

CASE REPORT

Open Access



Social anxiety disorder in an adolescent with agenesis of the corpus callosum: a case report

Runnan Yang¹, Yuan Cao^{2,3}, Danmei He⁴, Wen Dang⁴, Changjian Qiu^{1*} and Wei Zhang^{1*} 

Abstract

Background: The agenesis of corpus callosum (ACC) could impair the connectivity of the hemispheres of the cerebral cortex and cause cognitive impairments, social and behavioral issues, and even psychiatric disorders. Although social deficits are common in ACC patients, it is rare for a social anxiety disorder to occur.

Case presentation: To report a 17-year-old adolescent with complete ACC associated with social anxiety disorder, depression, impulsive behavior, and other neurodevelopmental defects such as intellectual disabilities. His avoidance and fear were improved after treatment with sertraline.

Conclusions: This is the first report of social anxiety disorder in ACC patients. The possible relationship between brain structural abnormalities and anxiety syndrome should be investigated in more studies.

Keywords: Agenesis of the corpus callosum, Social anxiety disorder, Social phobia, Psychiatric disorders, Case report

Background

The corpus callosum, consisting of over 190 million axons, is like a bridge connecting the two cerebral hemispheres, which is associated with transferring and integrating meaningful information of the brain [1]. The agenesis of the corpus callosum (ACC) is a rare congenital anomaly with the prevalence varied from 0.02% to 0.7% in the general population [2–5]. Depending on the extent of absence, it can be divided into total or partial agenesis of the corpus callosum. According to its imaging manifestation, the ACC can be divided into the complex ACC when additional abnormalities, such as absent cavum septum pellucidum (CSP), ventriculomegaly, gray matter heterotopia (GMH), cerebellar abnormalities, polymicrogyria [6–9] were detected, and isolated ACC that

no additional abnormalities were found [4]. The underlying risk factors of ACC can be, for example, gene mutations, disturbance of metabolism, intrauterine infections, and exposure to toxic substances such as alcohol [10].

The partial or total absence of corpus callosum can result in deficits in social functioning including emotion recognition, language comprehension, theory of mind [11], executive function impairment, and behavioral problems [10–13]. Besides, patients would be put at risk of mental retardation and have a worse outcome than isolated ACC if they had a complex ACC problem [14]. Some studies suggested that the prevalence of callosal disorders among children with intellectual disabilities was at approximately 2–3% [15–17]. Also, it's worth mentioning that ACC syndrome may overlap with the profile of autism spectrum disorder (ASD) for they both display social, attentional, and behavioral problems. And experts had investigated that among children and adolescents with ACC, 35–50% of them showed obvious autistic symptomatology [18].

*Correspondence: qiuchangjian@wchscu.cn; weizhanghx@163.com

¹ Mental Health Center, West China Hospital, Sichuan University, 28 Dianxin Street, Chengdu, Sichuan, China

Full list of author information is available at the end of the article



Until now, studies have reported the comorbidity of ACC with schizophrenia [1, 19–21], depression disorder [22, 23], bipolar disorder [24], and even personality disorder [24]. Notably, social difficulties existed in ACC and also are characterized in social anxiety disorder (SAD). The key features of SAD are intense fear of social situation and anxious about being negatively evaluated [25]. It affects more subjective distress in male compared to female [26, 27]. The etiology of SAD can be associated with brain structural and functional changes (e.g., overactive of fear circuit) [28, 29]. Nonetheless, a link between SAD and ACC has not been reported yet. Thus, it is of great importance to report this case.

Case presentation

A 17-year-old teenager was admitted to our hospital for unwillingness to interact with others and associated with a depressed mood. He was a full-term natural infant at his birth without a family history of psychiatric disorders. He was a left-behind child raised by his grandparents and sisters. Family members had noticed that the boy was an introvert and hardly interacted with his classmates when he was in elementary school. Besides, he shows poor academic performance which might be due to his learning difficulties. At the age of 14 years old, the behavior problem showed up. He took things away from stores without paying for them several times but had no awareness of the faults. The store owner once called the police, and then his father beat him hard. Since then, he began to be withdrawn and reluctant to go to a place where there were many people. He feared his inappropriate behavior would allow him to be judged and punished again. He often covered his eyes with his hands so that he can avoid eye contact when he met unfamiliar people. He usually stayed at home alone playing video games. He was diagnosed with autism spectrum disorder at the age of 15 years old and received sertraline and risperidone for treatment. However, he still feared interacting with unfamiliar people but was able to communicate with his mother or sisters. Also, he easily showed irritability and hostility towards his father. After graduating from junior high school, he moved to the city where his mother living, and had a new environment to make a living. However, he turned to feeling worthless and had suicide ideation 2 months prior to admission.

