Manuscript title: Pre- and post-surgical cognitive trajectories and quantitative MRI changes in Rasmussen syndrome.

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Abstract

Objective: To quantify the longitudinal cognitive trajectory, before and after surgery, of Rasmussen syndrome (RS), a rare disease characterised by focal epilepsy and progressive atrophy of one cerebral hemisphere.

Method: Thirty two patients (mean age=6.7 years; 17 males, 16 left hemispheres affected) were identified from hospital records. The changes in intelligence scores during two important phases in the patients' journey to treatment were investigated: (1) during the pre-operative period (n=28, mean follow-up 3.4 years) and (2) from before to after surgery (n=21 patients, mean time to follow up 1.5 years). A volumetric MRI analysis of longitudinal changes in grey matter volume was conducted in a subsample of 18 patients.

Results: (1) IQ during the pre-operative period: At baseline assessment (on average 2.4 years after seizure onset), the left RS group had lower verbal than non-verbal intellectual abilities, whereas the right group exhibited more difficulties in non-verbal than verbal intellect. Verbal and non-verbal scores declined during the follow-up in both groups, irrespective of the affected side. Hemispheric grey matter volumes declined over time in both groups in affected as well as unaffected hemispheres. (2) Post-operative IQ change: The left surgery group declined further in verbal and non-verbal intellect. The right group's non-verbal intellect declined after surgery, while verbal abilities did not. Patients with higher abilities pre-operatively experienced large declines, whereas those with poorer abilities showed little change. Post-operative seizures negatively impacted on cognitive abilities.

Significance: During the chronic phase of the disease parallel decline of verbal and non-verbal abilities suggest progressive bilateral hemispheric involvement, supported by evidence from MRI morphometry. Post-surgical cognitive losses are predicted by greater pre-surgical ability and continuing seizures. A shorter duration from seizure onset to surgery could reduce the post-operative cognitive burden by minimizing the decline in functions supported by the unaffected hemisphere.

Introduction

Rasmussen syndrome (RS) is a rare paediatric, progressive disease which affects previously normally developing children. It is characterised by atrophy of one cerebral hemisphere and associated neurological deficits, such as epileptic seizures, hemiparesis and cognitive deterioration[1, 2], presumed to be the result of an underlying autoimmune encephalitis. The medical treatment of RS is challenging and includes anti-epileptic medications and anti-inflammatory therapy. Hemidisconnection of the affected side of the brain is the only effective cure for seizures with long-term seizure freedom in 70-80% of cases[3]. Consequences, however, include hemiplegia, hemianopia and aphasia[4]. Severity of seizures is one of the major factors that informs surgical decision making, although loss of motor skills, reorganisation of language functions to the non-dominant hemisphere and the neuropsychological profile are also considered[2]. The neuropsychological trajectory of RS during the period of disease progression has yet to be formally elucidated.

Longitudinal investigations are crucial as the impact of repeated seizures on the unaffected, contralateral hemisphere may cause additional neuropsychological loss[2]. Previous EEG and MRI investigations have hinted that some individuals may experience compromise to the unaffected hemisphere[5,6]. This possibility highlights the importance of determining the optimal timing for hemidisconnection and suggests that further knowledge of the cognitive trajectory in RS will help inform this challenging decision.

The post-operative neuropsychological status has been characterised in one notable study[7]. This showed that at both pre- and post-surgery time points left (dominant) hemisphere RS patients had full-scale IQ and language scores lower than the right surgery group, although surgery only impacted on expressive language, irrespective of side of resection. Otherwise, mean full-scale IQ did not change in either group and remained on average around a score of 70, however post-surgery follow-up varied widely, ranging from 1 to 26 years.

While this study represents the largest neuropsychological sample in RS to date, it provided no information on the important issue of cognitive change immediately following surgery: i) will patients with preserved cognition before surgery suffer large losses and ii) will those with low pre-operative scores be able to recover functioning after surgical removal and seizure control? These issues are of utmost importance for clinical decision making as they inform the prognosis for educational progress in the years following surgery and the requirements for additional support.

The current study charts the longitudinal neuropsychological trajectory of individuals with RS seen at a single epilepsy centre over a 22-year period. Intellectual trajectory was characterised (1)

preoperatively as well as (2) from pre- and to around 1.5-years post-surgery. In addition, we performed a longitudinal MRI morphometric analysis of grey matter change between two pre-operative time points in a subsample of patients.

Methods

Study design and participant selection

We conducted a retrospective case-note review of patients treated at our centre from 1994-2016. Inclusion criteria were a formal consensus diagnosis of RS according to the clinical presentation and radiological features[8], and at least two formal neuropsychological assessments. The study was approved by the Great Ormond Street Hospital (GOSH) clinical audit department as a service evaluation (No. 1443), according to the guidelines set by NHS Research Ethics Committee Review.

We performed separate analyses in partially overlapping groups (**Table 1, Supporting Figure 1**): (1) longitudinal pre-operative trajectory and (2) pre- to post-operative trajectory. Analysis 1 included patients who had two cognitive assessments prior to surgery: 'baseline' was defined as the first neuropsychological assessment after seizure onset and 'preoperative' as the most recent assessment prior to surgery. Analysis 2 included the patient's preoperative assessment and their first post-operative follow-up. For patients who had only one pre-operative assessment the baseline IQ score was also the preoperative value. This separation into two analysis stages was done in order to maximise statistical power, however, a final exploration included all patients (n=17) for whom IQ data from all three assessment points (baseline, preoperative, postoperative) were available.

Investigations and outcome measures

Neuropsychological test results and clinical data were acquired from records. Intellectual functioning was estimated using the age-appropriate version of the Wechsler Intelligence Scales: WISC-IV (number of assessments n=45), WISC-III (n=30), WISC-R (n=4), WPSSI-R (n=2), WPSSI-III (n=3), WAIS-III (n=5), WASI (n=3), WAIS-R (n=1), WASI-IV (n=2). In analysis 1, four participants changed test version and in analysis 2 ten participants changed test version, often reflecting the most age-appropriate test for the patient at that stage. All Wechsler Intelligence scales include composite standard scores for verbal intellectual ability (Verbal Comprehension Index or Verbal IQ (VIQ)) and non-verbal or perceptual intelligence (Perceptual Reasoning Index or Performance IQ (PIQ)). As the VIQ and PIQ were the only consistently-acquired cognitive constructs in our sample, they were used here as estimates of verbal and non-verbal intellect. VIQ-PIQ discrepancy scores were also examined,

as an indirect measure of lateralised brain injury[9]. The last pre-surgical neuropsychological assessment preceded surgery by a variable time (median 1 year, range 0-2.5).

MRI acquisition and analysis

Three-dimensional volume T_1-weighted, preoperative MRI scans were available for 18 patients (9 left-sided RS, 9 females, mean age= 10.8 (SD 2.0) years). Prior to 2007, 3 scans were obtained on a 1.5T Siemens Vision System (Erlangen, Germany) using a MPRAGE sequence (repetition time 10ms; echo time 4ms; flip angle 12°; voxel size 1.0x1.0x1.25mm). Scans acquired after 2007 were obtained on a 1.5 T Siemens Avanto System, using a 3DFLASH sequence (repetition time 11ms; echo time 5ms; flip angle 15°, voxel size 1.0x1.0x1.0mm). A reference group of healthy control participants (n=18, 9 females, mean age= 12.1 (SD 1.4) years) was also scanned using the latter settings.

