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CONNECTOME-GUIDED AWAKE SURGERY FOR DIFFUSE GLIOMAS: NETWORK-LEVEL MAPPING OF LANGUAGE, EXECUTIVE FUNCTION, AND NEUROCOGNITIVE RESERVE

Abstract

Background. In diffuse low- and high-grade gliomas involving eloquent and associative networks, neurosurgical decisions remain difficult because traditional localizationist mapping protects a limited set of cortical sites but may overlook distributed white-matter pathways and higher-order networks responsible for executive control, semantic integration, social cognition, and adaptive behavior.

Materials and methods. A structured narrative review is proposed using clinical trials, prospective cohorts, diagnostic-accuracy studies, systematic reviews, and relevant technical investigations. Evidence is organized by biological plausibility, technical performance, patient selection, safety, clinical effectiveness, reproducibility, and implementation. A prospective comparative study is specified for adults with unilateral supratentorial diffuse glioma adjacent to language, motor, salience, default-mode, or frontoparietal control networks, with conventional awake mapping focused primarily on motor and language tasks as the reference strategy.

Results. The synthesis addresses five domains: limitations of cortical localization, white-matter constraints on resection, higher-order cognitive mapping, neuroplasticity and staged surgery, functional outcomes beyond gross motor and language scales. The proposed primary endpoint is rate of return to preoperative work or study without persistent language, executive, or social-cognitive decline at six months; secondary endpoints include extent of resection, network disconnection score, postoperative aphasia, executive dysfunction, quality of life, seizure control, and longitudinal plasticity. Originality derives from linking technical accuracy to patient-centered outcomes, explicitly modeling uncertainty, and requiring external validation.

Conclusion. Standardized endpoints support reliable clinical comparison. Independent adjudication strengthens causal interpretation. Longitudinal follow-up clarifies therapeutic durability. Rigorous independent external validation remains essential.

Keywords: connectome; awake craniotomy; diffuse glioma; direct electrical stimulation; tractography; neuroplasticity; cognitive mapping.

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КОННЕКТОМ-ОРИЕНТИРОВАННАЯ ХИРУРГИЯ ДИФФУЗНЫХ ГЛИОМ В СОЗНАНИИ: СЕТЕВОЕ КАРТИРОВАНИЕ РЕЧИ, ИСПОЛНИТЕЛЬНЫХ ФУНКЦИЙ И НЕЙРОКОГНИТИВНОГО РЕЗЕРВА

Аннотация

Актуальность. При диффузных глиомах низкой и высокой степени злокачественности, вовлекающих функционально значимые и ассоциативные нейронные сети, принятие

нейрохирургических решений остается сложной задачей. Традиционное локализационное картирование позволяет сохранить ограниченное число корковых участков, однако может не учитывать распределенные проводящие пути белого вещества и нейронные сети высшего порядка, обеспечивающие исполнительный контроль, семантическую интеграцию, социальное познание и адаптивное поведение.

Материалы и методы. Предложен структурированный нарративный обзор, включающий клинические исследования, проспективные когортные исследования, работы по оценке диагностической точности, систематические обзоры и релевантные технические исследования. Доказательства систематизированы по биологической обоснованности, технической эффективности, критериям отбора пациентов, безопасности, клинической результативности, воспроизводимости и возможности внедрения в практику. Разработан дизайн проспективного сравнительного исследования с участием взрослых пациентов с односторонней супратенториальной диффузной глиомой, расположенной вблизи речевых, моторных, салиентных, дефолтных или лобно-теменных сетей исполнительного контроля. В качестве референтной стратегии определено стандартное картирование в условиях операции с пробуждением пациента, ориентированное преимущественно на оценку моторных и речевых функций.

Результаты. Синтез доказательств охватывает пять основных направлений: ограничения корковой локализации, роль проводящих путей белого вещества в определении границ резекции, картирование высших когнитивных функций, нейропластичность и этапные хирургические вмешательства, а также оценку функциональных исходов, выходящих за пределы стандартных моторных и речевых шкал. Предлагаемой первичной конечной точкой является частота возвращения пациентов к дооперационной трудовой или учебной деятельности без стойкого речевого, исполнительного или социально-когнитивного снижения через шесть месяцев после операции. Вторичные конечные точки включают степень резекции, показатель сетевой дисконнекции, частоту послеоперационной афазии, исполнительной дисфункции, качество жизни, контроль эпилептических приступов и динамику нейропластичности при длительном наблюдении. Научная оригинальность определяется взаимосвязью технической точности картирования с клиническими исходами, значимыми для пациента, явным моделированием неопределенности и обязательным проведением внешней валидации.

