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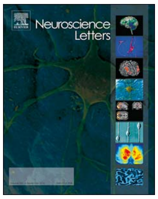

Research article

Callosotomy affects performance IQ: A meta-analysis of individual participant data

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ABSTRACT

Morphometric neuroimaging studies on healthy adult individuals regularly report a positive association between intelligence test performance (IQ) and structural properties of the corpus callosum (CC). At the same time, studies examining the effect of callosotomy on epilepsy patients report only negligible changes in IQ as result of the surgery, partially contradicting the findings of the morphometry studies. Objective of the present meta-analysis of individual participant data (IPD) of 87 cases from 16 reports was to re-investigate the effect of callosotomy on full scale IQ as well as on the verbal and performance subscale under special consideration of two possible moderating factors: pre-surgical IQ levels and the extent of the surgery (complete vs. anterior transsection). The main finding was that callosotomy selectively affects performance IQ, whereby the effect is modulated by the pre-surgical level of performance. Patients with an above-median pre-surgery performance IQ level show a significant average decrease of -5.44 (CI$_{95\%}$: -8.33 to -2.56) IQ points following the surgery, while the below-median group does not reveal a significant change in IQ (mean change: 1.01 IQ points; CI$_{95\%}$: -1.83 to 3.86). Thus, the present analyses support the notion that callosotomy has a negative effect on the patients' performance IQ, but only in those patients, who at least have an average performance levels before the surgery. This observation also lends support to the findings of previous morphometry studies, indicating that the frequently observed CC-IQ correlation might indeed reflect a functional contribution of callosal interhemispheric connectivity to intelligence-test performance.

1. Introduction

The intellectual and cognitive abilities usually summarized as intelligence are supported by a large-scale brain network encompassing association cortices in frontal, parietal, and temporal lobes [6,13]. As this network is distributed across both cerebral hemispheres, it has been suggested that hemispheric interaction via the commissures has an important role in higher intellectual abilities [1,5,16,30]. This notion, is supported by a series of neuroimaging studies demonstrating an association between intelligence scores (IQ) and corpus callosum (CC) measures [4,7,14,22,25,26,31]. In healthy adult individuals, for example, a thicker mid-sagittal CC [14] or higher callosal fractional anisotropy (indicative for stronger axon myelination) [7] has been found to be positively predictive for higher intellectual performance. Evidence for a common genetic origin for CC size or fractional anisotropy with IQ scores from heritability studies [11] and target-gene approaches [21] also support this view. The correlational nature of the above studies prevents, however, any strong conclusion regarding the "causal" relevance, or necessity, of hemispheric connectivity for high intellectual performance [9]. In fact, it has been suggested that this CC-IQ correlation might be in itself "non-functional" and rather reflect differences in the neuron population in the interconnected cortices that only secondarily affect callosal connectivity [25]. However, one way to substantiate the notion of a causal link is to study the effect of severing the corpus callosum (callosotomy) on intelligence in a pre- vs. post-operative comparison. Such comparison usually reveals that the effect of callosotomy—traditionally performed as treatment to reduce the effect of epileptic seizure—on IQ is negligible [15,19,27]. For example, Mamelak et al. [15] examined 15 epilepsy patients aged between 9 and 31 years and found no substantial change in verbal (mean change in v-IQ: 0.38, SD = 3.52) or performance IQ (change in p-IQ: 1.23, SD = 3.56).

Nevertheless, reviewing the available literature it is also obvious that two important factors which potentially might influence the effect of the callosal surgery have not been systematically addressed. These are the level of pre-surgical intelligence and the extent of the surgery (i.e., whether a complete or partial transection was performed). Thus, the objective of the present meta-analysis of individual participant data (IPD) was to assess the effect of callosal surgery on intelligence test

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performance under consideration of these potential moderating factors in order to supplement the correlational evidence from previous neuroimaging studies.

