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'Moderate global aphasia': A generalized decline of language processing caused by glioma surgery but not stroke

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abstract

Unlike stroke, neurosurgical removal of left-hemisphere gliomas acts upon a reorganized language network and involves brain areas rarely damaged by stroke. We addressed whether this causes the profiles of neurosurgery- and stroke-induced language impairments to be distinct. K-means clustering of language assessment data (neurosurgery cohort: N = 88, stroke cohort: N = 95) identified similar profiles in both cohorts. But critically, a cluster of individuals with specific phonological deficits was only evident in the stroke but not in the neurosurgery cohort. Thus, phonological deficits are less clearly distinguished from other language deficits after glioma surgery compared to stroke. Furthermore, the correlations between language production and comprehension scores at different linguistic levels were more extensive in the neurosurgery than in the stroke cohort. Our findings suggest that neurosurgery-induced language impairments do not correspond to those caused by stroke, but rather manifest as a ‘moderate global aphasia’ – a generalized decline of language processing abilities.

Keywords

aphasia; glioma; neurosurgery; stroke; k-means clustering

1. Introduction

Similar to stroke, surgical removal of gliomas in the language-dominant hemisphere often causes language impairments. Moderate-to-severe impairments occur in up to 100% of individuals who underwent left-hemisphere glioma surgery (Duffau et al., 2003; Sanai et al., 2008) at the early phase. However, to a large extent, these impairments resolve over the course of weeks to months, often leaving only persistent anomia (Sanai et al., 2008; Wilson et al., 2015). A detailed understanding of the patterns of language impairments early after glioma surgery is still lacking. In particular, whether these impairments are aphasic sensu stricto – that is, mirror the linguistic patterns traditionally distinguished in chronic stroke-induced aphasia (Benson & Geschwind, 1971; Luria, 1966; Pedersen et al., 2003) – remains unknown. We aim to address this question by directly comparing the patterns of language impairments caused by glioma surgery and stroke.

Several etiology-specific factors may cause the profiles of language impairments to be distinct between glioma surgery and stroke. First, language impairments are typically absent before surgery in the cases of slow-growing low-grade gliomas regardless of their volume and the involvement of the perisylvian language areas (Anderson et al., 1990; Duffau et al., 2008; Ilmeberger et al., 2008; Satoer et al., 2013). This suggests that gliomas induce a large-scale compensatory reorganization of the language network before surgery (Duffau, 2005; Piai et al., 2020). Therefore, while stroke abruptly damages a typically organized language network, surgery acts upon a reorganized language network, especially in the cases of low-grade gliomas. In addition, while the neuroanatomical distribution of stroke lesions is constrained by vasculature, the neuroanatomical distribution of gliomas is not. For example, gliomas are often located in the temporal pole (Noll et al., 2016) or the supplementary motor area (Krainik et al., 2001), which are less often damaged by stroke (Wu et al., 2015). However, these regions do contribute to language and semantic processing (Ardila, 2020; Hickok & Poeppel, 2007; Jefferies, 2013; Lambon Ralph et al., 2009); therefore, their neurosurgical damage could result in language impairments not evident in stroke-induced aphasia.

Previous studies offer limited possibility to address the differences between the profiles of neurosurgery- and stroke-induced language impairments. Multiple studies only report composite scores or group-level data of individuals with heterogeneous tumor localization (Duffau et al., 2003; Ilmberger et al., 2008; McCarron et al., 2017; Sanai et al., 2008; Thomas et al., 1995; Whittle, 1998), which precludes differentiation between the linguistic profiles. In part, this was addressed in several studies that utilized the Western Aphasia Battery (WAB, Kertesz, 1982) to diagnose the syndromes of aphasia caused by neurosurgery (Davie et al., 2009; Wilson et al., 2015). However, WAB incorporates the diagnosis of the classical aphasia syndromes distinguished in stroke-induced aphasia. Therefore, when applied in individuals who underwent glioma surgery, it neglects any potential differences

between neurosurgery- and stroke-induced language impairments. A direct comparison of WAB results between individuals with neurosurgery- versus stroke-induced language impairments (Davie et al., 2009) showed that the occurrence of the classical aphasia syndromes was different between these two etiologies. Specifically, the occurrence of anomia was higher after neurosurgery than after stroke, whereas global aphasia was more common in stroke-induced aphasia (Davie et al., 2009). Thus, while these prevalence data indirectly support the notion that these profiles are different, they cannot reveal in detail the nature of the etiology-driven differences between the linguistic profiles in these two clinical groups.

Recently, Brownsett et al. (2019) addressed the limitations of syndrome-based aphasia assessment by complementing it with the Comprehensive Aphasia Test (CAT; Swinburn et al., 2005) in a group of 26 individuals at the chronic phase after glioma surgery. CAT is designed to characterize impairments in various aspects of language processing without resorting to pre-defined aphasia syndromes. Therefore, it is well-suited to reveal the profiles of impairments that do not meet the definitions of the classical aphasia syndromes. Brownsett et al. (2019) found that participants who were not classified as having aphasia by WAB in fact did present with impairments in CAT. In almost a third of these participants (6 out of 20), the impairments spanned both production and comprehension at various linguistic levels, in oral and written modalities. However, these impairments did not show any consistent pattern. These data further suggest that the profiles of neurosurgery-induced language impairments do not follow the syndromes traditionally distinguished in stroke-induced aphasia (Brownsett et al., 2019).

We aimed to address the gaps in the existing literature by directly comparing the profiles of language impairments caused by left-hemisphere glioma surgery versus stroke in two large clinical cohorts. We performed detailed language assessments in these cohorts using the Russian Aphasia Test (RAT; Ivanova et al., 2021). RAT is a new comprehensive standardized aphasia test that taps into language production and comprehension at all major linguistic levels: phonological, lexical-semantic, syntactic, and discourse. First, we analyzed the language assessment data using k-means clustering. This analysis technique groups individual observations into distinct clusters without relying on any a-priori information about cluster properties. When applied to language assessment data, it delineates clusters of participants that have distinct profiles of language impairments (Akinina et al., 2020; Goldstein, 2013; Hoffman et al., 2017). Secondly, we correlated the language scores in each patient cohort to test whether different etiologies cause the relations between various aspects of language processing to be distinct. This enabled us to comprehensively compare the linguistic profiles of neurosurgery- and stroke-induced language impairments without resorting to a-priori defined aphasia types.