Заключение. Стандартизированные конечные точки обеспечивают надежность клинических сравнений. Независимая экспертная оценка результатов повышает достоверность причинно-следственной интерпретации. Продолжительное динамическое наблюдение позволяет оценить устойчивость терапевтического эффекта. Проведение строгой и независимой внешней валидации остается обязательным условием.

Ключевые слова: коннектом; краниотомия в сознании; диффузная глиома; прямая электрическая стимуляция; трактография; нейропластичность; когнитивное картирование.

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DIFFUZ GLIOMALARDA KONNEKTOMGA YO‘NALTIRILGAN UYG‘OQ JARROHLIK: NUTQ, IJRO FUNKSIYALARI VA NEYROKOGNITIV REZERVNI TARMOQ DARAJASIDA XARITALASH

Annotatsiya

Dolzarblik. Funksional jihatdan muhim va assotsiativ neyron tarmoqlarni qamrab olgan past hamda yuqori darajali diffuz gliomalarda neyroxirurgik qaror qabul qilish murakkabligicha qolmoqda. An’anaviy lokalizatsion xaritalash usuli cheklangan miqdordagi kortikal sohalarni saqlab qolishga imkon beradi, biroq ijro nazorati, semantik integratsiya, ijtimoiy kognitsiya va adaptiv xulq-atvorni ta’minlovchi taqsimlangan oq modda o‘tkazuvchi yo‘llari hamda yuqori darajali neyron tarmoqlarni yetarli darajada hisobga olmasligi mumkin.

Material va usullar. Klinik tadqiqotlar, prospektiv kohort tadqiqotlari, diagnostik aniqlikni baholovchi ishlar, tizimli sharhlar va tegishli texnik izlanishlarni qamrab oluvchi strukturaviy narrativ sharh taklif etildi. Dalillar biologik asoslanganlik, texnik samaradorlik, bemorlarni tanlash mezonlari, xavfsizlik, klinik natijadorlik, takrorlanuvchanlik va amaliyotga joriy etish imkoniyatiga ko‘ra tizimlashtirildi. Nutq, motor, saliyent, standart holat yoki frontoparietal ijro nazorati tarmoqlariga yaqin joylashgan bir tomonlama supratentorial diffuz gliomali katta yoshli bemorlar uchun prospektiv qiyosiy tadqiqot dizayni ishlab chiqildi. Asosan motor va nutq vazifalariga yo‘naltirilgan an’anaviy uyg‘oq kraniotomiya sharoitidagi xaritalash referent strategiya sifatida belgilandi.

Natijalar. Dalillar sintezi beshta asosiy yo‘nalishni qamrab oladi: kortikal lokalizatsiyaning cheklovlari, rezeksiya chegaralarini belgilashda oq modda o‘tkazuvchi yo‘llarining ahamiyati, yuqori darajali kognitiv funksiyalarni xaritalash, neyroplastiklik va bosqichma-bosqich jarrohlik, shuningdek, standart motor va nutq shkalalaridan tashqaridagi funksional natijalarni baholash. Taklif etilgan birlamchi yakuniy ko‘rsatkich operatsiyadan olti oy o‘tgach turg‘un nutqiy, ijroiy yoki ijtimoiy-kognitiv pasayishlarsiz bemorning operatsiyadan oldingi ish yoki o‘qish faoliyatiga qaytish darajasidir. Ikkilamchi yakuniy ko‘rsatkichlarga rezeksiya darajasi, tarmoq uzilishi ko‘rsatkichi, operatsiyadan keyingi afaziya, ijro disfunksiyasi, hayot sifati, epileptik tutqanoqlar nazorati va neyroplastiklikning uzoq muddatli dinamikasi kiradi. Tadqiqotning ilmiy yangiligi xaritalashning texnik aniqligini bemor uchun klinik ahamiyatga ega natijalar bilan bog‘lash, noaniqlikni aniq modellashtirish va tashqi validatsiyani majburiy talab qilish bilan belgilanadi.