2. Material and methods

2.1. Study and case identification

As IQ scores are usually reported to give a closer description of the patients without being of interest for the primary study (which addressed a wide variety of different research questions), the aim of the literature search was to identify all articles in which one or more callosotomy patients are described and screen these for relevant data. Thus, in May 2017 the literature search in ISI Web of Knowledge (apps.isiknowledge.com) and PubMed (www.ncbi.nlm.nih.gov/pubmed) was conducted, with the search terms: “callosotomy”, “callosal sect*”, “commissurotom*”and “split-brain”. The “commissurotom*” search was further filtered to exclude the cardio vascular “mitral commissurotomy”. The search revealed 933, 350, 345, and 776 articles, respectively, also there was an overlap in the results, which in total gave 1646 unique articles. These were successively screened for IQ data. The reference lists of identified articles were used to locate further potentially relevant studies. A total of 16 studies published between 1969 and 2011 providing data on 87 independent patients/cases (an overview of the included studies can be found in the supplementary material Table S1). All included cases fulfilled the following criteria: (a) numerical IQ data for patients is presented for a time point before (pre) as well as after the surgery (post), or as difference score between pre- and post-surgery scores; (b) the callosal transsection was the only surgical intervention between pre and post assessment; (c) the age of the patient was at time of surgery at least 10 years; (d) the provided pre-operational IQ was at least 40 (as the reliability below this level can be questioned); and (e) if more than one surgery was conducted (e.g., a step-wise callosotomy) the data of the first surgery was used. The mean age of the total sample was 23.8 (s.d.: 8.4) years at first surgery (range 10–53 years). The sex of the patients was not always reported (missing in 35 of 87 cases), preventing a systematic analysis of a potential sex differences [7].

2.2. Dependent variables of interest

Full-scale IQ (fsIQ), verbal IQ (vIQ), and performance IQ (pIQ) were considered as variables of interest. For all but three of the included studies, it was possible to verify that intelligence test were applied that used a test norm with an expected mean of 100 and a standard deviation of 15 IQ points. (i.e., any version of the Wechsler Adult Intelligence Scale, Wechsler-Bellevue test, Wechsler Intelligence Scale for Children, Stanford Binet test, Ottawa Wechsler test). For one study T-scores were provided, which were transformed to the IQ scale using linear transformation. For two further studies, it was not possible to determine the exact test that was used, but the range of data presented or previous publications of the same group allowed to assume that also here the standard IQ norm was applied. For details see supplementary material Table S1.

An overview of the final sample size and number of studies per IQ score type can be found in Table 1. As not all articles provided both subscale and fsIQ data for the studied patients, and vice versa, the samples were not fully overlapping. Thus, where only subscale scores were available, we additionally estimated fsIQ (efsIQ) by averaging vIQ and pIQ scores for these subjects, and added this data to the fsIQ. However, it has to be noted that due to the separate transformation of raw test scores to the norm-deviation IQ scores for raw full and subscales [28], respectively, the average rank position (i.e., the mean of vIQ and pIQ) will not necessarily be equivalent to the rank in fsIQ or the full scale. Thus, the efsIQ scores can only be seen as an approximation of fsIQ and has to be interpreted with caution. Nevertheless, efsIQ was considered here in order to utilise as much data as possible and increase the sample size. Finally, for each of the four IQ scores, change scores were determined by subtracting the pre-surgery IQ from the respective post-surgery IQ, henceforth referred to as ΔfsIQ, ΔefsIQ, ΔvIQ, and ΔpIQ. Positive pre-post change scores represent an increase and negative score a decrease in IQ. The change scores served as dependent variables in the statistical analysis.