2. Methods

2.1. Participants

Participants were 115 individuals with gliomas, and 120 individuals with stroke who met the following inclusion criteria: had a single left-hemisphere glioma or a stroke based on a clinical diagnosis, had no prior neurosurgical intervention other than a biopsy (in

individuals with gliomas), is right-handed native speaker of Russian (balanced bilingual speakers were also included), does not have any uncorrected vision or hearing impairments. Individuals with gliomas were recruited at seven medical centers in Russia: National Medical and Surgical Center named after N.I. Pirogov, Moscow (N = 40); National Medical Research Center for Neurosurgery named after N.N. Burdenko, Moscow (N = 34); Federal Neurosurgical Center, Novosibirsk (N = 15); Privolzhsky Research Medical University, Nizhny Novgorod (N = 14); Federal Centre of Treatment and Rehabilitation of the Ministry of Healthcare of the Russian Federation, Moscow (N = 10); Research Center of Neurology, Moscow (N = 1); Central Clinical Hospital with Outpatient Health Center of the Business Administration for the President of the Russian Federation, Moscow (N = 1). Individuals with stroke were recruited at the Center for Speech Pathology and Neurorehabilitation, Moscow (N = 120).

We excluded participants who did not have any speech and/or language impairment (for criteria, see Section 2.2. below). By doing so, we balanced the two cohorts for the presence of language impairments. Furthermore, since k-means clustering does not allow missing data, we excluded participants with missing subtest scores if these scores could not be inferred from other comparable subtests. Note that for participants with missing scores, a decision to not administer a certain subtest only took into account his/her physical condition (e.g., headaches) but not performance in other subtests. Therefore, exclusion of participants with missing scores did not introduce any systematic bias to the samples. After applying the exclusion criteria, 88 individuals with neurosurgery-induced aphasia (NS aphasia) and 95 individuals with stroke-induced aphasia (ST aphasia) were selected for the cluster analysis. Table 1 summarizes their demographic and clinical information. Figure 1 presents the lesion overlay maps for each cohort.

The study was approved by the HSE Committee on Interuniversity Surveys and Ethical Assessment of Empirical Research and the Ethical Committee of the National Medical and Surgical Center named after N.I. Pirogov. All participants signed an informed consent form upon admission to the hospital, and additionally gave an oral or a written informed consent for undergoing a language assessment for research purposes.

2.2. Language assessment

Language assessment was performed using a comprehensive standardized aphasia test – the Russian Aphasia Test (RAT; Ivanova et al., 2021). RAT assesses oral production, repetition, and auditory comprehension at different linguistic levels. The production subtests include picture-based naming (objects and actions), sentence, and discourse production. The repetition subtests include non-word, word, and sentence repetition. The comprehension subtests include non-word discrimination, lexical decision, single-word comprehension (nouns and verbs), sentence, and discourse comprehension. The design of each subtest, scoring procedure, and standardization data are described in detail by Ivanova et al. (2021). The assessment materials were the same for both cohorts, with the minor variations in the sentence production, discourse production, and discourse comprehension subtests (for details, see the Supplementary Materials). To account for the differences in task materials in these instances, we recalculated the normative cut-off scores for each version of the task

that differed from the standardized version reported in Ivanova et al. (2021); otherwise, the original normative data from Ivanova et al. (2021) were used to determine abnormal performance. A participant's performance in a given subtest was defined as impaired if the accuracy score fell below the 5-th percentile of the score distribution of healthy age-matched individuals. A participant was considered to have a speech and/or language impairment if he/she showed abnormal performance in at least one subtest of the RAT. The outcome measures entered into the cluster analyses were individual accuracies (proportions of correct responses) in each subtest.

2.3. Neuroimaging

Magnetic resonance imaging (MRI) was available for 64 out of 95 individuals with stroke, and for 86 out of 88 individuals who underwent glioma surgery (only the scans acquired immediately after surgery were analyzed). MRI always included a whole-brain high-resolution T1-weighted image (voxel size 0.39 – 1.25 by 0.39 – 1.25 by 0.55 – 1 mm in all participants but one; in one participant, voxel size was 0.5 × 0.5 × 6 mm). In addition, it included whole-brain T2- and/or FLAIR-weighted images in the majority of cases (NS cohort: 86%, ST cohort: 100%; voxel size 0.34 – 1 by 0.34 – 1 by 0.49 – 6.5 mm). Using SPM12, each participant's T1-weighted image was realigned to the AC-PC coordinate system and resliced to the MNI template. Other available modalities were then co-registered to the resulting T1 image. Based on all available modalities, we manually delineated lesions in ITK-SNAP (Yushkevich et al., 2006). Lesion masks included resection cavities in individuals who underwent glioma surgery, and any left-hemisphere pathological tissue in individuals with stroke. Lesion masks were normalized using the non-enantiomorphic normalization algorithm in the Clinical Toolbox (Rorden et al., 2012). Since individuals with gliomas were generally younger than individuals with stroke, we normalized the resection cavities to an MNI template derived from a younger population, and stroke lesions to one derived from an older population. Lesion overlay maps were computed using MRIcron. To obtain a more detailed description of lesion localization, we have calculated each participant's lesion loads in various left-hemisphere grey-matter regions included in the Automated Anatomical Labelling atlas (Tzourio-Mazoyer et al., 2002).

2.4. Data analysis

Data analysis was performed in R (Version 1.2.5019). For the NS cohort, the descriptive statistics of RAT scores were calculated both for the pre- and post-operative assessments to comprehensively characterize the sample. However, since our primary goal was to characterize the language impairments caused by neurosurgery, all analyses described below were performed using only the post-operative RAT scores.