Xulosa. Standartlashtirilgan yakuniy ko‘rsatkichlar klinik natijalarni ishonchli taqqoslash imkonini beradi. Natijalarni mustaqil ekspert baholashi sabab-oqibat bog‘liqligini talqin qilishning ishonchliligini oshiradi. Uzoq muddatli dinamik kuzatuv terapevtik ta’sirning barqarorligini aniqlash imkonini beradi. Qat’iy va mustaqil tashqi validatsiya o‘tkazilishi muhim talab bo‘lib qolmoqda.

Kalit so‘zlar: konnektom; uyg‘oq kraniotomiya; diffuz glioma; to‘g‘ridan-to‘g‘ri elektr stimulyatsiya; traktografiya; neyroplastiklik; kognitiv xaritalash.

Introduction. Neurosurgery is increasingly defined by the tension between anatomical precision and biological uncertainty. In diffuse low- and high-grade gliomas involving eloquent and associative networks, the surgeon must act on information that is incomplete, time dependent, and distributed across imaging, physiology, pathology, electrophysiology, and patient-specific functional reserve. The conventional operative paradigm is therefore being replaced by a data-rich model in which preoperative planning, intraoperative sensing, and postoperative surveillance are treated as a

continuous decision process. This evolution is clinically important because technical success cannot be reduced to target acquisition or implant placement; it must also preserve neurological function, reduce treatment burden, and improve survival or participation. Contemporary evidence supports this shift, but also shows that many innovations remain supported by retrospective cohorts, selected populations, and heterogeneous endpoints [1, 2, 10, 13]. The central scientific problem is not simply whether a new device or algorithm performs accurately, but whether it changes a decision at the correct time and improves a patient-centered outcome. The specific rationale for connectome-guided awake glioma surgery arises from a persistent limitation: traditional localizationist mapping protects a limited set of cortical sites but may overlook distributed white-matter pathways and higher-order networks responsible for executive control, semantic integration, social cognition, and adaptive behavior. This limitation creates several forms of uncertainty. Anatomical uncertainty concerns where the clinically relevant target or boundary is located. Biological uncertainty concerns whether a visible or measurable abnormality represents viable disease, reversible dysfunction, treatment effect, or nonactionable tissue injury. Functional uncertainty concerns how much intervention can be tolerated without compromising language, cognition, mobility, independence, or quality of life. Finally, temporal uncertainty concerns how rapidly physiology, anatomy, or disease burden changes during and after treatment. Existing methods usually address only one of these dimensions. The proposed innovation-a connectome-based awake mapping protocol that combines patient-specific tractography, resting-state network analysis, direct cortical and subcortical stimulation, task switching, and longitudinal neuropsychological phenotyping-is intended to combine them within a single clinically interpretable framework [3, 7, 12, 15].

The potential advantages of this approach are mechanistically plausible. Relevant processes include direct electrical stimulation of cortical and subcortical pathways, patient-specific diffusion tractography, resting-state functional connectivity, intraoperative multitask paradigms, longitudinal network reorganization. When these processes are measured independently, the clinician receives fragmented signals with different spatial resolutions, temporal resolutions, and error structures. Integration can theoretically reduce uncertainty by allowing one modality to compensate for the weaknesses of another. However, multimodal integration can also amplify hidden bias, propagate registration error, and create false confidence if outputs are presented without uncertainty estimates. For that reason, a clinically responsible system must reveal both its prediction and the conditions under which that prediction may fail. This requirement is particularly important in neurosurgery, where small errors can produce irreversible disability and where intraoperative decisions are often made under severe time constraints [8, 9, 25]. Five evidence gaps justify a dedicated original investigation: heterogeneous task batteries, limited normative neuropsychological data, tractography false-positive and false-negative pathways, inconsistent reporting of return-to-work outcomes, scarce multicenter prospective validation. These gaps are not merely methodological details. They determine whether results can be generalized across hospitals, whether a platform remains reliable after software or hardware changes, and whether the observed benefit reflects the technology rather than expert operator selection. A further problem is that technical publications often emphasize accuracy metrics while clinical publications emphasize outcome, leaving a translational gap between algorithmic performance and therapeutic value. The proposed study therefore uses rate of return to preoperative work or study

without persistent language, executive, or social-cognitive decline at six months as its primary endpoint and includes extent of resection, network disconnection score, postoperative aphasia, executive dysfunction, quality of life, seizure control, and longitudinal plasticity as secondary endpoints. This endpoint architecture is intended to prevent a statistically impressive but clinically irrelevant result [6, 13, 28].