On hospital admission, his general and neurological examination were normal. Two experienced psychiatrists observed nervous looks, blushed, avoiding eye contact, a decrease of speech, hypobulia, and depression. He showed shyness and tension and hid his face when sitting around with his teenage roommates. But he could have a normal conversation and be relaxed when staying with his sister alone.

Routine blood analyses were normal. The patient's score on Raven's Standard Progressive Matrices was 21, which percentile rank was 4%, equal to Intelligence Quotient (IQ) score was 74. It suggested that the boy had intellectual disabilities. The Mini-Mental State Examination (MMSE) score was 18. The electrocardiogram (ECG) and electroencephalogram (EEG) were normal. Brain Magnetic resonance imaging (MRI) demonstrated a partial defect of the body of corpus callosum, absent septum pellucidum, and connected lateral ventricles. Besides, the short superior vermis of the cerebellum and upward displacement of the tentorium can be observed. Moreover, there were microgyria and polymicrogyria of bilateral frontal-parietal lobes. The shape of the sulci was also involved (Fig. 1).

During hospitalization, this boy showed marked anxiety and persistence avoidance that was provoked by social situations involving peers and adults. And fear of judgement by others for his inappropriate acting way. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), he was considered as have a SAD [30]. Moreover, he has no restricted or repetitive behavior pattern and showed a reciprocal communication form when interacting with familiar people. Given this, we exclude the diagnosis of ASD. We began the administration of sertraline 50 mg per day to him. We observed the distinct social avoidance, he had a shy look and refused to interact when teenage patients invited him to play. Especially when we went rounds, he started covering his face with his hands and blushed, we could not have an effective conversation because he either rarely spoke or answered with "I don't know, go ask my sister". Still, he showed harmonious behavior and emotional reactions when playing with his sister. He was treated with sertraline 100 mg daily one week later. His mood brightened but the situation of social avoidance still existed.

One month after discharge, we learned via the follow-up phone call that the boy's depressed mood lightened and his sister noticed that he no longer covered his face when walking on the street. He seemed more relaxed but still showed irritability to his parents. The boy had an outpatient visit two months after discharge. He rarely had eye contact with strangers, but he was not looking obvious sheepish and didn't cover his face anymore. "I feel much better", he answered us. We encourage him to conduct social skill-training with the assistance of his sister.

Discussion and conclusions

Here we reported a 17-year-old Chinese juvenile who was suffering from ACC with comorbid social anxiety disorder, and accompanied by behavior problems, psychiatric symptoms. Individuals with ACC would suffer from