First, we filled missing lexical decision scores (NS cohort: N = 5; ST cohort: N = 2) with available word comprehension scores, and vice versa, as these tests tap into language processing at the same level and modality. Otherwise, participants with missing scores were excluded (see Section 2.1. above). We then tested whether the NS and ST cohorts were balanced in aphasia severity. We fitted a linear regression with the composite RAT

score (average of all subtest scores) as the dependent variable, and cohort, age, and their interaction as the independent variables.

K-means clustering was performed for each cohort with subtest scores of the RAT (in single-word comprehension and naming, the individual subtest scores for nouns and verbs were first averaged) using the packages *'cluster'* and *'factoextra'*. This analysis requires a pre-defined number of clusters (K). To determine the optimal K, we used the gap statistic (Tibshirani et al., 2001). It utilizes within-cluster variance (WCV) to identify the optimal number of clusters. WCV captures the heterogeneity of observations within a cluster. In the extreme case, when every observation belongs to a separate cluster (that is, K equals the number of observations), WCV equals zero. Decreasing K causes an increase in WCV: larger clusters progressively become more heterogeneous. At a certain K = a, WCV increases more drastically than at the previous (K = a + 1) step, indicating that clusters became markedly more heterogeneous. Therefore, K = a + 1 is optimal: it is the minimal number of clusters that still remain well-separated and homogeneous. The gap statistic formally determines such optimal K when a transformed WCV value significantly differs from its null (reference) distribution (Tibshirani et al., 2001).

K-means clustering was performed with randomly initiated cluster centers in 100 iterations, separately for individuals with NS and ST aphasia. To validate the clustering output, we calculated the silhouette scores (SS) for individual participants and averaged it within clusters. A larger positive SS value of an individual participant indicates that his/her linguistic profile more closely resembles that of the other participants in the cluster, and is more distinct from the other clusters. A smaller positive SS value indicates that the participant's performance equally resembles those of several clusters; a negative SS value indicates that the participant was classified incorrectly. Finally, we compared the resulting clusters with respect to the RAT scores, the volumes and neuroanatomical distributions of lesions, and the type of pathology (low- vs. high-grade gliomas, hemorrhagic vs. ischemic stroke).

Pearson correlations were calculated between all subtests of the RAT, separately for each cohort. The correlations were based on complete pairwise observations. Significance level was set at 0.0009, which corresponds to a Bonferroni correction for the number of statistical inferences within one correlation matrix (55).

3. Results

Table 2 summarizes the descriptive statistics of the RAT subtest scores. Linear modelling of the composite RAT score (CRS) showed that greater age was associated with a lower CRS ($\beta = -0.004$, SE = 0.002, $t = -2.67$, $p = 0.008$), whereas the main effect of cohort and the cohort by age interaction were non-significant (both $p > 0.4$; for full model statistics, see Supplementary Table 2). Thus, the two cohorts were balanced in overall aphasia severity, and the effect of age on the CRS did not differ between the cohorts. This rules out the possibility that between-cohort age differences (Table 1) contribute to the potential differences between their linguistic profiles.

3.1. Cluster analysis

To identify distinct linguistic profiles in each cohort, we performed a k-means clustering for each cohort using participants' scores in each subtest of the RAT. Figure 2 presents the results of k-means clustering in the NS and the ST cohorts. First, using the gap statistic (Tibshirani et al., 2001), we determined the optimal number of clusters to be K = 2 for individuals with NS aphasia, and K = 3 for individuals with ST aphasia (Suppl. Fig. 1A, C). Individuals with NS aphasia were split into clusters of sizes 12 and 76. Individuals with ST aphasia were split into clusters of sizes 11, 25, and 59.

The average silhouette score was 0.76 for individuals with NS aphasia (Cluster NS1: 0.51, Cluster NS2: 0.80; Suppl. Fig. 1B) and 0.55 for individuals with ST aphasia (Cluster ST1: 0.46, Cluster ST2: 0.41, Cluster ST3: 0.62; Suppl. Fig. 1D). Individual participants' silhouette scores were all positive. This confirms the validity of the obtained classification.

Next, we aimed to characterize the differences and similarities between the clusters in each cohort, and between the cohorts. Unequal cluster sizes precluded us from performing direct between-cluster comparisons of the RAT scores using inferential statistics. Instead, for each cluster we performed a cluster-wise linear regression modelling with the RAT scores as the dependent variable, and subtest as the independent categorical variable with 10 levels. The levels were encoded using the deviation scheme. Under this coding scheme, the intercept represents the average of the dependent variable across all levels of the categorical variable (the cluster-specific CRS), and inferences for each subtest indicate whether its score significantly differs from the intercept. Together, this captures the profile of language impairments in each cluster relative to its CRS, and enables us to compare the profiles between clusters of different size. Figure 3 presents the models' β coefficients and their standard errors for each cluster. Supplementary Table 4 presents these statistical models in detail. Below, we only summarize the results that were significant after applying the Bonferroni correction for five models.

In Cluster NS1, the CRS was 0.26. Non-word discrimination and word-level comprehension scores were significantly higher than the CRS. Sentence repetition and production scores were significantly lower than the CRS. In Cluster NS2, the CRS was 0.9. Word-level comprehension and word repetition scores were significantly higher than the CRS. Sentence repetition, sentence production, and discourse comprehension scores were significantly lower than the CRS.

Clusters NS1 and NS2 dissociated in terms of lesion distributions (Fig. 2C, D) and volumes. In Cluster NS1, the mean volume of resection cavities was 66.0 cm^3 (SD 35.2, range 35.3 – 132.5 cm^3). Resection cavities primarily involved the perisylvian areas, with peak overlaps in the insula and its underlying white matter. In Cluster NS2, the mean volume of resection cavities was 26.3 cm^3 (SD 16.5, range 4.7 – 83.0 cm^3). Resection cavities were similarly distributed around the perisylvian areas but also extended to ventral temporal areas, with the peak overlap located in the temporal pole.