The objective of this article is to provide a structured, current, and testable framework for connectome-guided awake glioma surgery. The first aim is to synthesize the biological and technical rationale. The second is to define a reproducible evidence-review method and a prospective comparative study design. The third is to describe expected patterns of benefit, failure, and heterogeneity without fabricating patient-level results. The fourth is to present an originality matrix that clearly distinguishes the proposal from routine practice. The working hypothesis is that a connectome-based awake mapping protocol that combines patient-specific tractography, resting-state network analysis, direct cortical and subcortical stimulation, task switching, and longitudinal neuropsychological phenotyping will outperform conventional awake mapping focused primarily on motor and language tasks only when patient selection, data quality, operator training, and uncertainty management are prespecified. In other words, the hypothesis concerns a complete clinical system rather than an isolated device.

Materials and methods. A structured narrative review with a prospectively defined translational framework was selected because the field contains randomized trials, observational cohorts, diagnostic-accuracy studies, engineering reports, and implementation analyses that cannot be combined responsibly through a single pooled effect estimate. Searches should cover MEDLINE, Embase, Scopus, Web of Science, the Cochrane Library, and major trial registries from January 2015 through July 2026, while allowing earlier landmark studies when they established the current standard. Core search concepts should combine the disease or procedure, the intervention components, and outcome terms related to safety, neurological function, accuracy, and effectiveness. Citation chaining should be used to identify technical validation papers that may not be indexed under conventional clinical terminology [1, 4, 7]. Eligible evidence should include adult or mixed-age human studies directly evaluating connectome-guided awake glioma surgery; studies of adults with unilateral supratentorial diffuse glioma adjacent to language, motor, salience, default-mode, or frontoparietal control networks; and investigations reporting at least one clinically interpretable outcome. Exclusion criteria should include purely conceptual commentaries without original data, nonvalidated simulations, duplicated cohorts, and reports in which the contribution of the target technology cannot be separated from unrelated interventions. For diagnostic and algorithmic studies, the reference standard, unit of analysis, handling of repeated measurements, and patient-level data split must be extracted. For therapeutic studies, eligibility criteria, crossover, rescue treatment, missing data, and outcome adjudication must be recorded. The distinction between internal validation, temporal validation, geographic external validation, and prospective clinical validation is essential [2, 5, 8]. Data extraction should be organized into six domains: patient characteristics; disease or anatomical complexity; technical configuration; operator experience; safety; and clinical outcome. The technical domain should record hardware, software version, preprocessing, calibration, registration, data latency, and failure handling. The clinical domain should record rate of return to preoperative work or study without persistent language, executive, or social-cognitive decline at six months and extent of

resection, network disconnection score, postoperative aphasia, executive dysfunction, quality of life, seizure control, and longitudinal plasticity. Risk of bias should be assessed with tools appropriate to study type, including RoB 2 for randomized trials, ROBINS-I for nonrandomized intervention studies, QUADAS-2 for diagnostic accuracy, and PROBAST or an equivalent framework for prediction models. Certainty should be interpreted according to consistency, directness, precision, and evidence of selective reporting [3, 6, 9].

The proposed original study is a prospective, multicenter, assessor-blinded comparative investigation involving adults with unilateral supratentorial diffuse glioma adjacent to language, motor, salience, default-mode, or frontoparietal control networks. Participants should be enrolled consecutively to reduce spectrum bias. The intervention arm should receive a connectome-based awake mapping protocol that combines patient-specific tractography, resting-state network analysis, direct cortical and subcortical stimulation, task switching, and longitudinal neuropsychological phenotyping; the control arm should receive conventional awake mapping focused primarily on motor and language tasks. Randomization is preferred when clinical equipoise exists. If randomization is impractical, a pragmatic stepped-wedge or prospective registry design with propensity weighting and center-level random effects should be used. The primary endpoint is rate of return to preoperative work or study without persistent language, executive, or social-cognitive decline at six months. Secondary endpoints are extent of resection, network disconnection score, postoperative aphasia, executive dysfunction, quality of life, seizure control, and longitudinal plasticity. Outcome assessors should remain blinded to technical allocation whenever possible, and adverse events should be adjudicated by an independent committee.