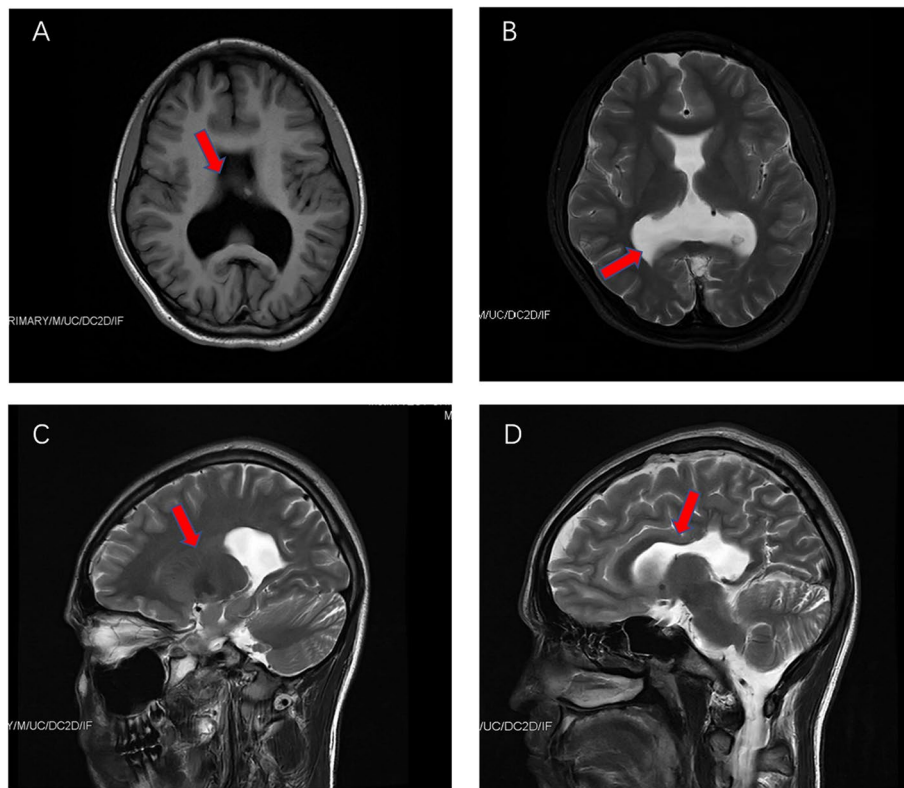


Fig. 1 Brain MRI examination of a 17-year-old boy on admission. **A** and **B** axial T1-weighted images and T2-weighted images, showing absent septum pellucidum, connected lateral ventricles, and enlarged pedunculus posterior. **C** and **D** sagittal T2WI FLAIR images, presenting partial defect of the body of corpus callosum. And the cerebral convolutions adjacent to the absent corpus callosum region enlarged and shifted downward

social function deficiency. The ACC caused callosal connectivity reduction may result in the decrease of information processing and impair cognition development, thus limiting the capacity of the theory of mind [11], humor comprehension [31], facial expression understanding [32]. To explore anxiety disorders in ACC patients, we searched the ACC cases with anxiety published previously, and the summary is shown in Table 1. To the best of our knowledge, this is the first case of ACC with SAD.

In terms of the pathological mechanism of social anxiety disorder, according to the research [25], poor social skills are independent risk factor of social anxiety. It especially may play a critical role in maintaining social phobia in children than it does in adults. Besides, genetic influence cannot be ignored. Prior twin studies and recent genome-wide association analysis (GWAS) study had revealed that SAD has a heritability basis [37, 38], shared genetic risk with extraversion. That is, children with high behavioral inhibition (BI), which refers to caution, fear, low rate of approach, and passive withdrawal in novel situations [39], may evolve to social phobia in their growth. ACC is often associated with those psychiatric disorders with social behavior deficits, such as autism and

schizophrenia. The research of the complex mechanism of ACC suggested that the modifier genes that affect callosal formation may overlap with genes that lead to mental disorders [40]. And studies have shown that the risk of social anxiety in first-degree relatives of autism patients increased tenfold than that in relatives of patients with other neurodevelopmental disorders (e.g., Down's syndrome) [41]. It is possible that ACC disease significantly increased the risk of social anxiety disorder. Indeed, more research is needed to detect the possibility of comorbidity. What's more, the changes of brain networks in both diseases seem to have something in common. The resting-state functional connectivity research of ACC patients demonstrated that impaired functional connection occurred in dorsolateral pre-frontal (DLPFC), posterior cingulate cortex (PCC), posterior parietal cortex (PPC), and parietal-occipital (PO) cortices regions [42, 43]. Alternatively, it is common that a reduced volume of the right ventral anterior cingulate gyrus and left inferior frontal gyrus in anxiety disorders [44].

There are some limits in this case. First, it was difficult to determine whether social deficits belong to primary ACC symptoms or the comorbidity of ACC. Second, we did