In Cluster ST1, the CRS was 0.29. Non-word discrimination and word-level comprehension scores were significantly higher than the CRS. Non-word repetition, naming, sentence

repetition and production scores were significantly lower than the CRS. In Cluster ST2, the CRS was 0.65. All comprehension scores and word repetition scores were significantly higher than the CRS. All production scores, and non-word and sentence repetition scores were significantly lower than the CRS. In this cluster, a notable dissociation between word and non-word repetition emerged: Higher word repetition scores (+0.11 relative to cluster-specific CRS) were accompanied by significantly lower non-word repetition scores (–0.21 relative to cluster-specific CRS). In Cluster ST3, the CRS was 0.87. Word- and sentence-level comprehension scores, and word repetition scores were significantly higher than the CRS. Sentence repetition, sentence production, and discourse comprehension scores were significantly lower than the CRS.

The three clusters differed in lesion volumes (Cluster ST1: mean volume 151.7, SD 35.1, range 126.9 – 176.5 cm^3; Cluster ST2: mean volume 86.1, SD 51.6, range 6.6 – 183.0 cm^3; Cluster ST3: mean volume 43.1, SD 56.1, range 0.2 – 332.1 cm^3). However, lesion overlay maps (Fig. 2E–G) did not suggest any clear-cut dissociations between the lesion distributions in each of the three clusters. It should be noted, however, that MRI data were not available for 33% of the cohort, and thus the maps may not reliably represent potential dissociations in lesion distributions.

To confirm that the behavioral differences between the cohorts were intrinsic to the data, rather than artificially introduced by choosing the different number of clusters, we additionally classified the NS cohort into three clusters, as we did for the ST cohort. The results of this validation analysis are presented in Supplementary Materials. In brief, two out of three clusters were qualitatively similar to the Clusters NS1 and NS2, whereas the remaining cluster comprised five participants with most severe aphasia. Thus, when the number of NS clusters was equal to that of ST, the results of classification remained qualitatively the same.

Finally, we compared the clusters in terms of glioma grades and stroke types (ischemic or hemorrhagic). High-grade gliomas were diagnosed in 7 out of 12 participants (58%) in Cluster NS1, and 27 out of 76 participants (36%) in Cluster NS2 (for 3 participants in this cluster, the histopathological analyses were not available). Hemorrhagic stroke was diagnosed in one out of 11 participants (9%) in Cluster ST1, 4 out of 25 participants (16%) in Cluster ST2, and 10 out of 59 participants (17%) in Cluster ST3.

Overall, cluster-wise linear regression analysis yielded a consistent pattern for all clusters regardless of etiology. That is, comprehension scores were equal to or higher than the cluster-specific CRS, whereas the production scores were equal to or lower than the cluster-specific CRS. Still, the cluster analysis might have lacked sensitivity to detect subtler differences in aphasia profiles between the NS and the ST aphasia. To address this issue, we additionally performed a correlation analysis of the RAT subtests.

3.2. Correlation analysis

The goals of the correlation analysis were two-fold. First, it provided means for an independent validation of the conclusions implied by the cluster analysis. The clustering results suggest that overall aphasia severity is the primary factor that differentiates the

clusters in both NS and ST aphasia. This predicts that the subtests of the RAT would show strong positive severity-dependent correlations in both cohorts. Secondly, correlation analysis offered an opportunity to obtain a more nuanced picture of the potential etiology-driven behavioral differences. For this, we calculated partial correlations with lesion volume entered as a covariate. Lesion volume served as a proxy measure for aphasia severity, as previous studies report moderate-to-strong correlations between lesion volume and aphasia severity in stroke-induced aphasia (Hope et al., 2018; Thye & Mirman, 2018; Yourganov et al., 2016). In our data, larger lesion volume was associated with lower CRS in both cohorts (NS cohort: N = 85, $r = -0.65$, $p < 0.0001$; ST cohort: N = 64, $r = -0.44$, $p = 0.00024$). Therefore, partial correlations with lesion volume as a covariate elucidate the relations between different linguistic impairments that are severity-independent. Thus, these relations represent the nature of syndromes that pertain to each etiology.

Figure 4 presents the correlations between the RAT scores (Fig. 4A, C) and the partial correlations between the RAT scores with lesion volume as a covariate (Fig. 4B, D) for each cohort. To facilitate comparisons between the correlation matrices in Figure 4, we equalized the number of observations by randomly selecting 64 observations (the number of individuals with ST aphasia whose lesion volumes were available) for each matrix. Supplementary Figure 2 presents correlation matrices calculated using all available data.

In individuals with NS aphasia, all subtests of the RAT showed moderate-to-strong positive correlations (Fig. 4A and Suppl. Fig. 2A). Including lesion volume as a covariate into correlation analyses did not affect the correlation matrix in individuals with NS aphasia (Fig. 4B and Suppl. Fig. 2B). In individuals with ST aphasia, the correlations were overall sparser (Fig. 4C and Suppl. Fig. 2C). Including lesion volume as a covariate only slightly affected the correlation matrix by rendering several of the correlations insignificant (Fig. 4D).

The direct comparison of partial correlations between the NS and the ST cohorts (Fig. 4B vs. 4D) revealed major differences between their linguistic profiles. In general, partial correlation coefficients were significantly higher in the NS cohort compared to the ST cohort (two-sample t-test: $t(87.43) = 9.49$, $p < 0.0001$; mean r in the NS cohort: 0.67; mean r in the ST cohort: 0.34). Comprehension subtests showed much sparser correlations with production subtests in individuals with ST aphasia compared to NS aphasia. Critically, by contrast to NS aphasia, the strongest correlations in individuals with ST aphasia were primarily constrained to the subtests tapping into strongly related linguistic abilities. For example, the strongest correlations were evident between non-word and word repetition, between naming and higher-level (sentence and discourse) production subtests. By contrast, in the NS cohort, the strongest correlations were evident among most comprehension subtests and among most production subtests.