2.3. Statistical analysis

Four IPD meta-analyses were conducted for each of the four dependent measures: ΔfsIQ, ΔefsIQ, ΔvIQ, and ΔpIQ. Each meta-analysis was set up using a one-stage analysis approach based on linear-mixed models [3]. The factor Source Study was modelled as random effect to account for between-study heterogeneity, and the variables of interest were modelled as fixed effects, whereby the variables of interest were conceptualized as two-factorial design with Pre-Surgery IQ (coding above or below median pre surgery IQ) and Type of Section (partial vs. complete section), and the interaction of these two variables. Effect coding was employed so that intercept of each model represents the mean pre-post change across groups. All analyses were calculated using restricted maximum likelihood estimations (full covariance matrix; Cholesky parameterization) and fitted with the “fitlme” function provided with MATLAB (R2015b, MathWorks). Significance threshold was set to $\alpha = 0.05$. Effect sizes were calculated as proportion of explained variance (e.v. = [sum of squares effect]/[total sum of squares]) based on the fixed effect sum of squares. The proportion of the variance explained by the random effects variable was taken as measure of inhomogeneity among studies (I^2). The analysis was supplemented with test power calculations using G*Power software (version 3.1) to estimate sensitivity (i.e., the minimum population effect size which can be reliably excluded with a test power of 0.80, given the present statistical design, sample size, and α-threshold) for the fixed-effect part. Of note, as the here re-analysed IQ data is not object of the original analysis and rather is reported as information of the patient, no systematic file-drawer bias should be expected.

3. Results

In none of the four analyses, a significant change in IQ from pre- to post-surgery was found (for the intercept all $p > 0.32$; see Table 2 for details). However, considering pre-surgical performance level, a significant difference it the change of pIQ was found between the below and above median group as indicated by a significant main effect of Pre-Surgery IQ ($t(72) = 2.77$, $p = 0.007$, e.v. = 0.11; see Fig. 1 left panel). The ΔpIQ did not only differ between the two groups, in the above median group the observed mean decrease in performance of ΔpIQ = −5.44 was also significant by itself, with $CI_{95\%} = [-8.33; -2.56]$ not including zero. The mean ΔpIQ of 1.01 observed in the below median group was not significant ($CI_{95\%} = [-1.83, 3.86]$). For neither ΔvIQ nor the full-scale IQ measures (ΔfsIQ, ΔefsIQ), a comparable effect was detected (all $p > 0.08$, all e.v. < 0.05, see Fig. 1 and Supplementary Fig. 1). The main effect of Type of Section (all $p > 0.17$, all e.v. < 0.03) and the interaction (all $p > 0.33$, all e.v. < 0.01) did not reach significance for any of the dependent variables (for details see Table 2). The power analysis yielded a sensitivity of 0.08 proportion of explained variance for the ΔpIQ and ΔvIQ analyses, and of 0.10 and 0.07 for the ΔfsIQ and ΔefsIQ analysis, respectively, so that population effects above these values can be reliably excluded by the present analysis.

4. Discussion

The main finding of the present analysis is that callosotomy selectively affects performance IQ scale whereby the severity of the effect is modulated by the pre-surgical level of performance. In the above-median pre-surgery pIQ group a significant average decrease of 5.44 IQ

Table 1
Overview sample in relation to independent variables.

Analysis	Cases	Studies	Surgery Type part/comp[b]	Sex f/m/nr[c]	Age at Surgery	Pre-Surgery IQ		
	(N)	(k)[a]	(n)	(n)	mean (s.d.)	mean (s.d.)	median	min/max
fsIQ	58	13	22/36	19/33/35	24.5 (9.4)	80.2 (16.2)	81.5[d]	40/113
efsIQ	87	16	36/51	14/27/17	23.8 (8.4)	80.4 (15.5)	82	40/113
vIQ	76	12	28/48	16/27/33	24.8 (8.3)	83.6 (14.0)	83	48/115
pIQ	76	12	28/48	16/27/33	24.8 (8.3)	82.8 (13.8)	85	46/110.5[d]

Notes.
[a] A list of the included studies and cases can be found in Table S1, Supplementary material.
[b] Number of patients with partial (part) and complete (com) section of the corpus callosum.
[c] Number of female (f) and male (m) patients, together with the number of patients for which sex was not reported (nr).
[d] Fractional IQ values result from transforming T-scale to IQ-scale values using linear transformation.