Table 1 Review on previous reports of ACC patients with anxiety symptoms

Author (Year)	Age/Gender	Anxiety signs	Behavior problems	Other psychiatric disturbances	Intelligence level	Imaging performance	Associated with other Lesions
Russell [33] (1955)	19, Female	MMPI results: hypochondriasis; hysteria; psychasthenia	NA	depression; emotional instability; impaired concentration	Wechsler-bellevue test score: 61	complete absence of the corpus callosum	dilation of both lateral ventricles; Middle cerebral aqueduct the stenosis; the third ventricle was enlarged superiorly and posteriorly; the left cerebellar hemisphere was smaller than normal
Spak [34] (2019)	12, Male	generalized anxiety; aggression; stress	obsessive–compulsive disorder	attention deficit disorder; unable to concentrate on completing drumming and talking	IQ 68	partial agenesis of the corpus callosum (posterior)	NA
Párraga [35] (2003)	11, Male	irrational fears; anxiety attacks; separation anxiety; poor eye contact	hyperactivity; poor impulse control; difficulties relating to other children	visual and auditory hallucinations; marked distortions of reality; sleep difficulties	IQ 85	agenesis of the corpus callosum (unspecified)	colpocephaly
David [24] (1993)	10, Female	agitated movement	hyperactivity; temper outbursts; oppositional; lying; stealing; destruction	emotional; sleep difficulties	IQ 102	partial agenesis of the corpus callosum (the rostrum and the body)	colpocephaly
Ernst [36] (1999)	33, Male	fear; acute anxiety episodes	set fire; attack neighbors	mannerisms; hallucinations; delusions	IQ 78	partial agenesis of the corpus callosum	NA
Ernst [36] (1999)	15, Female	alexithymia; chronic pain; stressful events lead to an increase in pain	NA	NA	NA	agenesis of the corpus callosum (unspecified)	Chiari II Malformation; hydrocephalus

Abbreviations: *MMPI* Minnesota Multiphasic Personality Inventory, *NA* Not available, *IQ* Intelligence quotient

not conduct a functional MRI test, which limits the richness of the results. Third, we are failing to follow patients for long-term so that we cannot acquire the condition changes and therapeutic effect. Finally, we collect history mostly depending on the verbal report of the patient's family, which may not be able to explain his inner experience.

In summary, this is the first report of an ACC patient combined with social anxiety disorder. The relationship between structural abnormalities of the brain in stress-related disorder and congenital developmental disorder remains unclear. There is a need for prospective studies in the future.

Abbreviations

ACC: Agenesis of corpus callosum; CSP: Cavum septum pellucidum; GMH: Gray matter heterotopia; ASD: Autism spectrum disorder; SAD: Social anxiety disorder; IQ: Intelligence Quotient; MMSE: Mini-Mental State Examination; ECG: Electrocardiogram; EEG: Electroencephalogram; MRI: Magnetic resonance imaging; DSM-5: The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders; GWAS: Genome-wide association analysis; BI: Behavioral inhibition; DLPFC: Dorsolateral pre-frontal; PCC: Posterior cingulate cortex; PPC: Posterior parietal cortex; PO: Parietal-occipital.

Acknowledgements

The authors would like to thank the mother and sister of this patient for giving us opportunity to learn from the patient's medical condition and write this case report.

Authors' contributions

RY collected patient's data, followed up the patient and wrote the manuscript. YC acquired the neuroimaging data and edited the draft. RY, DH and WD revised the draft critically for important intellectual content. CQ and WZ treated this patient and reviewed the diagnostic results, contributed to the planning, draft, revision of the manuscript. All authors read and gave the final approval of the version to be published.

Funding

This work was supported by the National Natural Science Foundation of China (Grant no. 81871061), Department of Science and Technology of Sichuan Province (Grant nos. 2020YFS0582, 2020YFS0231), the Postdoctoral Foundation of West China Hospital to Dr. M.Y. (Grant no.2020HXBH041). The funders were not involved in the collection case information or in writing the manuscript.

Availability of data and materials

No datasets besides those reported in the article were generated during the current study.

Declarations

Ethics approval and consent to participate

Written informed consent to participate was obtained from the patient's family. A copy of the signed written consent is available for review by the editor of this journal.

Consent for publication

Written informed consent was obtained from the patient's mother and sister. A copy of the signed written consent to publish is available for review by the editor of this journal.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Mental Health Center, West China Hospital, Sichuan University, 28 Dianxin Street, Chengdu, Sichuan, China. ²Department of Nuclear Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China. ³Huaxi MR

Research Center (HMRR), Department of Radiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China. ⁴West China Biomedical Big Data Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China.