4. Discussion

In this study, we sought to identify and compare the profiles of language impairments caused by surgical removal of gliomas (NS aphasia) versus stroke (ST aphasia). The motivation for this study came from evidence that gliomas cause a functional reorganization of the language network prior to surgery (Anderson et al., 1990; Piai et al., 2020), whereas stroke

abruptly damages a typically organized language network. Moreover, gliomas often involve inferior temporal and supplementary motor areas (Krainik et al., 2001; Noll et al., 2016), which are rarely damaged by stroke. These differences between the etiologies warrant a comparison of their resulting linguistic manifestations. We performed a k-means clustering of individuals with NS and ST aphasia whose language abilities were comprehensively assessed using a standardized aphasia test, the RAT (Ivanova et al., 2021). This allowed us to identify the linguistic profiles intrinsic to each etiology, and compare them without resorting to a-priori defined aphasia types. In addition, we correlated the RAT scores in each cohort. This provided us with a means to validate the conclusions entailed by the cluster analysis, and obtain a more nuanced picture of the etiology-specific relations between the participants' language abilities.

The cluster analyses split the NS and the ST cohort into two and three clusters, respectively, based on aphasia severity (Fig. 2A, B). All clusters showed a consistent pattern of performance regardless of etiology: Production and repetition scores were equal to or lower, and comprehension scores were equal to or higher compared to the cluster-specific composite RAT scores. Consistent with the previous studies (Akinina et al., 2020; Hoffman et al., 2017), k-means clustering of language assessment data failed to reveal clusters of participants that differ along more specific linguistic variables, such as phonological, lexical-semantic, or syntactic deficits. A plausible explanation is that overall aphasia severity occupies most variance in the test scores, whereas these specific linguistic deficits account for a smaller proportion of the variances. Consequently, the specific linguistic deficits only made a negligible contribution to the clustering output relative to overall aphasia severity. In line with this interpretation, multiple subtests of the RAT showed significant positive correlations (Fig. 4A, C and Suppl. Fig. 2A, C) in both cohorts. Thus, the primary factor that differentiated the clusters was overall aphasia severity, rather than deficits in specific linguistic abilities.

Still, the cluster analysis revealed differences between the NS and ST aphasia. A notable feature of Cluster ST2 was that higher word repetition scores (+0.11 relative to cluster-specific CRS) were accompanied by significantly lower non-word repetition scores (−0.21 relative to cluster-specific CRS; Figure 3). Both tasks require the subjects to map phonological representations onto an articulatory motor sequence. Therefore, this behavioral pattern stems neither from a low-level acoustic processing deficit, nor from a general apraxia of speech. On the other hand, since the non-words lack any lexical information, their repetition critically relies on intact phonological processing. Therefore, lower performance in non-word versus word repetition points to a deficit in phonological processing in Cluster ST2. None of the two NS aphasia clusters showed this pattern. Critically, this remained the case when we equalized the number of clusters to three for both cohorts. Thus, this difference was intrinsic to the data, rather than introduced by the different number of clusters. This suggests that in NS aphasia, a phonological deficit cannot be as clearly distinguished from other linguistic deficits as in ST aphasia.

In addition, the two cohorts differed in lesion distributions that gave rise to the observed impairments. In Cluster NS1 and in all ST clusters, lesions were distributed around the perisylvian areas, with the peak overlaps in the insula. By contrast, in Cluster NS2, the

lesions primarily involved the temporal pole and, to a lesser extent, the perisylvian areas. The extension of lesions to the temporal pole in the NS cohort is expected, as temporal pole is frequently involved by gliomas (Noll et al., 2016). However, we did not obtain evidence that lesions to the temporal pole in Cluster NS2 are associated with any pronounced or specific language impairment that is not evident in individuals with ST aphasia. Instead, these participants only show mild aphasia comparable to that in Cluster ST3. This is surprising in light of the current neuroanatomical models of language processing (Hickok & Poeppel, 2007), which posit that the anterior temporal areas contribute to lexical-semantic processing. One explanation is that unlike bilateral degeneration of the temporal pole in the semantic dementia, unilateral temporal pole resection may be insufficient to cause any pronounced language impairment in individuals with gliomas. This explanation is in line with the evidence that unilateral transcranial magnetic stimulation of the temporal poles only slows down semantic processing but does not affect the accuracy (Jefferies, 2013; Lambon Ralph et al., 2009). Alternatively, slow-growing gliomas may have caused other, non-lesioned areas to take over the temporal pole functions (Duffau, 2005), thereby preventing postoperative lexical-semantic deficits (Campanella et al., 2009). Further studies are needed to disentangle between these alternative accounts.

Correlation analyses enabled us to further delineate the differences between the linguistic profiles of the NS and the ST aphasia. We calculated partial correlations between the RAT subtests with lesion volume as a covariate. By doing so, we sought to regress out the score variances that reflected overall severity. This was motivated by evidence that lesion volume correlates with aphasia severity from both the previous studies (Hope et al., 2018; Thye & Mirman, 2018; Yourganov et al., 2016) and our current data. Thus, the partial correlations aimed at revealing the severity-independent associations between impairments in different aspects of language processing. We found both quantitative and qualitative differences between the partial correlations in the NS and the ST cohorts. The quantitative difference was that the significant partial correlations were more extensive in the NS cohort compared to the ST cohort. Furthermore, the correlation coefficients were significantly higher in the NS versus the ST cohort. These differences are unlikely to be driven by ceiling effects or insufficient score variances. Indeed, mean scores and variances of most RAT subtests were comparable between the cohorts (Table 2). Thus, these differences demonstrate that the linguistic patterns intrinsic to each etiology are distinct. Namely, they indicate that the linguistic abilities of individuals with NS aphasia show fewer dissociations compared to individuals with ST aphasia. This complicates, or even precludes, the identification of a clear locus of impairment in NS aphasia by contrast to ST aphasia.

The lack of impairment locus in NS aphasia is further supported by the qualitative comparison between the partial correlations in the NS and the ST cohorts. In the ST cohort, the strongest correlations were primarily confined to the subtests that measure most similar language processing abilities (e.g., non-word and word repetition) or those at related linguistic levels (e.g., non-word and sentence repetition, naming and sentence production). This pattern generally replicates the results in Ivanova et al. (2021) who also observed a differential pattern of associations between RAT subtests in a large sample of stroke-induced aphasia after factoring out overall aphasia severity (as measured by an independent language test). Critically, both findings are in line with the syndromic nature of ST aphasia.

