ile**	84th %ile	–
NEPSY-II Theory of Mind (Verbal)	11–25th %ile	51–75th %ile	–
NEPSY-II Theory of Mind (Total)	11-25 %ile	>75th %ile	–

[a] Son (III-1) and daughter's (III-2) scores derived from Baron-Cohen et al. (2001b, pp. 8-10-year-old males $n = 8$, $M = 18.1$, $SD = 4.7$; 10-12-year-old females $n = 10$, $M = 21.0$, $SD = 2.4$) and mother's (II-1) scores from Baron-Cohen et al. (2001a; $n = 122$, $M = 26.2$, $SD = 3.6$).

conditions) (Jones-Gotman & Milner, 1977), and Gesture Fluency (meaningless and meaningful conditions) (Jason, 1985; Robinson et al., 2021).

2.4.5. *Social cognition*

To assess social and affective cognition skills, the mother completed the Emotion Attribution Task (van Harskamp, Rudge, & Cipolotti, 2005), The Awareness of Social Inference Test–Emotion Attribution (TASIT-A) (McDonald, Flanagan, & Rollins, 2002), and the Reading the Mind in the Eyes Test–Revised (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). The son and daughter completed the child version of the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001b), as well as the NEPSY-II Affect Recognition and Theory of Mind subtests.

3. Results

3.1. *Neuroimaging*

Tractography of the corpus callosum for each family member is shown in Fig. 1. A sigmoid bundle connecting, via the callosal remnant, the left frontal cortex with contralateral parieto-occipital cortex, was found in the son (III-1) but not the mother (II-1) or daughter (III-2). The sigmoid bundle is highly asymmetric in the son, as indicated by the inverse configuration generating far fewer streamlines. Corticospinal tract projections were reconstructed symmetrically in all family members, and average FA values were comparable between individuals.

3.2. *Neuropsychological assessment*

All cognitive and language baseline test scores are reported in Tables 1–5

3.2.1. *Cognitive and language baseline*

The son's (III-1) overall intellectual abilities were impaired (see Table 1). While he was able to recall details of a passage and unfamiliar faces at a low average level, there was evidence of memory impairment across tasks of memory for names, list learning and recall, and recall of a complex figure. His language abilities were impaired, with reduced spontaneous speech on complex scene description tasks, very slowed naming, and somewhat reduced comprehension of instructions. Academically, his word reading, phonemic understanding, and spelling were poor, and his numeracy skills were very impaired. His spatial perception was intact; however, he had significant difficulty recognising unfamiliar faces.

The daughter's (III-2) verbal and non-verbal abilities were in the average range overall. She performed within normal limits for most tasks of memory functioning, language, literacy and numeracy, and visual/spatial perception. In contrast, her memory for unfamiliar faces was impaired, and her spontaneous speech was reduced.

The mother (II-1) performed in the average range for verbal abilities and in the high average to superior range for non-verbal abilities. She also performed within normal limits across most tasks of memory functioning, language, literacy and numeracy, visual/spatial perception, and psychomotor speed. Her memory for unfamiliar faces was impaired, and her spontaneous speech was reduced.

3.2.2. *Praxis and motor functions*

The son (III-1) was able to produce meaningless gestures with both hands; however, his fine dexterity and speed was impaired across a number of tasks (see Table 2). Behaviourally, mirror movements were observed on all tasks, characterised by residual 'twitching' in the opposite hand even when he was directed to try to suppress the movement. The mother (II-1) and daughter (III-2) generally performed within normal limits on tasks of praxis and motor functions.

3.2.3. *Executive functions and attention*

The son (III-1) demonstrated a clear pattern of impairment across tasks of executive functioning and attention. His performance was reduced on tasks of selective and sustained auditory attention, selective visual attention, and divided auditory/visual attention (see Table 3). His immediate auditory attention and working memory was also reduced. While he performed in the average range on a task of set shifting and inhibition, his initial sustained and selective verbal attention was poor. He also demonstrated significant difficulty with inhibition/suppression, cognitive switching, and concept formation. His sister (III-2) also demonstrated weaknesses in sustained auditory attention, inhibition, and cognitive switching, although she performed within normal limits on