Received: 21 April 2022 Accepted: 22 October 2022

Published online: 16 November 2022

References

- Paul LK, Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, et al. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nat Rev Neurosci*. 2007;8(4):287–99.
- Dobyns WB. Absence makes the search grow longer. *Am J Hum Genet*. 1996;58(1):7–16.
- Grogono JL. Children with agenesis of the Corpus Callosum. *Dev Med Child Neurol*. 1968;10(5):613–6.
- Bayram AK, Kütük MS, Doganay S, Özgün MT, Gümüş H, Başbuğ M, et al. An analysis of 109 fetuses with prenatal diagnosis of complete agenesis of corpus callosum. *Neurol Sci*. 2020;41(6):1521–9.
- Stoll C, Dott B, Roth M-P. Associated anomalies in cases with agenesis of the corpus callosum. *Am J Med Genet A*. 2019;179(10):2101–11.
- Mandelstam SA, Leventer RJ, Sandow A, McGillivray G, van Kogelenberg M, Guerrini R, et al. Bilateral posterior periventricular nodular heterotopia: a recognizable cortical malformation with a spectrum of associated brain abnormalities. *AJNR Am J Neuroradiol*. 2013;34(2):432–8.
- Manganaro L, Bernardo S, De Vito C, Antonelli A, Marchionni E, Vinci V, et al. Role of fetal MRI in the evaluation of isolated and non-isolated corpus callosum dysgenesis: results of a cross-sectional study. *Prenat Diagn*. 2017;37(3):244–52.
- Tang PH, Bartha AI, Norton ME, Barkovich AJ, Sherr EH, Glenn OA. Agenesis of the corpus callosum: an MR imaging analysis of associated abnormalities in the fetus. *AJNR Am J Neuroradiol*. 2009;30(2):257–63.
- Shen O, Gelot AB, Moutard ML, Jouannic JM, Sela HY, Garel C. Abnormal shape of the cavum septi pellucidum: an indirect sign of partial agenesis of the corpus callosum. *Ultrasound Obstet Gynecol*. 2015;46(5):595–9.
- Edwards TJ, Sherr EH, Barkovich AJ, Richards LJ. Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes. *Brain*. 2014;137(Pt 6):1579–613.
- Lábadi B, Beke AM. Mental state understanding in children with agenesis of the corpus callosum. *Front Psychol*. 2017;8:94.
- Brown WS, Paul LK. The neuropsychological syndrome of agenesis of the corpus callosum. *J Int Neuropsychol Soc*. 2019;25(3):324–30.
- Siffredi V, Anderson V, McIlroy A, Wood AG, Leventer RJ, Spencer-Smith MM. A neuropsychological profile for agenesis of the corpus callosum? cognitive, academic, executive, social, and behavioral functioning in school-age children. *J Int Neuropsychol Soc*. 2018;24(5):445–55.
- Bernardes da Cunha S, Carneiro MC, Miguel SA M, Rodrigues A, Pina C. Neurodevelopmental outcomes following prenatal diagnosis of isolated corpus callosum agenesis: a systematic review. *Fetal Diagn Ther*. 2021;48(2):88–95.
- Jeret JS, Serur D, Wisniewski K, Fisch C. Frequency of agenesis of the corpus callosum in the developmentally disabled population as determined by computerized tomography. *Pediatr Neurosci*. 1985;12(2):101–3.
- Fratelli N, Papageorgiou AT, Prefumo F, Bakalis S, Homfray T, Thilaganathan B. Outcome of prenatally diagnosed agenesis of the corpus callosum. *Prenat Diagn*. 2007;27(6):512–7.
- Bedeschi MF, Bonaglia MC, Grasso R, Pellegrini A, Garghentino RR, Battaglia MA, et al. Agenesis of the corpus callosum: clinical and genetic study in 63 young patients. *Pediatr Neurol*. 2006;34(3):186–93.
- Paul LK, Corsello C, Kennedy DP, Adolphs R. Agenesis of the corpus callosum and autism: a comprehensive comparison. *Brain*. 2014;137(Pt 6):1813–29.
- Rane S, Kose S, Gore JC, Heckers S. Altered functional and structural connectivity in a schizophrenia patient with complete agenesis of the corpus callosum. *Am J Psychiatry*. 2013;170(1):122–3.
- Micoulaud-Franchi JA, Bat-Pitault F, Da Fonseca D, Ruffo M. Early onset schizophrenia and partial agenesis of corpus callosum. *Arch Pediatr*. 2011;18(2):189–92.
- Hallak JEC, Crippa JAdS, Pinto JP, Machado de Sousa JP, Trzesniak C, Dursun SM, et al. Total agenesis of the corpus callosum in a patient with childhood-onset schizophrenia. *Arq Neuropsiquiatr*. 2007;65(4B):1216–9.