Namely, at the individual level, impairments in specific aspects of language processing manifest themselves in distinct patterns of performance within and across language domains. Therefore, at the group level, correlations are constrained to the subtests that tap into similar language processing abilities. By contrast, in individuals with NS aphasia, the strongest correlations spanned most comprehension and most production subtests. These non-specific correlations are best explained by concurrent impairments in multiple aspects of language processing. Thus, our findings suggest that NS aphasia manifests itself as a 'moderate global aphasia', that is, a generalized decline of language processing without any clear locus of impairment.

A potential limitation of the current study is that the NS and ST cohorts differed in time post-onset: we analyzed the data from the early phase after glioma surgery and subacute-to-chronic phase after stroke. This raises a possibility that the observed linguistic differences have been driven by the differences in time post-onset, rather than the etiology per se. However, both our data and the previously reported data make this possibility highly unlikely. First, early after stroke, language impairments are global in more than 30% of cases (Pedersen et al., 2003). By contrast, early after glioma surgery, severe impairments occurred in less than 15% of participants (Cluster NS1, 12 out of 88 participants) who showed any language impairments in our sample. Secondly, at the chronic stage, ST aphasia often persists, whereas the NS aphasia largely resolves (Sanai et al., 2008; Wilson et al., 2015). Thus, even when the time post-onset is comparable between the cohorts, the NS aphasia nevertheless differs from ST aphasia. Critically, our specific goal was to test whether the linguistic profiles of NS aphasia differ from the classical aphasia syndromes. Since these are poorly distinguished at the early phase after stroke due to the high prevalence of global aphasia (Pedersen et al., 2003), individuals with subacute-to-chronic stroke-induced aphasia were a particularly relevant reference group for the present research question. Finally, we are currently conducting follow-up language assessments of the NS cohort and in the future hope to provide more insight on language recovery patterns following glioma surgery.

The primary methodological limitation of the current study is that a large proportion of the data needed to be excluded because of missing scores and/or lesion data. However, exclusion of participants with missing scores did not introduce any systematic bias to the samples, since a decision to not administer a given subtest only took into account a participant's physical condition but not his/her performance in other subtests. In addition, the analyzed samples remained large (above 80 in the cluster analyses and above 60 in the correlation analyses). Therefore, we consider that they still comprehensively represented the behavioral variability associated with each etiology. Another limitation is a lack of gold standard for choosing the number of clusters, which may critically affect the conclusions. However, we consider that the latter limitation is largely ameliorated by our multiple validation approaches. These included a formal procedure for determining the optimal number of clusters for each dataset, followed by an independent validation using silhouette scores and an additional analysis that equalized the number of clusters. Most importantly, the language assessment and analysis procedure were held constant for both cohorts, which makes our analytical approach well-suited for comparing the cohorts.

The current study is among the first attempts to directly compare the profiles of language impairments caused by glioma surgery versus stroke. Our data reveal that the profiles of surgery-induced language impairments do not follow the syndromic patterns traditionally distinguished in the stroke-induced aphasia. Instead, they represent a generalized decline of language processing abilities without any clear locus of impairment. This opens an avenue for future research aiming to dissociate the contributions of various grey- and white-matter regions to the different symptoms of this generalized decline. From a clinical perspective, this warrants further studies testing whether the treatment and outcome prediction strategies applied in stroke-induced aphasia are equally effective in patients who underwent glioma surgery, or need to be tailored taking into account the etiology-specific linguistic patterns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Glioma surgery and stroke cause distinct profiles of language impairments
- Specific phonological deficit is less evident after glioma surgery than stroke
- Various linguistic measures correlate more extensively after glioma surgery than stroke
- Glioma surgery causes a generalized decline of language processing abilities

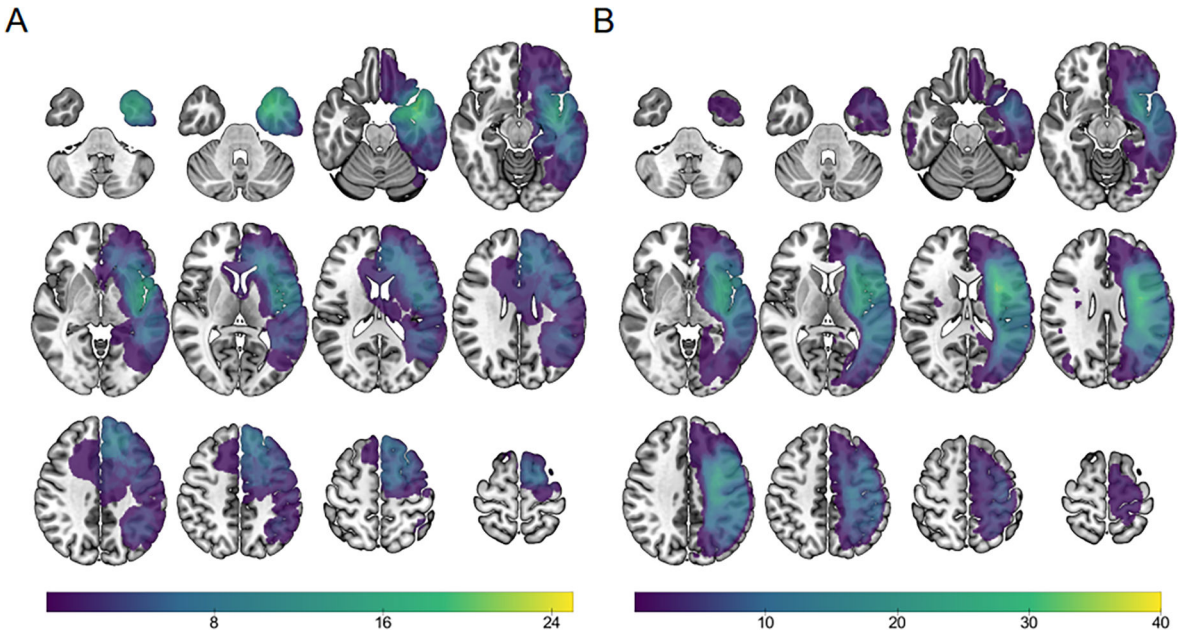

Figure 1.