points was found, while no significant effect was detected in the below-median group. Thus, structural interhemispheric connectivity appears to support pIQ only above a certain level of performance while a lower performance level appears not to rely to a comparable degree on the integrity of the corpus callosum. This is in line with previous studies on healthy individuals, which have demonstrated that the distribution of task processing between cerebral hemispheres is associated with higher-level of performance [18] especially in more complex task situations [2,30]. Furthermore, this performance benefit has been shown to rely on structural and functional connectivity between the hemispheres [5] underlining the importance of an efficient communication between the hemisphere [7]. Thus, transsected callosal connections might restrict or abolish beneficial collaboration between the hemispheres and preclude higher levels of performance in these individuals (which otherwise would benefit from it). Nevertheless, it also has to be considered that the patients in the above-median group may at best be characterised as having average performance in the intelligence tests. The median split was done at a pre-surgery pIQ of 86 while the maximum pre-surgery pIQ in the sample was at 110.5, so that the above-median group was well within one standard deviation below and above the to-be-expected normative mean of 100 [28]. While such reduced IQ in patients with epilepsy can be expected [8], the lack of patients with above average IQ level naturally restricts the generalisation of the present findings. It appears tempting to speculate that CC transsection would have even more severe consequences in patients with above average pIQ levels. However, any such interpretation awaits further empirical evidence.

At the same time, it was also demonstrated that the extent of the callosal surgery does not influence the outcome significantly so that substantial effects can be excluded with reasonable test power. Whether an anterior or complete callosal section was performed did neither by itself show a main effect on the pre-post change in IQ measures nor did it interact with the pre-surgery level effect. Of note, the anterior corpus callosum (i.e., the genu) is severed by the surgery in both types of

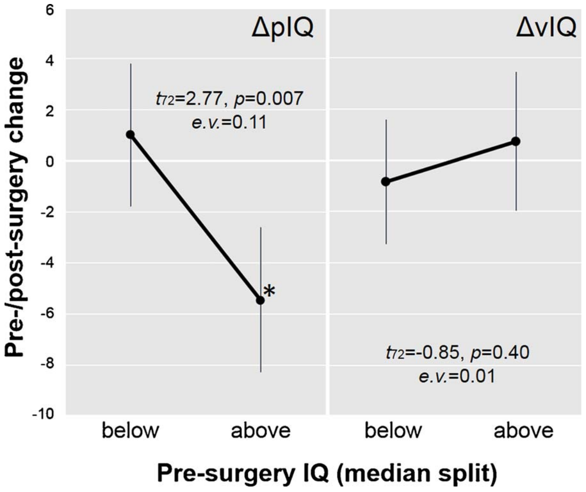

Fig. 1. Main effect of pre-surgery IQ on the change in performance IQ (left panel, ΔpIQ) and verbal IQ (right panel, ΔvIQ) which was significant for the ΔpIQ but not for the ΔvIQ analysis. Of note, regarding the ΔpIQ analysis, in the above median group the observed mean decrease of −5.44 was also significant as the 95% confidence limits (visualised by the error bars), i.e. $CI_{95\%} = [-8.33; -2.56]$, did not include zero (*). Abbreviations: e.v. = explained variance.

Table 2
Overview of results by analysis regarding the fixed-effect part of the analysis.

DV	Efect	b-value	s.e.	t-value	df	p-value	e.v.
ΔfsIQ	Intercept (mean change)	−0.45	1.83	−0.25	54	0.81	
($I^2 = 0.06$)	Type of Surgery (TS)	0.30	1.46	0.21	54	0.84	0.001
	Pre-surgery fsIQ (Pre fsIQ)	1.99	1.29	1.54	54	0.13	0.048
	Interaction TS × Pre fsIQ	0.33	1.32	0.25	54	0.80	0.001
ΔefsIQ	Intercept (mean change)	−0.53	1.28	−0.42	83	0.68	
($I^2 = 0.04$)	Type of Surgery (TS)	0.42	0.96	0.44	83	0.66	0.003
	Pre-surgery efsIQ (Pre efsIQ)	1.66	0.93	1.78	83	0.08	0.043
	Interaction TS × Pre efsIQ	−0.89	0.90	−0.99	83	0.33	0.012
ΔvIQ	Intercept (mean change)	−0.05	0.93	−0.05	72	0.96	
($I^2 < 0.01$)	Type of Surgery (TS)	−0.53	0.93	−0.57	72	0.57	0.004
	Pre-surgery vIQ (Pre vIQ)	−0.79	0.93	−0.85	72	0.40	0.010
	Interaction TS × Pre vIQ	−0.61	0.93	−0.65	72	0.52	0.006
ΔpIQ	Intercept (mean change)	−2.22	2.19	−1.01	72	0.32	
($I^2 = 0.08$)	Type of Surgery (TS)	1.71	1.23	1.38	72	0.17	0.031
	Pre-surgery pIQ (Pre pIQ)	3.23	1.17	2.77	72	0.0072	0.109
	Interaction TS × Pre pIQ	0.00	1.09	0.00	72	1.00	< 0.001