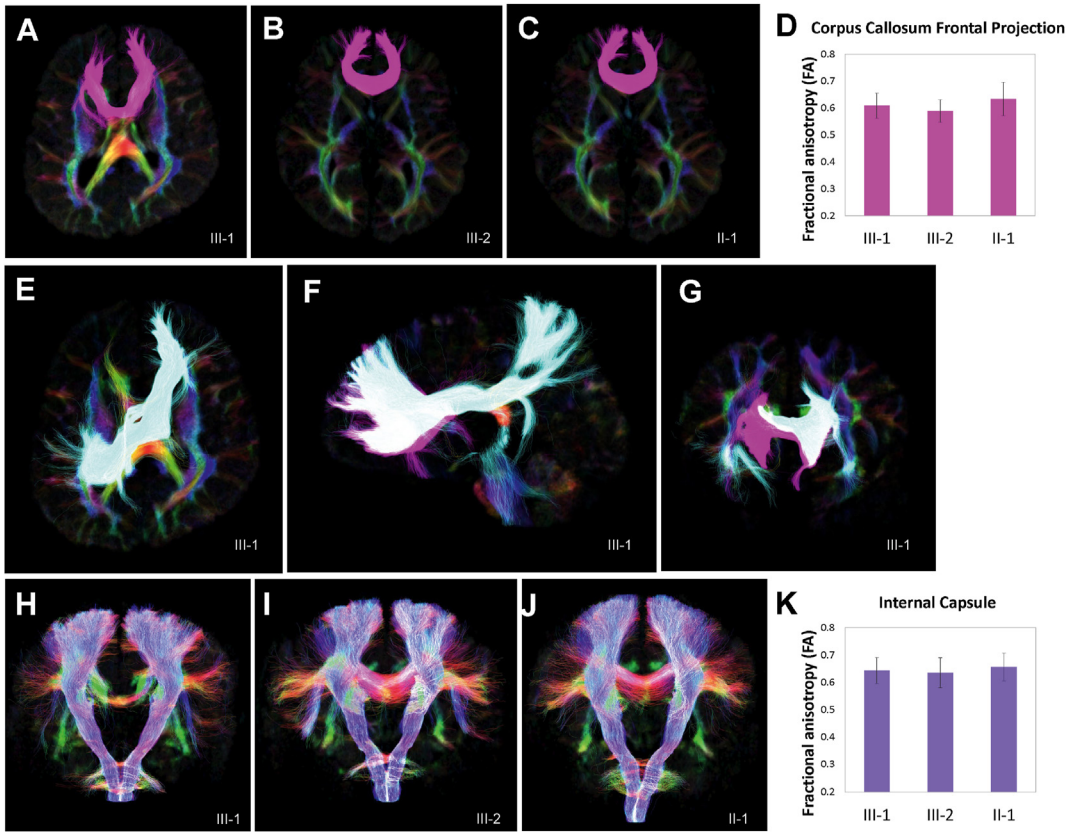

Fig. 1 – Tractography of the corpus callosum and internal capsule in *DCC* mutation carriers. The frontal projections of the corpus callosum via the forceps minor can be reconstructed by probabilistic (iFOD2; purple streamlines) tractography in the son (A; III-1), daughter (B; III-2), and mother (C; II-1), all in axial orientation. D. Sampling of the fractional anisotropy, a diffusion tensor measure indicating white matter integrity, along streamlines within this tract demonstrates comparable values between family members (mean of 1000 streamlines ± standard deviation). Unlike daughter and mother, the son (III-1) uniquely demonstrates a sigmoid bundle (light blue streamlines) connecting, via the callosal remnant, the left frontal cortex with contralateral parieto-occipital cortex (E, axial; F, sagittal; G coronal views). The inverse configuration generated far fewer (yellow) streamlines, indicating that the sigmoid bundle is highly asymmetric in this individual. By contrast, corticospinal tract projections could be reconstructed symmetrically in all family members (directionally colour-coded streamlines in H-J), and average fractional anisotropy values were comparable between individuals (K; mean of 1000 streamlines per tract ± standard deviation). All tractography results are projected onto directionally-encoded colour track density maps in radiological convention.

other of executive functions and attention. The mother (II-1) performed within normal limits on all tasks of attention and executive functioning.