For a voxel-based morphometry (VBM) analysis images were segmented into grey matter (GM), white matter (WM) and CSF using the Computational Anatomy Toolbox (CAT12; http://dbm.neuro.uni-jena.de/cat/) for SPM12. We used a module for processing of longitudinal data, with an inverse-consistent realignment step and spatial normalisation of the mean image derived from both scans, and normalization into ICBM space. Tissue segments were resampled to a voxel size of 1.5x1.5x1.5mm. Global GM and WM volumes were extracted for ipsi-lesional and contra-lesional hemispheres. Summation of GM, WM and CSF volumes provided total intracranial volume (TIV). Across all RS participants images were spatially aligned so that the affected hemisphere was displayed on the left side, by flipping the segmented images of right-sided RS individuals around the z axis using the flipdim command of the Imcalc toolbox. Images were smoothed using a 10mm full-width half-maximum Gaussian kernel.

A general linear model with factors group (RS, control) and covariates of no interest (TIV and age) was used to identify the group-wise pattern of GM and WM atrophy in RS at baseline. A flexible factorial design with factor time and covariates (TIV, age, scan type (MPRAGE, 3DFLASH)) was used to evaluate longitudinal GM and WM change in the RS group. Statistical maps of volume change were displayed using a voxel-wise threshold of $p<0.001$ with a cluster size of ≥200. Post-hoc analyses using Mann-Whitney tests explored if medication use (corticosteroids, azathioprine) during the follow-up period impacted on GM volumes.

Statistical analyses

For both analyses 1 and 2 the impact of the laterality of affected hemisphere (between-subject *factor 'side'*) and time of assessment (within-subject *factor 'time'*) on IQ scores was investigated using repeated-measures (RM) ANOVA. Post-hoc t-tests were conducted as appropriate. Change scores were

computed by subtracting the pre- from the post-operative scores so that negative values indicate IQ losses and positive scores gains. Total hemispheric GM volume changes were also compared using RM-ANOVA with factors time and group, covaried for TIV and age.

Non-parametric Spearman correlation was used to examine the association of pre-operative IQ score and post-operative change according to side of surgery, as well as between age at surgery and duration of epilepsy with IQ change. The effect of post-operative seizure freedom on IQ change was examined using Mann-Whitney tests. Educational status was compared between laterality groups using Chi^2-test.

Results

Out of the total cohort of 37 RS patients who had been seen by the neuropsychology service over this period 32 individuals fulfilled the inclusion criteria (**Table 1**).

Longitudinal pre-operative cognitive trajectory

At the baseline assessment, 50% of patients presented with either IQ score below 80 (**Figure 1**). The laterality of RS had a differential impact on verbal and non-verbal IQ scores: the left group's VIQ scores were significantly lower at both preoperative assessments compared with the right group (effect of side: $F(1,26) = 4.4$, $p=0.048$). The reverse pattern was observed for PIQ, where a trend for a lower score was observed in the right group compared to the left ($F(1,26)=3.1$, $p=0.092$). This hemisphere-specific pattern was even more prominent for VIQ-PIQ discrepancy scores (at baseline: left group=-13.7 (SD 14.7), right group=7.9 (SD 12.1), $t(26)=4.27$, $p<0.0001$).

Although the individual pre-operative intellectual trajectories were highly variable, there were nevertheless consistent declines in both RS groups as illness progressed (effect of time: VIQ: $F(1,26)=24.0$, $p<0.0001$; PIQ: $F(1,26)=7.4$, $p=0.011$). There were no time by side interaction effects (both $p>0.7$) and within-group post-hoc tests are indicated in Figure 1. Earlier onset of epilepsy was associated with greater decline in PIQ scores over time ($Rho=0.464$, $p=0.013$). There were no differences between cases who were surgically treated during the follow-up period and those who were not in IQ scores or their change over time (all $p>0.392$), nor in any other clinical variable except a lower seizure burden ($p=0.022$) and a later year of presentation in those without surgery.

Volumetric MRI changes

Global hemispheric grey matter volumes were examined combined for the left and right RS group between baseline and preoperative time points (**Figure 2, A**). GM volume of the affected hemisphere was smaller than the unaffected (effect of side: $F(1,17)=66.0$, $p<0.001$) but both hemispheres decreased in cortical volumes with follow-up time ($F(1,17)=8.58$, $p=0.009$). A trend-level

time by side interaction (F(1,17)=4.33, p=0.053) suggests that volume loss on the affected side exceeded the atrophy of the unaffected hemisphere. This difference was confirmed when the loss was expressed as rate of change per year (t=2.36, p=0.030) (Figure 2). Furthermore, GM loss in both hemispheres was greater with longer duration between scans (rho=-0.488, p=0.040). Exploratory analyses of possible medication effects did not show evidence that volume loss was influenced by corticosteroid treatment (Mann-Whitney tests: all p>0.633) or azathioprine use (all p>0.061).

We explored if hemispheric GM volume change correlated with cognitive change over the follow-up period. After excluding three individuals with a combined gap each of >2.5 years between MRI and neuropsychology assessments, we found a correlation between VIQ loss and left hemisphere GM volume reduction (Rho=0.618, p=0.014). The analogous correlation of right hemisphere GM loss with PIQ change did not reach significance (p=0.199).

A voxel-wise comparison of the combined RS group at baseline with healthy controls confirmed the extensive loss of cortical tissue in the affected hemisphere (**Figure 2, B**). Atrophy was most pronounced in frontal and perisylvian regions and also involved homotopic areas of the contralateral hemisphere. Widespread subcortical white matter reductions mirrored the cortical changes bilaterally (not shown), albeit at a lower threshold (p<0.001). Over follow-up time, however, focal cortical losses were more pronounced in the unaffected hemisphere, in particular in mesial frontal and insular cortices. Focal white matter reductions were noted in the inferior genu/rostrum of the corpus callosum, albeit at a lower statistical threshold (p=0.005) than used for displaying GM differences. Of note is that all but one patient in the VBM sample had contra-lateral spread of discharges documented on EEG.

Post-operative cognitive change

Varying degrees of cognitive deterioration were seen in most individuals, apart from those who were already in the impaired range prior to surgery (**Figure 3**). The left group's compromised VIQ (effect of side: F(1,19)=25.0, p<0.0001) declined further after surgery, while the right group's VIQ score did not change (time by side interaction: F(1,19)=5.1, p=0.035; post-hoc tests are indicated in Figure 3).

This hemisphere-specific pattern did not apply to PIQ scores which declined across both groups (effect of time: F(1,19)=10.7, p=0.004) without an effect of side (F(1,21)=0.5, p=0.475) or a side by time interaction (F(1,19)=0.0, p=0.9).