22. Popoola O, Olayinka O, Azizi H, Ojimba C, Khan T, Kallikkadan J, et al. Neuropsychiatric manifestations of partial agenesis of the corpus callosum: a case report and literature review. *Case Rep Psychiatry*. 2019;2019:5925191.
23. Chiarello C. A house divided? cognitive functioning with callosal agenesis. *Brain Lang*. 1980;11(1):128–58.
24. David AS, Wacharasindhu A, Lishman WA. Severe psychiatric disturbance and abnormalities of the corpus callosum: review and case series. *J Neurol Neurosurg Psychiatry*. 1993;56(1):85–93.
25. Rapee RM, Spence SH. The etiology of social phobia: empirical evidence and an initial model. *Clin Psychol Rev*. 2004;24(7):737–67.
26. Weinstock LS. Gender differences in the presentation and management of social anxiety disorder. *J Clin Psychiatry*. 1999;60(Suppl 9):9–13.
27. Merikangas KR, Avenevoli S, Acharyya S, Zhang H, Angst J. The spectrum of social phobia in the Zurich cohort study of young adults. *Biol Psychiatry*. 2002;51(1):81–91.
28. Ayling E, Aghajani M, Fouche JP, van der Wee N. Diffusion tensor imaging in anxiety disorders. *Curr Psychiatry Rep*. 2012;14(3):197–202.
29. Brühl AB, Delsignore A, Komossa K, Weidt S. Neuroimaging in social anxiety disorder—a meta-analytic review resulting in a new neurofunctional model. *Neurosci Biobehav Rev*. 2014;47:260–80.
30. Leichsenring F, Leweke F. Social anxiety disorder. *N Engl J Med*. 2017;376(23):2255–64.
31. Symington SH, Paul LK, Symington MF, Ono M, Brown WS. Social cognition in individuals with agenesis of the corpus callosum. *Soc Neurosci*. 2010;5(3):296–308.
32. Bridgman MW, Brown WS, Spezio ML, Leonard MK, Adolphs R, Paul LK. Facial emotion recognition in agenesis of the corpus callosum. *J Neurodev Disord*. 2014;6(1):32.
33. Russell JR, Reitan RM. Psychological abnormalities in agenesis of the corpus callosum. *J Nerv Ment Dis*. 1955;121(3):205–14.
34. Spak D, Card E. Music, movement, and mind: use of drumming to improve strength, balance, proprioception, stamina, coordination, and emotional status in a 12-year-old with agenesis of the corpus callosum: a case study. *J Holist Nurs*. 2019;38(2):186–92.
35. Párraga HC, Párraga MI, Jensen AR. Cognitive, behavioral, and psychiatric symptoms in two children with agenesis of the corpus callosum: case report. *Int J Psychiatry Med*. 2003;33(1):107–13.
36. Ernst H, Key JD, Koval MS. Alexithymia in an adolescent with agenesis of the corpus callosum and chronic pain. *J Am Acad Child Adolesc Psychiatry*. 1999;38(10):1212–3.
37. Stein MB, Jang KL, Livesley WJ. Heritability of social anxiety-related concerns and personality characteristics: a twin study. *J Nerv Ment Dis*. 2002;190(4):219–24.
38. Stein MB, Chen C-Y, Jain S, Jensen KP, He F, Heeringa SG, et al. Genetic risk variants for social anxiety. *Am J Med Genet B Neuropsychiatr Genet*. 2017;174(2):120–31.
39. Belsky J, Rha J-H, Park S-Y. Exploring reciprocal parent and child effects in the case of child inhibition in US and Korean samples. *Int J Behav Dev*. 2000;24(3):338–47.
40. Paul LK, Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, et al. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nat Rev Neurosci*. 2007;8(4):287–99.
41. Piven J, Palmer P. Psychiatric disorder and the broad autism phenotype: evidence from a family study of multiple-incidence autism families. *Am J Psychiatry*. 1999;156(4):557–63.
42. Hinkley LBN, Marco EJ, Findlay AM, Honma S, Jeremy RJ, Strominger Z, et al. The role of corpus callosum development in functional connectivity and cognitive processing. *PLoS ONE*. 2012;7(8):e39804.
43. Owen JP, Li Y-O, Yang FG, Shetty C, Bukshpun P, Vora S, et al. Resting-state networks and the functional connectome of the human brain in agenesis of the corpus callosum. *Brain Connect*. 2013;3(6):547–62.
44. Shang J, Fu Y, Ren Z, Zhang T, Du M, Gong Q, et al. The common traits of the ACC and PFC in anxiety disorders in the DSM-5: meta-analysis of voxel-based morphometry studies. *PLoS ONE*. 2014;9(3):e93432.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