3.2.4. *Generation and fluency*

The son (III-1) and daughter (III-2) both showed significant reductions in their phonemic verbal fluency and a novel measure of non-verbal fluency, meaningful gesture production (see Table 4). However, we acknowledge the available normative data for the gesture fluency task is based on an adult sample. The son (III-1) also demonstrated reductions in fluency for designs, while the daughter (III-2) showed adequate skills in this area. The mother (II-1) performed within normal limits for all verbal and non-verbal fluency tasks.

3.2.5. *Social cognition*

The son's (III-1) ability to recognise emotions in others was significantly reduced, although he was better able to attribute the thoughts and emotions of others when he was able to see their eyes only, and he performed within normal limits on tasks of theory of mind. His family (III-2 and II-1) performed within normal limits on all tasks of social cognition (see Table 5).

4. Discussion

Corpus callosum dysgenesis is associated with a wide range of neuropsychological sequelae. *DCC* and its ligand Netrin-1 have been implicated in integral steps of corpus callosum formation (Depienne et al., 2011; Marsh et al., 2017). Mutations in this gene have been associated with agenesis of the corpus callosum (Marsh et al., 2017, 2018; Spencer-Smith et al., 2020). *DCC* mutations have also been associated with congenital mirror movement disorder (Depienne et al., 2011; Franz et al., 2015; Srour et al., 2010), which is characterised by involuntary

movements on one side of the body mimicking voluntary movements on the other (Depienne et al., 2011; Schott & Wyke, 1981). Here, we have reported a detailed case study of the neuroimaging and neuropsychological functioning of a family who presented with *DCC* mutations and mirror movements. The son additionally had ACC (partial dysgenesis of the corpus callosum).

Given all three family members exhibited mirror movements, praxis and motor functioning was investigated as an area of particular interest. While the son's production of meaningless, transitive and intransitive gestures was intact, his psychomotor speed and fine dexterity was severely reduced. Mirror movements were present on all tasks, despite his efforts to reduce these movements. His family members' praxis and motor functions were relatively intact. These results indicate that mirror movements do not necessarily impact upon praxis and motor functioning; however, reduced callosal connectivity may impact the speed with which these tasks can be completed.

The son was found to have general intellectual impairments, with deficits across multiple cognitive domains, including verbal and non-verbal intelligence, some aspects of memory, language, literacy and numeracy, and facial perception. Interestingly, these deficits were not uniform, and he demonstrated relative strengths in areas such as his memory for faces and narrative memory. The son was also generally slowed on timed tasks, indicating globally reduced processing speed (including but not limited to the interhemispheric transfer of complex information), but his most pronounced impairments were in the domains of attention and executive functioning. He had severely impaired performance across tasks of selective and sustained auditory attention, selective visual attention, divided attention, inhibition, switching, and concept formation. This is largely consistent with the corpus callosum dysgenesis literature, as complex, higher-order cognitive skills are among the most commonly reported domains of cognitive dysfunction, based on group studies including adults, adolescents, and children (Brown et al., 2012; Brown & Paul, 2000, 2019; Marco et al., 2012; Siffredi, et al., 2013, 2018). It is important to note that a portion of individuals with callosal dysgenesis (complete or partial) have intellectual functioning within normal limits (Brown & Paul, 2019; Siffredi et al., 2018), suggesting that the son's cognitive impairments may not be entirely due to the *DCC* mutation alone or his pACC, and perhaps he has other neurological abnormalities not evident on imaging. However, neuropsychological outcomes are extremely heterogeneous; for example, in a paediatric cohort (aged 8–16 years), including children with complete and partial callosal dysgenesis, full scale IQ ranged from severely impaired to superior (14.8% moderately-severely impaired; 66.7% mildly impaired; 18.5% above average) (Siffredi et al., 2018). We also note that individuals with callosal dysgenesis may differ in hemispheric connectivity (i.e., the areas connected via callosal remnants), and that the presence of a sigmoid bundle (found in the son) has been anecdotally associated with poorer cognitive outcomes in individuals with pACC (Tovar-Moll et al., 2007).

The son's impairments in executive and attentional skills are perhaps unsurprising given his overall intellectual functioning, though we note that attention was an area of severe deficit for him. Neuroimaging of the son revealed aberrant asymmetric white matter tracts (sigmoid bundle) between the left frontal region and posterior areas; this abnormal frontal connectivity may have contributed to difficulties with executive and attentional tasks, which are supported by the frontal lobes. Attention and executive functioning deficits can have profound impacts upon the individual's ability to engage in academic activities and function well in society. Thus, these areas of functioning are crucial in assessment of and interventions with those with corpus callosum dysgenesis. The sister also demonstrated some fluctuations in sustained attention, and reduced performance on inhibition and switching tasks, suggesting that mild impairments in these domains may be present in individuals with *DCC* mutations without callosal dysgenesis, and perhaps should be screened for.