Pre-operative intellectual ability had an important influence on the change in cognition after surgery (**Figure 4**), showing a negative relationship between both scores (for the left surgery group: VIQ change: Rho= -0.732, p=0.010; PIQ change: Rho= -0.493, p=0.123, for the right group: VIQ change:

Rho= -0.770, p=0.003; PIQ change: Rho= -0.864, p<0.001). Eleven patients (48%) showed post-operative losses (>10 points in either score), most of whom had preoperative scores above 70. In contrast, three (11%) patients with gains of 10 points or more had pre-operative scores below 80.

Impact of clinical variables: Age at onset and surgery as well as duration of disease did not correlated with cognitive change scores in this sample. Only post-operative seizure control impacted on changes in intellectual abilities. Across both groups, seizure-free patients experienced less decline (VIQ change= -3.7 (SD 11.3), PIQ change= -5.1 (SD 11.7)) compared to 5 patients with continuing seizures (VIQ change= -18.4 (SD 11.8), PIQ change= -20.8 (SD 8.2); Mann-Whitney tests: p=0.015, p=0.009, respectively).

Educational support: Pre-operatively, left and right RS patients did not differ in the type of school they were able to attend, with three in each group requiring special needs education (Fishers Exact p=1.00). In contrast, post-operatively, children in the left surgery group were more likely to attend a special needs school (8 out of 9), while in the right group 6 out of 9 were able to attend a mainstream school (Fisher's exact: p=0.050). Post-operative verbal ability was the only discriminating factor between patients who required special educational support compared to those who attended mainstream schools (p=0.011).

Finally, examination of IQ scores across all three assessment points, available in a subset of patients (n=17) confirms the findings from the above analyses (**Figure 5**), supported by statistical analysis in this smaller sample (VIQ: effect of time: F(2,13)=18.1, p<0.0001, side: F(1,14)=12.0, p=0.004, and interaction time by side: F(2,13)=5.4, p=0.019; PIQ: effects of side F(1,14)=3.4, p=0.087 and time: F(2,13)=8.8, p=0.004). Examination of IQ scores in a subsample of 10 patients who had a second post-operative assessment at about 3.6 years after surgery, revealed no further change (all p>0.797) (**Supplementary Figure 2**).

Discussion

We report several important findings with relevance for the management of patients with RS. At baseline assessment, patients presented with a hemisphere-specific profile of intellectual impairment. During the subsequent follow-up period, however, both verbal and non-verbal abilities declined regardless of the hemisphere affected. The suggestion of bilateral hemispheric involvement was confirmed using MRI morphometry in a subsample. Our study also highlights the impact of hemispheric disconnection on intellectual ability in the first years after surgery. Higher pre-operative ability and continuing post-operative seizures were related to further declines in intellectual functions.

Cognitive trajectory during the pre-operative period

At presentation to our service, on average about 2.4 years after seizure onset, the left RS group's verbal intellectual abilities were significantly poorer than those of the right group. Conversely, non-verbal abilities were more impaired in the right than the left group, in line with previous evidence [10,7]. Given that IQ scores capture the effects of such predominantly unilateral brain insult in previously normally developing children[9], the finding of almost parallel declines in both domains during follow-up was unexpected. The majority individuals in our sample (79%) deteriorated in verbal IQ scores, regardless of the affected hemisphere. A similar pattern was observed for non-verbal intellect.

The neuropsychological findings provide important converging evidence for the notion of gradual involvement of the unaffected hemisphere[5]. Previous MRI evidence during the acute phase of the disease, i.e. during the first 2 years after seizure onset, showed that about half of patients had grey matter volume declines in the unaffected hemisphere. These changes amounted to about 10-23% of the losses on the affected side[11,6]. In the current cohort, which was scanned during a more chronic phase, the hemispheric changes were of almost equal magnitude, with 78% of participants showing GM declines in the unaffected side. Of note is also that the degree of loss was in direct proportion to the elapsed time between scans, confirming its progressive nature.

In addition, the VBM analysis identified a pattern of cortical atrophy in comparison with controls, with greatest changes in frontal and insular cortices, which is entirely compatible with previous reports[6]. Our longitudinal analysis, however, showed more consistent focal GM changes in the unaffected hemisphere, despite the global loss evident in both hemispheres. This pattern of atrophy progressed in anatomically homologous frontal and insular regions, most likely due to Wallerian degeneration[11] and the impact of spreading seizure activity[5]. Although our method was not optimized for detecting white matter changes[12], the focal reduction in the genu/rostrum of the corpus callosum is anatomically in keeping with containing the connections between affected bilateral frontal cortices.

Post-operative cognitive trajectory

The second part of our study explored intellectual outcome after hemispherectomy with the aim of identifying factors influencing post-operative cognitive ability.

The left surgery group experienced a significant deterioration in verbal abilities after surgery, in line with previous reports[10,13]. Although non-verbal abilities remained more intact, they also declined following surgery. All but one patient with left-sided surgery had to be supported in special needs schools, in keeping with their intellectual disability. In contrast, the right surgery group did not

experience such significant deterioration and verbal intellect remained relatively preserved, which is in keeping with them being able to remain in mainstream education with support.

Apart from hemispheric side of surgery, we identified pre-operative intellectual ability as a major predictor of cognitive loss after surgery. Patients with more preserved intellect pre-operatively experienced larger declines after surgery, whereas those with poorer abilities showed either little change or made minor gains. 'Catch up' intellectual development after neurosurgical treatment has indeed been shown in patients with low pre-operative abilities[14,15]. Unfortunately, only three patients showed some post-operative recovery of IQ scores (gains of >10 points), which could be attributed to 'disinhibition' of the remaining hemisphere from the impact of seizure activity, as demonstrated in a remarkable case of Sturge-Weber disease after hemispherectomy [16]. However, large losses as reported in this sample with disconnection or removal of one entire hemisphere, are not commonly seen in focal surgery series[14,15]. Brain volume is a major determinant of intellectual ability in healthy and neurodevelopmental populations[17,18,19]. It is therefore not surprising to see declines of up to 35 IQ points in patients with previously well-developed pre-operative functions, in whom a large amount of functional brain tissue has been disconnected. The further decline of PIQ scores after left surgery may be due to the asymmetrical (left greater than right) hemispheric dependence of some cognitive constructs such as working memory and fluid intelligence, according to lesion evidence[20,21].

Overlapping this pattern is a detrimental effect of continuing seizures in a minority of cases, which amounted to an average decrement of 15 IQ points at follow-up, irrespective of the side of surgery, in line with evidence from focal epilepsy surgery follow-up[15].

The longer term post-surgical trajectory of intellectual development can only be inferred from few studies which included a mean follow-up of 5 years or more. The group mean IQ is reported to return to the pre-operative level[7], supported by other investigators[22,23]. Good post-operative recovery has been documented in 6 left surgery cases[13], showing gradual recovery of cognitive and language abilities by 2-6 years after surgery. Such trajectory is currently not detectable in a similar number of cases in the present cohort who had further follow-up between 3-5 years after surgery. Of note is that the Bulteau et al. cohort[13] had a very short time from seizure onset to surgery, which has been implicated with better post-surgical cognitive recovery in some series[24,25,23].