The statistical analysis plan should be finalized before database lock. Continuous outcomes should be analyzed with mixed-effects models that account for center and repeated measurements. Binary endpoints should be reported with absolute risk differences, relative risks, and number needed to treat or harm when appropriate. Ordinal neurological outcomes should be analyzed with proportional-odds models after testing the proportionality assumption. Time-to-event outcomes require Kaplan–Meier estimation and multivariable Cox models. Diagnostic models must report discrimination, calibration, decision-curve analysis, and performance across clinically relevant subgroups. Missing data should be addressed through multiple imputation when assumptions are defensible, accompanied by complete-case and worst-case sensitivity analyses. Ethical oversight should recognize that advanced technology introduces risks beyond ordinary operative complications. These include privacy loss, cybersecurity failure, automation bias, inequitable performance, unplanned device downtime, and conflicts of interest arising from proprietary platforms. Consent documents should explain which decisions remain under surgeon control, whether data may be used for algorithm development, and how incidental findings will be managed. A data and safety monitoring structure should review not only adverse clinical events but also registration failures, algorithmic drift, protocol deviations, and cases in which the system recommendation was overridden. Such governance converts technological innovation into accountable clinical research [16, 23, 30].

Results. The structured synthesis is expected to identify a first domain centered on limitations of cortical localization. Across contemporary studies, the most consistent observation is that richer biological or anatomical characterization improves stratification, but reported gains vary according to

reference standards and population spectrum. Studies that use retrospective convenience samples commonly show higher performance than prospective consecutive cohorts. This difference is clinically meaningful because difficult cases, prior treatment, motion, artifact, and incomplete data are underrepresented in curated datasets. Accordingly, the likely result is not a universal performance value, but a gradient of reliability that depends on data quality, disease phenotype, and operator context [1, 2, 4]. A second domain concerns white-matter constraints on resection. The relevant literature suggests that intraoperative or procedure-time information is most valuable when it changes the operative plan rather than merely confirming a preoperative expectation. Clinically useful outputs therefore require low latency, stable registration, and a display format that can be interpreted without interrupting the procedure. The synthesis also indicates that human expertise remains necessary for resolving discordance between technology and anatomy. Systems designed as collaborative decision aids are more likely to improve workflow than systems designed as autonomous authorities. The proposed study will document every technology-related plan modification, the reason for the change, and whether the modification was subsequently supported by pathology, imaging, electrophysiology, or clinical outcome [8, 9, 25].

The third domain is higher-order cognitive mapping. Evidence in this area shows that temporal change is a central feature of neurosurgical care. Anatomy deforms, physiological reserve fluctuates, tissue characteristics evolve, and device signals drift. Static thresholds or one-time images therefore have limited validity. A dynamic strategy should update its estimate as new data arrive and should retain an audit trail of how recommendations changed. The anticipated result is that dynamic monitoring will reduce selected technical errors, but it may also increase false-positive alerts. This trade-off must be quantified through sensitivity, specificity, false-alert burden, and decision-curve analysis rather than described qualitatively[6, 13, 28]. The fourth domain, neuroplasticity and staged surgery, addresses the relationship between technical success and patient-centered benefit. Existing evidence often demonstrates improved localization, classification, or device accuracy without proving a reduction in disability or a durable improvement in survival. The proposed research framework therefore treats technical accuracy as an intermediate endpoint. The primary clinical endpoint remains rate of return to preoperative work or study without persistent language, executive, or social-cognitive decline at six months. Secondary analysis will evaluate whether technical improvement mediates clinical benefit and whether the effect differs by baseline risk. This mediation-oriented approach can distinguish a technology that is accurate but clinically redundant from one that enables a beneficial change in treatment. The fifth domain is functional outcomes beyond gross motor and language scales. Implementation outcomes are expected to vary substantially between high-volume academic centers and lower-resource hospitals. Capital costs, maintenance, calibration, data storage, staffing, and training may determine real-world effectiveness more strongly than laboratory accuracy. The framework therefore includes acquisition cost, consumables, room time, failed-case cost, revision avoidance, and staff workload. Equity analysis should determine whether the innovation narrows or widens access. A platform that performs well only in a highly selected tertiary environment should not be described as universally transformative [4, 7, 14].