Notes: DV = dependent variable; s.e. = standard error; df = degrees of freedom; e.v. = proportion explained variance; I^2 = study inhomogeneity.

callosal section, while the posterior corpus callosum is only affected in the complete section subgroup. Thus, transsecting the genu, which houses axons inter-connecting the frontal lobes [24], appears to be sufficient to produce the observed effects on pIQ. An additional transection of the posterior callosal segments does not appear to affect the results additionally. As selective posterior callosal sections are rare and could thus not be systematically studied in the present meta-analysis, it cannot be excluded that a posterior section alone would also affect performance. As the parieto-frontal integration theory (P-FIT) of intelligence [13] suggests that brain network encompassing association cortices in both frontal and parietal brain regions are relevant for intelligence, it might rather be predicted that also posterior callosal connections are relevant for intelligence performance. However, based on P-FIT anterior and posterior callosal axons might be engaged in different processes, with the posterior corpus callosum (interconnecting the parietal, occipital and temporal lobes [24]) being more relevant for early processing and integration of sensory information (see e.g. [32]), and the genu being involved in working memory operations such as task set maintenance, response selection, or inhibition (see e.g. [12]).

Finally, the callosotomy affected pIQ while effects of comparable effect size on vIQ can be excluded with reasonable test power. Thus, the benefits of hemispheric collaboration are particularly relevant for the pIQ tasks. Arguably one difference between the tasks utilised to assess pIQ and vIQ is the stronger weight of information processing speed in pIQ subscale [29]. In particular the timed digit symbol (coding) pIQ subtest, which is traditionally part of the Wechsler type IQ tests, is considered a measure of information processing speed, while subtests of the vIQ are thought to reflect less time-critical processing such as verbal knowledge and word comprehension [29]. On the other hand, processing speed previously has been shown to be an important mediator variable for the association white-matter tract fractional anisotropy and intelligence measures [20]. Also, callosotomy or callosal lesions result in a substantial increase in the time it takes for the hemispheres to interact [17,23] as the signal transfer appears to utilize alternative pathways which are slower than the direct callosal connections [23], emphasising the relevance of the callosal axons for efficient and rapid processing of sensory information. This interpretation is further supported by a series of studies revealing that anatomical CC variability in healthy participants is correlated with the speed of inter-hemispheric transfer assessed in simple response-time tasks to lateralised visual stimulation [10,32]. All in all, it appears conceivable that the pIQ subtests will be more strongly affected than the vIQ by the increased inter-hemispheric transfer time caused by the transection of the callosal connection. Nevertheless, previous neuroimaging studies revealed CC-IQ associations in healthy individuals not only for the pIQ [4,14], but also for vIQ [14] and fs-IQ (or g-factor) [4,7,14], indicating a more general rather than a selective relevance for pIQ. Again, as indicated above, differences in the sample characteristics between callosotomy studies and the morphometry studies have to be considered. Besides the underlying neurological condition, the here integrated callosotomy patient sample is characterised by lower intelligence levels than the (usual) student or population-based samples of the morphometry studies.

Despite of the discussed limitations and in contrast to previous claims [15,19,27], the present IPD meta-analysis indicates that callosotomy has an effect on the patients' pIQ, but only in those patients who have at least average performance levels before the surgery. Furthermore, the present results also inform the interpretation of previous morphometry studies, that is, the CC-IQ correlation frequently reported in healthy individuals [4,7,14] might indeed reflect a relevant contribution of callosal axons to the level of performance in tests designed to assess pIQ levels.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2017.11.040.

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