Limitations

It is important to acknowledge the limitation of this retrospective study, given the changes in clinical practice and diagnostic methods, which have occurred over a 22 year period. As a result, the timing of assessments (neuropsychology and MRI scans) as well as the intervals between assessments and surgery were not standardized which resulted in additional variability that could not be controlled

here. Nevertheless, we were able to capitalise on the consistency of the Wechsler intelligence scales and were able to chart, for the first time, the longitudinal cognitive profile of RS, supplemented by a volumetric MRI analysis. We were unable to exclude medication effects but exploratory analyses did not show evidence that IQ change or GM loss were influenced by corticosteroid treatment. Unfortunately, we could not account for the changes in intellectual ability that are related to emerging communication difficulties, as speech assessments were not systematically carried out in this cohort. Finally, the long-term trajectory of cognitive and educational progress in our cohort remains to be explored, together with the fate of the remaining hemisphere.

Conclusions

This study provides important insights into the cognitive trajectory of patients with RS and provides some guidance on optimizing post-operative cognitive outcomes. In general, a shorter interval from seizure onset to surgery may help in reducing the decline in functions subserved by the unaffected hemisphere. This will be of major benefit to patients with right hemisphere RS as it prevents decline in verbal abilities during the pre-operative period. This group tends not to decline further in verbal abilities after surgery, with benefit for educational progress. For patients with left (language-dominant) hemisphere RS the same consideration applies for preserving non-verbal cognition, but the decision for surgery is likely to be complicated by the risk to speech and language abilities. Nevertheless, many patients suffer losses in verbal abilities, at least during the first years after surgery, in proportion to their pre-operative level. This is important to consider when counselling patients and carers and for planning of post-surgical educational support. Future research should establish if avoiding progressive involvement of the unaffected hemisphere has benefit for post-operative seizure control and long-term cognitive outcome. Multi-centre collaboration is needed to determine the contribution of aetiological and clinical factors in optimizing treatment and outcomes of this rare but devastating disorder.

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Disclosures

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with

those guidelines.

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Key Points

- Case-note review of patients with Rasmussen syndrome revealed progressive decline of verbal and non-verbal intelligence scores over pre-operative period.
- MRI volumetry confirmed decline of grey matter volume in both the affected and unaffected hemispheres over the pre-operative period.
- Patients with higher level of intellect before surgery were more likely to suffer greater losses after surgery than patients with lower pre-operative scores.
- Cognitive losses are exacerbated by failure to control seizures post-operatively.

Figure legends:

Figure 1: Mean Preoperative IQ at baseline and preoperative assessments. Individual patient's trajectories for verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) are plotted on the right side, along the time from seizure onset in years.

Post-hoc tests showed that VIQ declined for both groups to a similar degree (left group: t=3.4, p=0.006; right group: t=3.6, p=0.003). The right group's PIQ score also declined (t=2.6, p=0.021) while the left group's PIQ change failed to reach significance (t=1.4, p=0.19). ** p<0.01, * p<0.05.

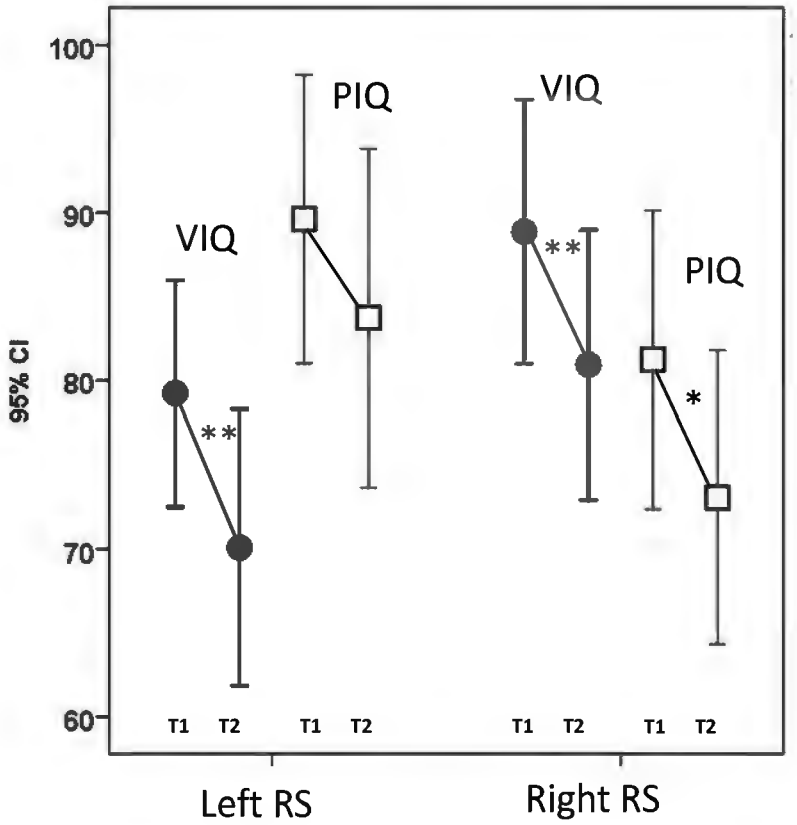
Figure 2: MRI morphometry analysis in a subsample of 18 patients: **A)** Top graph shows global hemispheric grey matter volumes (GMV) at baseline and preoperative assessments (scans separated by on average 3.4 years). Volumes of the affected and unaffected hemispheres declined over time. Bottom graph shows the average GMV loss per year of follow-up. The affected hemisphere declined at a faster rate than the unaffected one (* p=0.03). **B)** Results of a voxel-based analysis comparing RS patients to age-matched healthy controls (top right, displayed at family-wise error (FWE) corrected threshold of p=0.01), showing widespread focal grey matter (GM) atrophy in frontal and perisylvian regions of the affected hemisphere, which extend to homotopic regions in the unaffected hemisphere. Bottom graph shows focal GM changes over follow-up time in the RS sample (voxel-wise threshold of p<0.001 with a cluster size of ≥200). These changes appear more pronounced in frontal and perisylvian regions of the unaffected hemisphere.

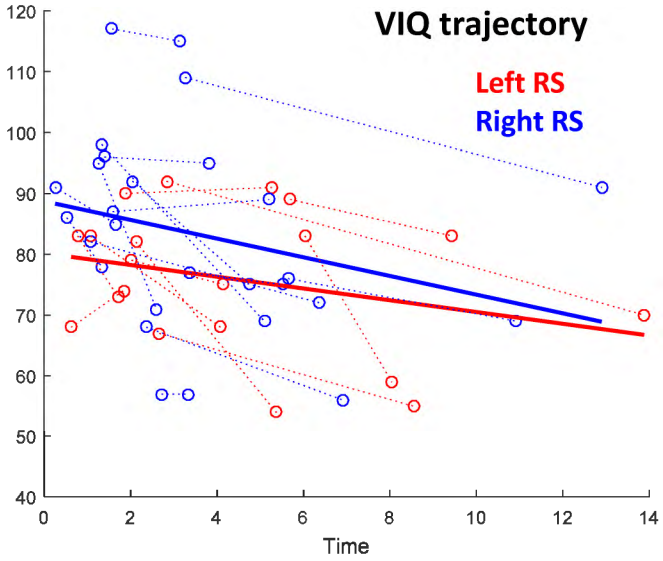
Figure 3: Left side: Mean IQ scores at pre- and post-operative assessments. Individual patient's trajectories for verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) are plotted on the right side, along the time before and after surgery in years (0 indicates time of surgery).