Fluency of speech and the rapid generation of novel ideas is integral to conversation and social integration. Reduced fluency and spontaneous speech in the context of intact core language skills is suggestive of a frontal dynamic aphasia profile, a pattern that has been documented in previous case studies of corpus callosum dysgenesis, albeit in more complicated cases with neuroanatomical abnormalities beyond callosal dysgenesis (Barker et al., 2021; Stickles et al., 2002). The son's generation and fluency of ideas was reduced across both verbal and non-verbal tasks. While the mother demonstrated good fluency, the sister's fluency performance was also somewhat reduced, and all three family members had a low rate of spontaneous speech output. These results provide additional evidence that a frontal dynamic aphasia pattern of language and fluency may be a feature of corpus callosum dysgenesis (Barker et al., 2021; Stickles et al., 2002), and suggest that perhaps a similar pattern, at least in terms of reduced spontaneous speech, may be observed *DCC* mutations in the absence of callosal dysgenesis. Frontal dynamic aphasia has previously been linked to lesions and degeneration of frontal regions (Robinson et al., 2005, 2015); therefore, it is possible that subtle alterations in frontal lobe connectivity in the current cases may have contributed to the observed deficits.

A wide range of social cognitive deficits have been reported in individuals, mainly high-functioning adults, with corpus callosum dysgenesis (see Brown & Paul, 2019, for a review). In our case, while the son was impaired in affect recognition, he was able to demonstrate good understanding of the thoughts and emotions of others (theory of mind), which is impressive in the context of his overall intellectual abilities. Since the son also showed poor facial recognition, it may be that his difficulty in affect recognition was underpinned by a fundamental facial perception deficit. In fact, his performance improved in a task where he was able to focus on eyes only, suggesting he may be reliant on a 'piecemeal' approach to facial processing when other facial features are present. This is consistent with a report of atypical facial scanning on an eye-tracking task in a group of adults with agenesis of the corpus callosum and

normal IQ (Bridgman et al., 2014). The mother and daughter were adept at affect recognition and theory of mind tasks. The son's social difficulties might be better explained by his poor executive functioning, including reduced spontaneous speech generation and fluency. This case highlights the importance of widely assessing functions associated with communication and social cognition where individuals present with poor social integration. Broader assessment of these areas of functioning in individuals with corpus callosum dysgenesis may help to elucidate the most useful targets for treatment or supports.

In the current study, the comprehensive description of neuropsychological outcomes provides detailed phenotyping of those with *DCC* mutations, causing mirror movements with or without corpus callosum dysgenesis. The son was found to be intellectually impaired and had reduced performance across a number of cognitive domains, particularly higher-order functions. The son is an example of an individual with relatively severe consequences of a *DCC* mutation, particularly in comparison to his family members with the same mutation. This indicates that there could be additional unknown genetic modifiers involved that impact his phenotype, or that other unidentified neurological or neuroanatomical factors may influence cognitive performance and give rise to differences between the three cases.

While the sister and mother in this family performed reasonably well on cognitive tasks overall, they demonstrated select deficits such as memory for faces and reduced spontaneous speech. This tentatively suggests that neuroanatomical abnormalities, such as impaired connectivity, may be present in individuals with *DCC* mutations, even in the absence of midline corpus callosum dysgenesis which can be observed by MRI, but this needs to be explored in future studies. Additionally, more needs to be understood in terms of the contributions of executive functions, generation and fluency, and social cognition to the ability of individuals with corpus callosum dysgenesis to integrate and function in society.

CRediT Roles

J.L. Knight: Writing – original draft; Investigation.
M.S. Barker: Writing – original draft.
T. Edwards: Formal analysis; Visualization.
J.M. Barnby: Writing – review & editing.
L.J. Richards: Funding acquisition; Writing – review & editing.
G.A. Robinson: Conceptualization; Funding acquisition; Supervision; Writing – review & editing; Project administration.

Declaration of competing interest

All authors declare no conflicts of interest.

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