Lesion overlay maps for individuals with NS aphasia (A) and ST aphasia (B). The color of an area denotes the number of participants with a lesion in this area. Images are displayed in radiological orientation.

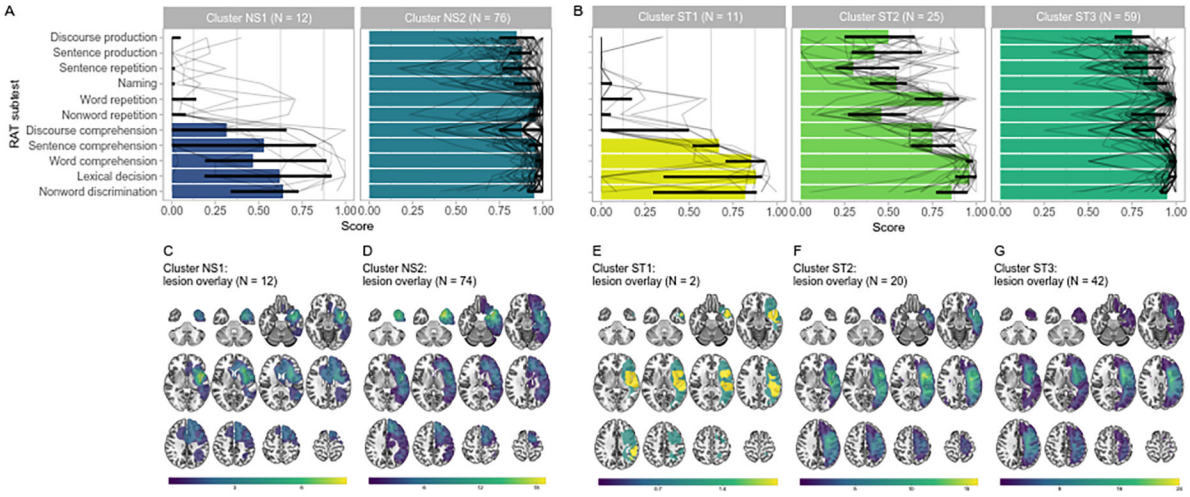

Figure 2.

K-means clustering results. A, B: RAT scores in each cluster of the NS cohort (A) and the ST cohort (B). Bars represent the medians; black lines represent 0.25 and 0.75 percentiles of the score distributions; grey lines represent individual participants' scores. C – G: Lesion overlays for each cluster of the NS cohort (C, D) and the ST cohort (E – G). In panels C – G, N is the number of lesions included in the overlay maps. Supplementary Table 3 summarizes the descriptive statistics of lesion loads in different grey-matter regions for each cluster.

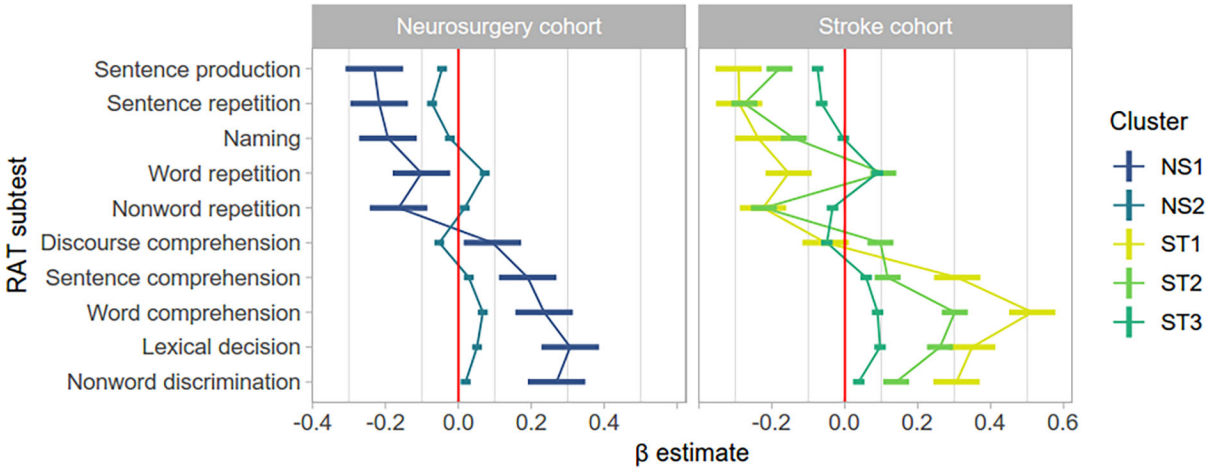

Figure 3.

Cluster-wise linear regression modelling. Each subtest value corresponds to its *ß* coefficient from the model. Bold lines represent the standard errors of the coefficients. The models' intercepts, which correspond to the cluster-specific composite RAT scores, are set to zero (red line). Note that the figure does not present values for the discourse production subtest because it was taken as the reference level in the model.