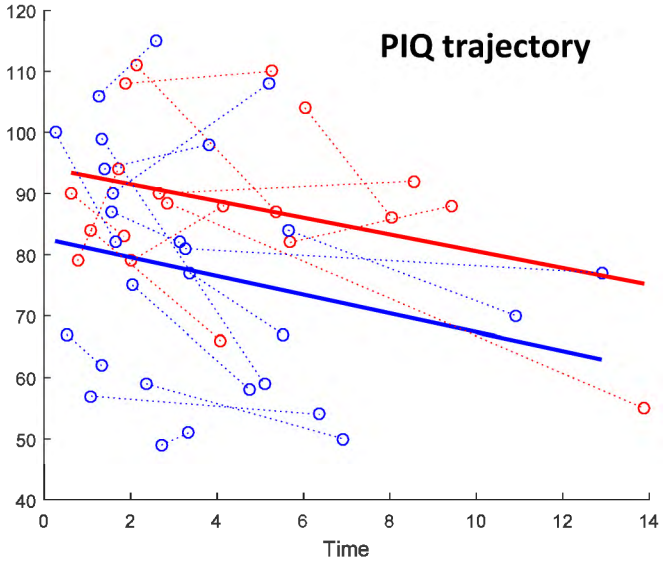
Figure 4: Postsurgical IQ change in relation to preoperative score, separately for VIQ (left) and PIQ (right). For both surgery groups IQ change is negatively predicted by its preoperative level, most strongly for the function which is assumed to be subserved by the affected hemisphere, e.g. VIQ change by preoperative VIQ in the left surgery group.

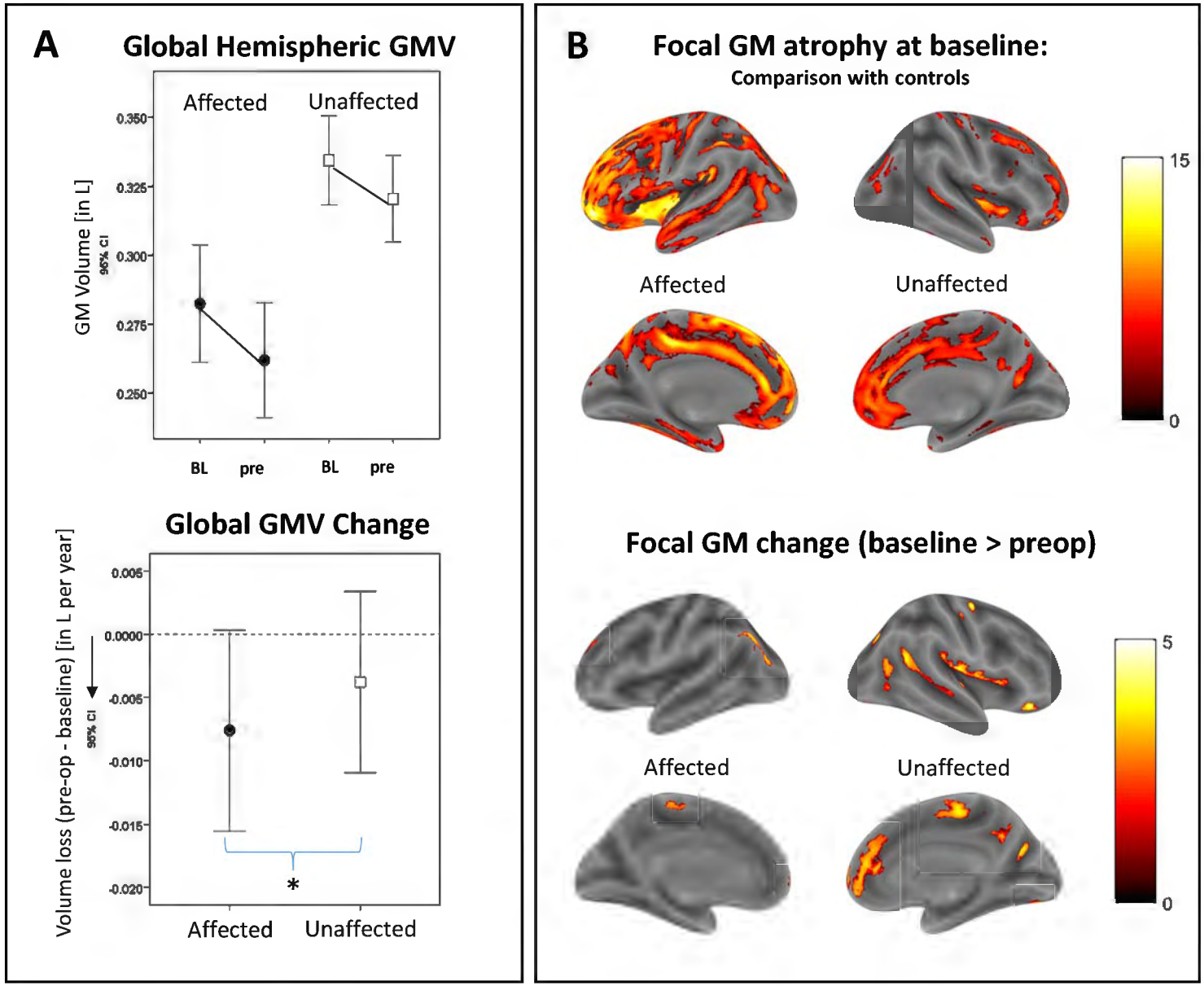
Figure 5: Pre-to postoperative IQ trajectories in the subsample of patients (n=17) who had all three assessments (BL=baseline, pre=pre-operative, post=post-operative) performed. The postoperative score is indicated by the open symbol (□). VIQ - verbal intelligence quotient, PIQ - performance intelligence quotient. The lower limit of the normal IQ range is indicated by dotted line (IQ=80).