Taken together, the expected evidence pattern supports cautious optimism. A connectome-based awake mapping protocol that combines patient-specific tractography, resting-state network analysis, direct

cortical and subcortical stimulation, task switching, and longitudinal neuropsychological phenotyping is likely to provide the greatest benefit in patients with high decision uncertainty and a realistic opportunity for management change. Benefit may be smaller in straightforward cases where standard practice already performs well. Harm may emerge from false reassurance, unnecessary extension of surgery, treatment delay, excessive alarms, or inappropriate extrapolation beyond the validated population. The originality tables below convert these observations into a testable study architecture and make clear which elements represent true innovation rather than repackaging of established practice.

Table 1. **Scientific originality matrix**

Domain	**Current standard or limitation**	**Proposed original contribution**
Functional model	Cortical eloquence map	Individualized cortico-subcortical network model
Awake tasks	Naming and motor testing	Adaptive multitask battery covering executive and social cognition
Outcome	Immediate deficit rate	Six-month cognitive participation and return-to-work endpoint
Resection boundary	Anatomic or fluorescence margin	Stimulation-defined network boundary with disconnection metrics
Plasticity	Assumed but unmeasured	Serial connectomics at 3, 6, and 12 months

Table 2. Proposed prospective study framework

Element	**Specification**
Population	adults with unilateral supratentorial diffuse glioma adjacent to language, motor, salience, default-mode, or frontoparietal control networks
Intervention	a connectome-based awake mapping protocol that combines patient-specific tractography, resting-state network analysis, direct cortical and subcortical stimulation, task switching, and longitudinal neuropsychological phenotyping
Comparator	conventional awake mapping focused primarily on motor and language tasks
Primary endpoint	rate of return to preoperative work or study without persistent language, executive, or social-cognitive decline at six months

Element	Specification
Secondary endpoints	extent of resection, network disconnection score, postoperative aphasia, executive dysfunction, quality of life, seizure control, and longitudinal plasticity
Design	Prospective multicenter randomized trial when equipoise permits; otherwise a stepped-wedge or rigorously adjusted prospective registry.
Validation	Internal, temporal, geographic, and subgroup validation with prespecified failure and uncertainty reporting.
Ethics	Independent safety adjudication, data governance, cybersecurity review, and transparent disclosure of proprietary interests.

Discussion. The principal interpretation is that connectome-guided awake glioma surgery should be evaluated as a sociotechnical intervention. The operative result emerges from interaction among the patient, surgeon, team, imaging or monitoring environment, software, hardware, institutional protocols, and rescue pathways. This explains why promising accuracy studies may not reproduce the same benefit after implementation. A technically excellent platform can fail if registration is unreliable, alerts are poorly prioritized, staff roles are unclear, or the output arrives too late to influence the decision. Conversely, a moderately accurate system can be clinically valuable when it addresses a high-impact uncertainty and integrates smoothly into workflow [1, 3, 5]. Patient selection is likely to be the main determinant of effect size. The target population is adults with unilateral supratentorial diffuse glioma adjacent to language, motor, salience, default-mode, or frontoparietal control networks, but not every eligible patient has the same probability of benefit. Selection should incorporate baseline function, disease burden, anatomical complexity, comorbidity, prior treatment, expected survival, and the availability of an actionable alternative. The intervention should not be offered merely because the technology is available. A decision-impact criterion is more appropriate: the patient should have a plausible management fork that the new information can resolve. This principle limits exposure to unnecessary complexity and improves the efficiency of prospective trials [3, 6, 10].

The choice of comparator is equally important. The relevant comparator is conventional awake mapping focused primarily on motor and language tasks, delivered by trained clinicians under a standardized protocol. Comparing an advanced platform with poorly defined historical care exaggerates benefit and does not inform contemporary practice. Expertise bias should be addressed by documenting operator experience in both arms and by separating the learning phase from the evaluative phase. When blinding the surgeon is impossible, blinded endpoint assessment, objective imaging or physiological criteria, and independent adjudication become essential. These safeguards are particularly important when the intervention itself changes the amount or duration of surgery. Safety must include both direct and indirect harm. Direct harm includes device- or procedure-related injury,

infection, hemorrhage, neurological deficit, or treatment toxicity. Indirect harm includes delay, over-treatment, under-treatment, false reassurance, automation bias, and diversion of resources. The proposed study therefore records technical failures and near misses even when no adverse clinical event occurs. A near miss may reveal a latent system weakness before it causes patient harm. Safety analysis should also examine whether complication patterns cluster by center, operator, hardware version, or patient subgroup [7, 9, 11].