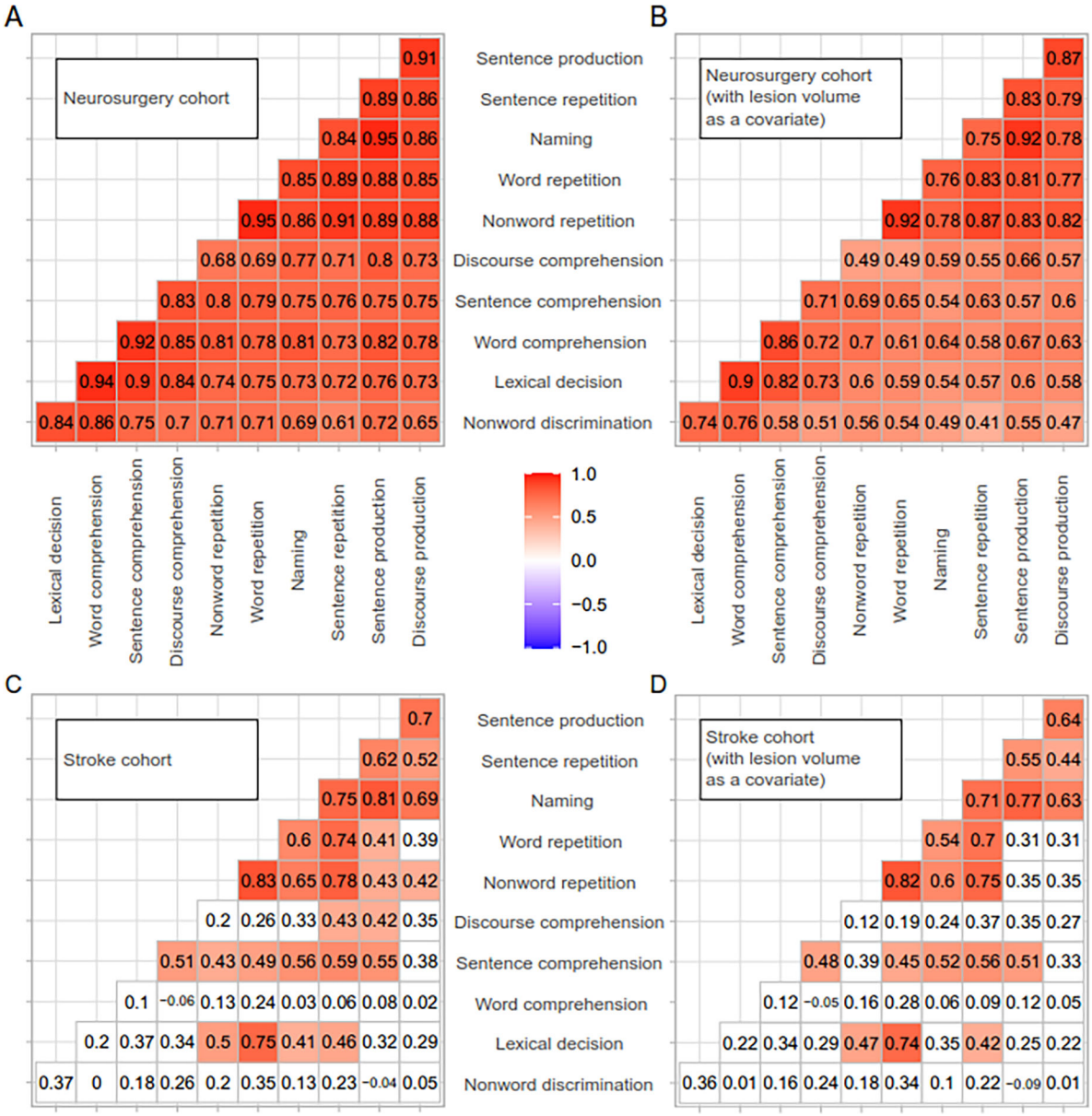

Figure 4.

Pearson correlations between the subtests of the RAT. A, B: full (A) and partial (B) correlations with lesion volume as a covariate in 64 randomly selected individuals with NS aphasia. C, D: full (C) and partial (D) correlations with lesion volume as a covariate in 64 individuals with ST aphasia. The scale refers to the correlation coefficient. Correlations that were not significant at $p = 0.0009$ (corresponding to a Bonferroni correction for 55 statistical tests) are shown on a white background.

Table 1

Participants' demographic and clinical information

Parameter	Neurosurgery cohort	Stroke cohort
N	88	95
Sex: female, N (%)	39 (44%)	31 (33%)
Age (years): mean (SD), range	37.8 (11.9), 17 – 74	57.4 (9.7), 25 – 80
Pathology type, N (%)	Low-grade glioma: 51 (58%) High-grade glioma: 34 (39%) NA: 3 (3%)	Ischemic: 80 (84%) Hemorrhagic: 15 (16%)
N (%) of individuals with gliomas who underwent an awake brain surgery with language mapping	65 (74%)	Not applicable
Lesion volume (cm^3): mean (SD), range	31.9 (24.3), 4.7 – 132.5	60.0 (59.5), 0.2 – 332.1
MRI available, N (%)	86 (98%)	64 (67%)
Time between stroke onset or surgery and language assessment: mean (SD), range	4.9 days (3.8), 1 – 32 days	26.9 months (33.7), 1 – 193 months

Table 2

Descriptive statistics of participants' performance in each subtest of the RAT

Subtest	Neurosurgery cohort, before surgery: mean (SD), range[1]	Neurosurgery cohort, after surgery: mean (SD), range	Stroke cohort: mean (SD), range
Nonword repetition	0.95 (0.1), 0.23 – 1	0.81 (0.32), 0 – 1	0.64 (0.32), 0 – 1
Word repetition	0.99 (0.07), 0.38 – 1	0.86 (0.31), 0 – 1	0.81 (0.29), 0 – 1
Naming	0.94 (0.11), 0.13 – 1	0.77 (0.32), 0 – 1	0.68 (0.3), 0 – 1
Sentence repetition	0.91 (0.13), 0 – 1	0.72 (0.32), 0 – 1	0.6 (0.33), 0 – 1
Sentence production	0.91 (0.12), 0 – 15	0.74 (0.31), 0 – 1	0.62 (0.32), 0 – 0.99
Discourse production	0.89 (0.15), 0 – 1	0.73 (0.3), 0 – 1	0.57 (0.29), 0 – 1
Nonword discrimination	0.95 (0.06), 0.59 – 1	0.87 (0.21), 0 – 1	0.84 (0.21), 0 – 1
Lexical decision	0.96 (0.05), 0.79 – 1	0.9 (0.21), 0 – 1	0.91 (0.18), 0 – 1
Word comprehension	0.98 (0.03), 0.78 – 1	0.9 (0.22), 0 – 1	0.94 (0.11), 0.50 – 1
Sentence comprehension	0.96 (0.06), 0.71 – 1	0.86 (0.24), 0 – 1	0.85 (0.15), 0.46 – 1
Discourse comprehension	0.86 (0.15), 0.38 – 1	0.78 (0.27), 0 – 1	0.73 (0.26), 0 – 1

Notes.

[1]One participant with a massive high-grade glioma showed global aphasia before surgery and, therefore, scored 0 across all RAT subtests. Since this participant's scores were outliers in multiple subtests, they were excluded when calculating the descriptive statistics.