Pre-operative IQ trajectory

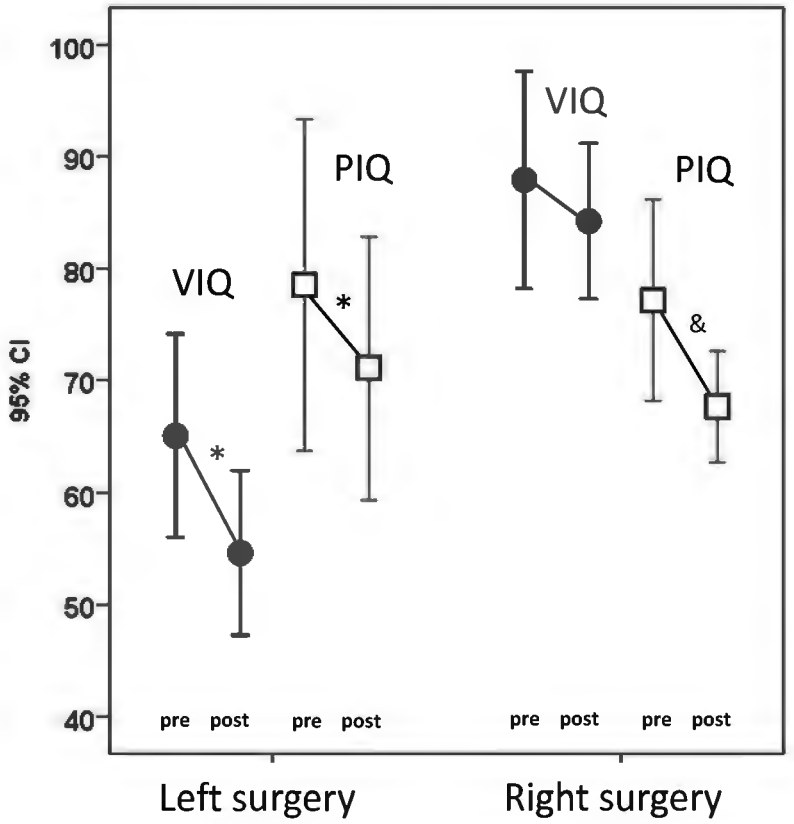


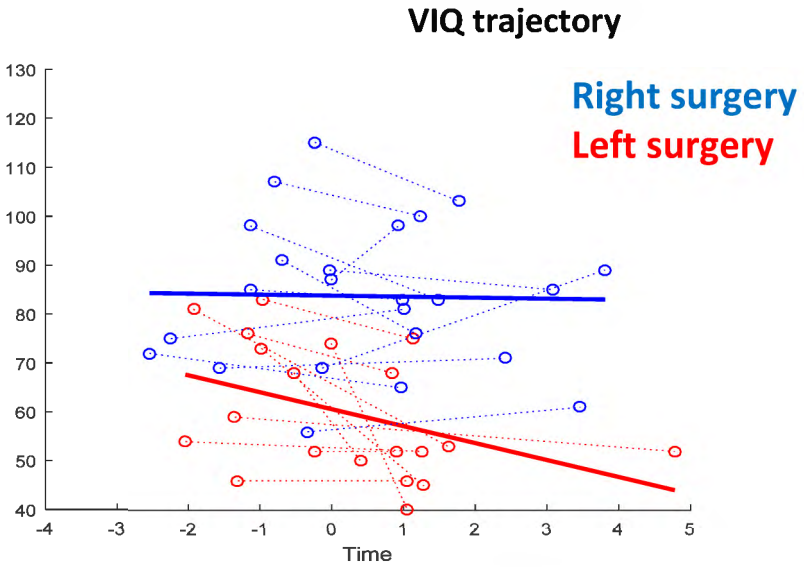


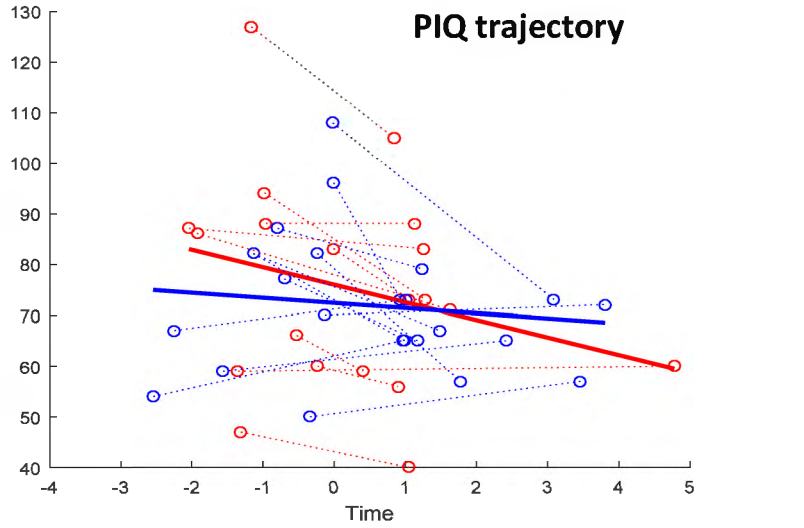



A
Global Hemispheric GMV
Affected
Unaffected
GM Volume [in L]
95% CI
0.350
0.325
0.300
0.275
0.250
BL
pre
BL
pre
Global GMV Change
Volume loss (pre-op - baseline) [in L per year]
95% CI
0.005
0.0000
-0.005
-0.010
-0.015
-0.020
*
Affected
Unaffected
B
Focal GM atrophy at baseline:
Comparison with controls
Affected
Unaffected
15
0
Focal GM change (baseline > preop)
Affected
Unaffected
5
0