Reproducibility requires more than publishing an average outcome. Investigators should report data provenance, inclusion flow, missingness, device and software versions, preprocessing, calibration, and protocol deviations. For algorithms, source code or a sufficiently detailed executable description should be available when intellectual-property constraints permit. For devices, the physical configuration and update history should be recorded. For complex clinical pathways, process maps should define who performs each step and how discordant information is resolved. External validation must be geographic and temporal, not merely a random split of one institutional dataset. Health-economic evaluation is necessary because high-cost neurosurgical technologies may displace other interventions. A complete assessment should compare acquisition, disposables, maintenance, training, operating-room time, length of stay, complications, revision procedures, rehabilitation, and long-term care. The relevant economic question is not whether the technology is expensive, but whether its incremental cost is justified by additional quality-adjusted survival, preserved independence, or avoided complications. Lower-cost adaptations should be studied deliberately rather than treated as inferior substitutes. This is especially important for regional centers and health systems with constrained capital budgets [8, 10, 12]. The framework also has implications for education. Training should include not only device operation but also interpretation of uncertainty, recognition of failure modes, and maintenance of manual rescue skills. Simulation can expose teams to registration error, data loss, unexpected anatomy, or discordant signals before clinical deployment. Competency should be measured through objective performance and scenario-based assessment rather than attendance at a vendor course. Credentialing should be periodically renewed when major software or hardware updates alter the workflow.

Several limitations should be acknowledged. First, a structured narrative synthesis is vulnerable to publication bias and cannot provide a single pooled treatment effect. Second, rapid technological evolution may make specific hardware obsolete before long-term outcomes mature. Third, the proposed endpoints may require large samples and extended follow-up. Fourth, standardized protocols can conflict with the individualized nature of neurosurgical care. Fifth, external validity may be limited in centers without equivalent imaging, pathology, engineering, or neurocritical-care infrastructure. These limitations do not negate the research question; they define the conditions under which evidence should be interpreted. Future research should prioritize multicenter pragmatic trials, interoperable data standards, shared outcome definitions, prospective failure registries, and patient involvement in endpoint selection. Adaptive trial designs may be useful when software evolves during recruitment, provided version changes are prespecified and analytically traceable. International collaboration can improve representation of scanner types, devices, languages, ethnic groups, and health-system conditions. Ultimately, the decisive evidence will come from demonstrating that the intervention

improves rate of return to preoperative work or study without persistent language, executive, or social-cognitive decline at six months while maintaining acceptable safety, cost, and equity.

A further translational issue is endpoint hierarchy. In connectome-guided awake glioma surgery, several intermediate outcomes may improve simultaneously, yet they should not be interpreted as equivalent. Technical accuracy is closest to the device; decision impact lies one step downstream; clinical benefit lies further downstream; and societal value incorporates cost, access, and long-term participation. A rigorous study should therefore define a causal chain before recruitment. The intervention must first produce a reliable signal, the signal must change a decision, the decision must alter treatment, and the altered treatment must improve outcome. Failure at any step can explain a neutral clinical trial even when the technology appears accurate. Recording each link in this chain will make negative results scientifically informative rather than simply disappointing [1, 5, 9].

Conclusion. Connectome-Guided Awake Surgery for Diffuse Gliomas: Network-Level Mapping of Language, Executive Function, and Neurocognitive Reserve represents a timely and clinically relevant research direction. The evidence supports biological and technical plausibility, but also demonstrates that isolated accuracy metrics are insufficient. The most defensible next step is a prospective multicenter evaluation of a connectome-based awake mapping protocol that combines patient-specific tractography, resting-state network analysis, direct cortical and subcortical stimulation, task switching, and longitudinal neuropsychological phenotyping against conventional awake mapping focused primarily on motor and language tasks, using rate of return to preoperative work or study without persistent language, executive, or social-cognitive decline at six months as the primary endpoint and extent of resection, network disconnection score, postoperative aphasia, executive dysfunction, quality of life, seizure control, and longitudinal plasticity as secondary measures. The proposed originality matrix, standardized methods, explicit uncertainty reporting, and patient-centered outcomes provide a foundation for an authentic IMRAD manuscript. The approach should be adopted only when its benefit is reproducible, transparent, equitable, and clinically meaningful.

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