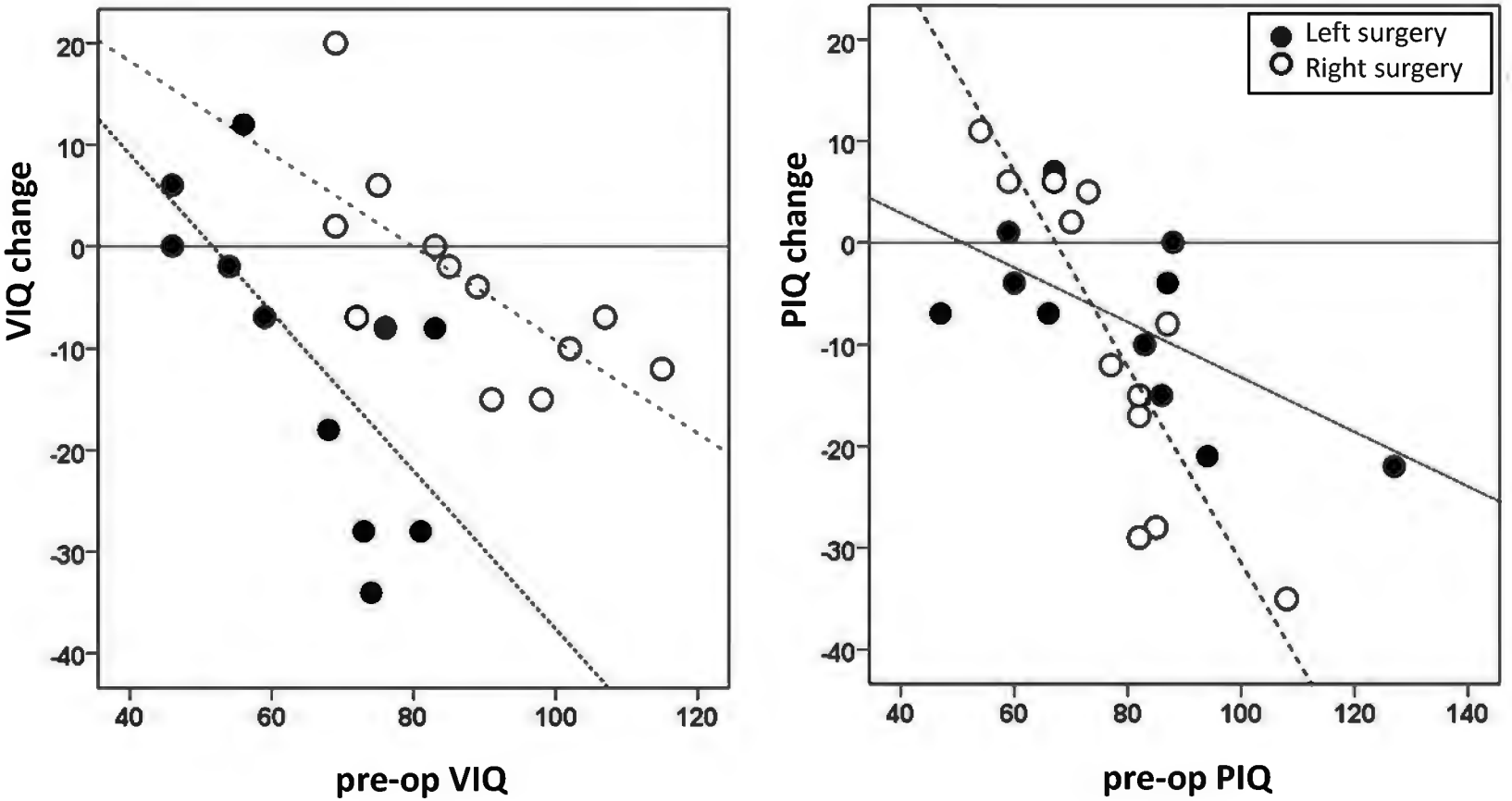
Pre- and post-surgical IQ



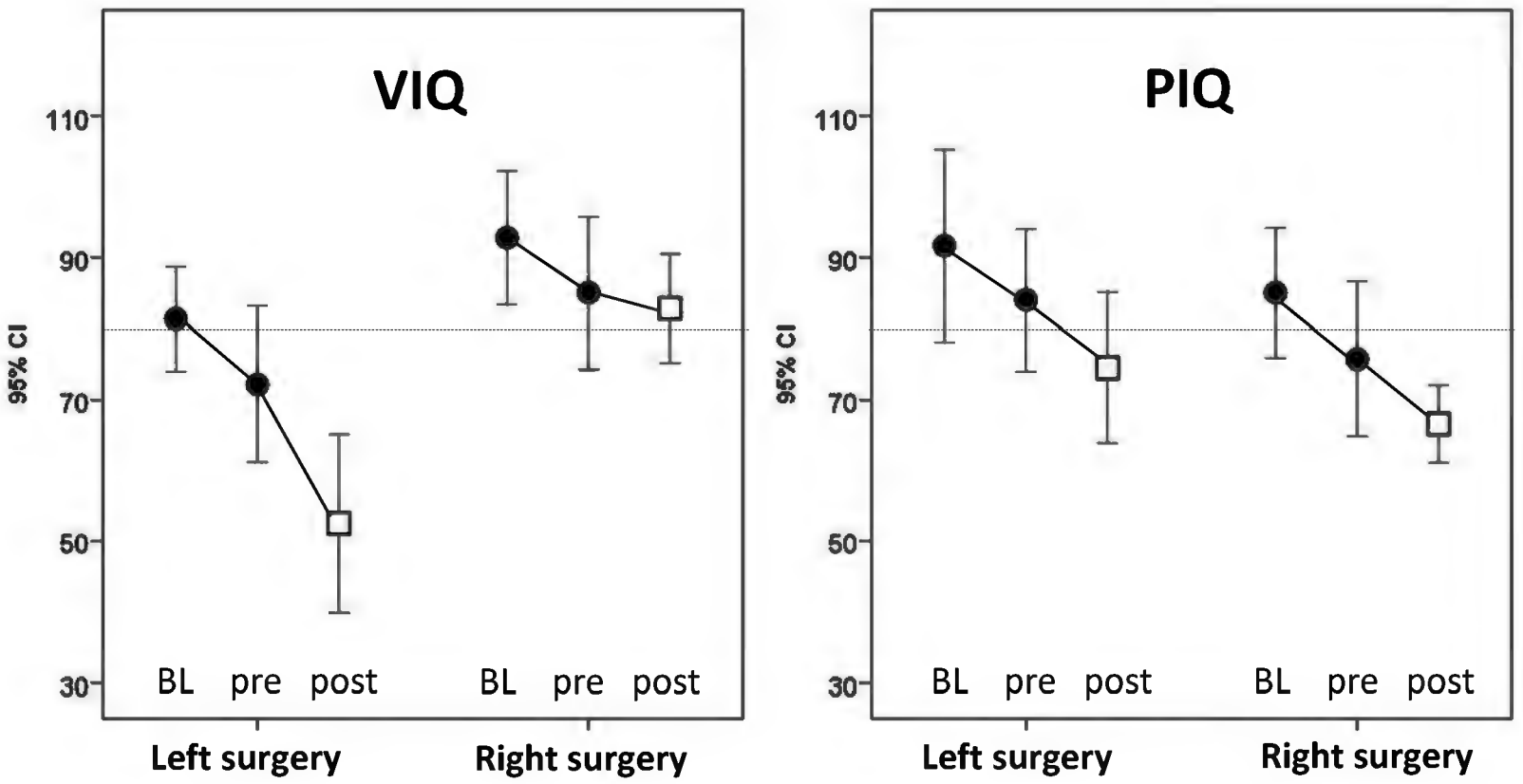




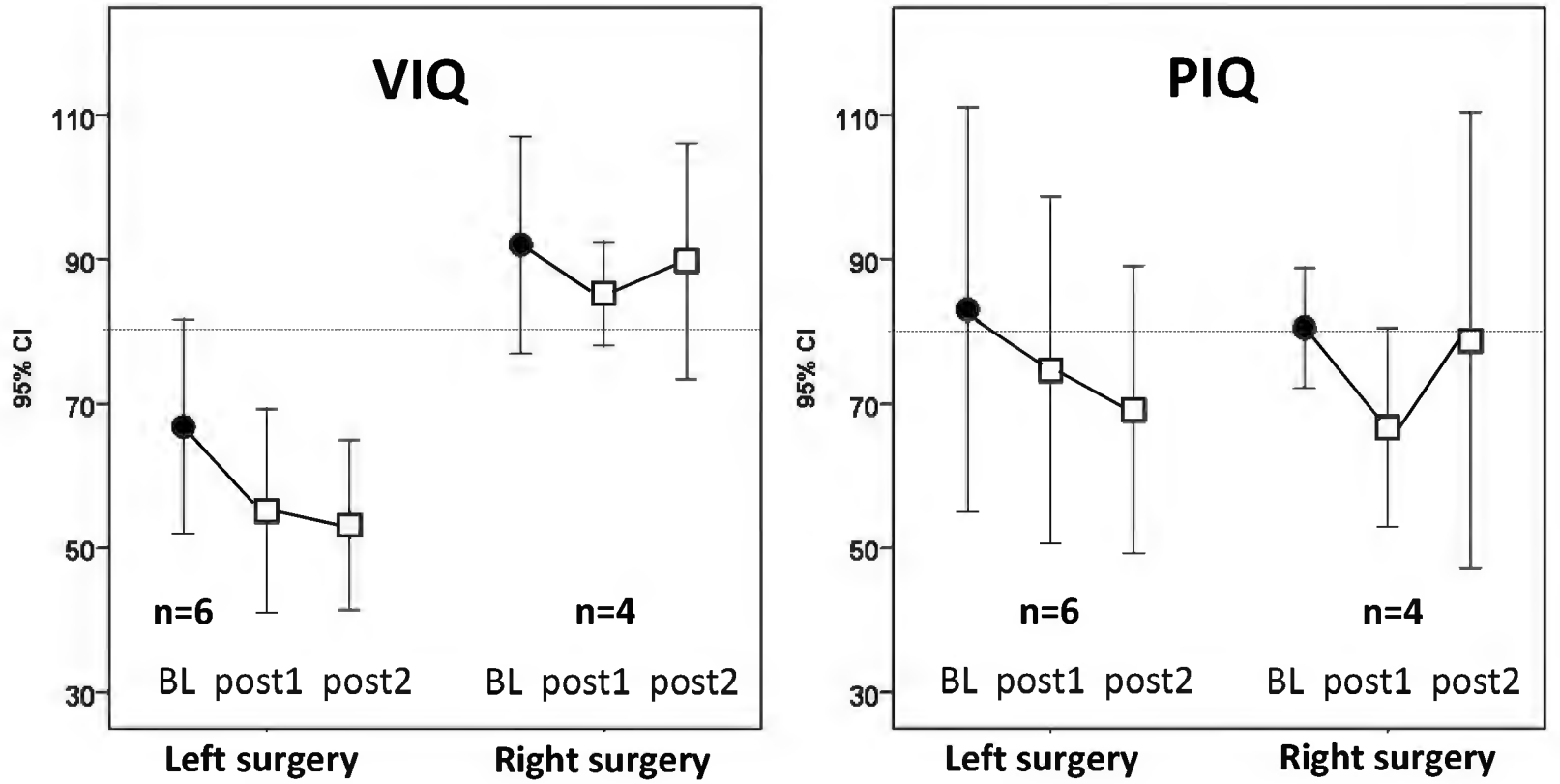
Pre-operative IQ predicts post-surgical change

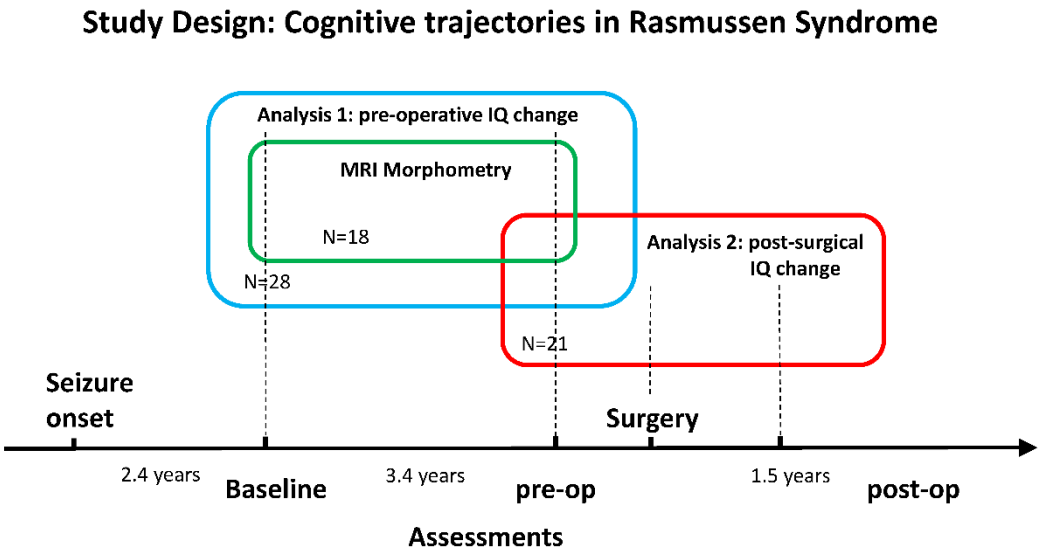


Pre- and post-operative IQ trajectory

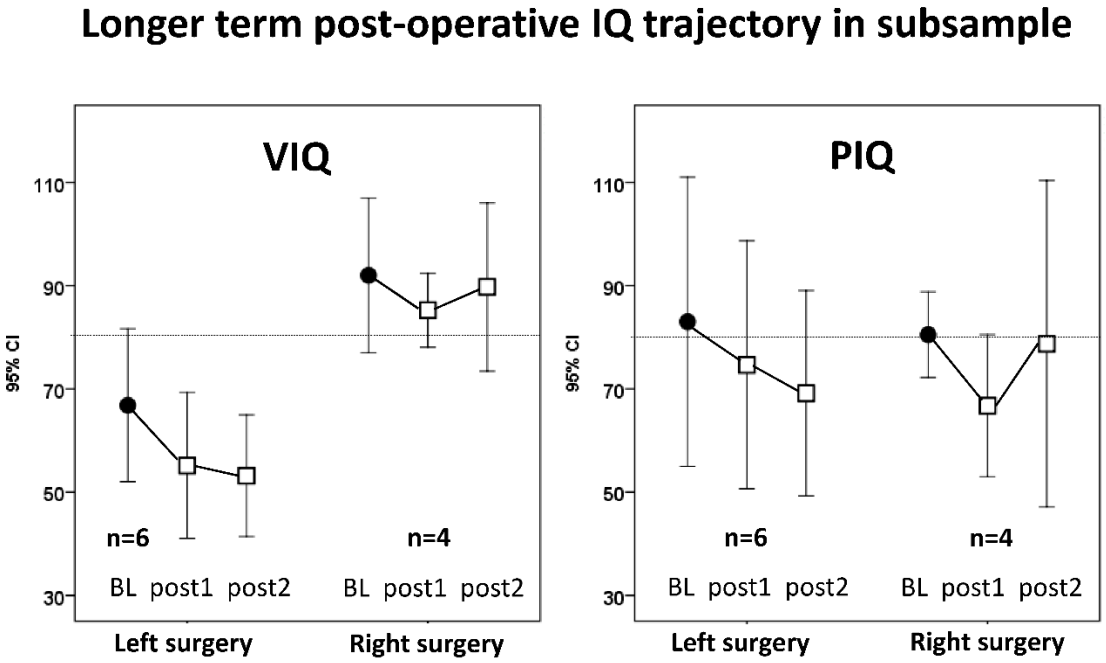


Longer term post-operative IQ trajectory in subsample





Supplementary Figure 1: Study design showing how the analyses performed in this study relate to the patient's journey from before to after surgical treatment (see also **Table 1**). **Analysis 1** explored the change in IQ scores from baseline neuropsychological assessment to a second time point, which in most patients was also their preoperative evaluation. **VBM Analysis** was performed in a subsample of Analysis 1. **Analysis 2** focused on IQ change from before to after surgery (17 of 21 patients were included in Analysis 1).



Supplementary Figure 2: Post-operative IQ trajectory in a subsample (n=10) of patients who had a second post-surgical follow-up between 3-5 years after surgery (post2), in addition to pre-operative baseline (BL) and first post-operative follow-up (post1).