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Individual-level neuroimaging of cognitive control: from basic science to brain tumor clinical applications

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ABSTRACT

Cognitive control is the ability to pursue goal-directed behavior, select relevant information, and flexibly adapt to changing environments. A wide range of cognitive control functions is subserved by distributed regions primarily in frontal and parietal cortices. The individualized neuroimaging approach emphasizes the importance of functional organization at the individual level to reveal fine-grained details of functional brain networks. Here, we first review how this approach elucidates the multifaceted neural substrates of cognitive control, focusing on the domain-general 'Multiple Demand' network. Critically, we highlight the translational promise of this approach in clinical research and practice, where brain mapping and prediction at the individual patient level is a primary goal. Individual-level neuroimaging in patients with brain tumors is introduced as a test case, with a particular focus on cognitive control processes. We demonstrate how integration of multiple modalities is used to achieve precise and comprehensive mapping to advance surgical treatment, clinical decision-making, and post-surgery cognitive outcome prediction, aiming to improve patients' quality of life. Finally, we discuss challenges and avenues to facilitate individualized multi-modality neuroimaging in translational research, promoting the development of personalized diagnosis and therapeutic strategies.

1. Introduction

Cognitive control, also known as executive function, refers to the mental processes that allow us to engage in deliberate, goal-directed behavior in all aspects of everyday life. It involves processes such as attention, working memory, information selection, reasoning, inhibition, and flexible thinking, enabling us to intentionally direct cognitive resources towards set goals, while flexibly adjusting to constantly changing environmental conditions. Neuroimaging techniques such as functional Magnetic Resonance Imaging (fMRI) have transformed the ability to investigate functional organization in the human brain, including the neural substrates associated with cognitive control. In recent years, an individual-oriented precision approach has emerged and has been increasingly used, presenting the advantages of focusing on individual-level functional organization over the traditional approach of group-level averaging (Saxe et al., 2006; Wang et al., 2015; Gordon et al., 2017; Kong et al., 2019; Fedorenko, 2021; Michon et al., 2022; Mattoni et al., 2025). The analysis at the individual level enables fine-grained characterization of the studied cognitive construct or functional network. To reduce within-participant variability and noise, large amounts of data per participant are often collected, in many cases at the expense of relatively small sample sizes. The benefits of the individual-oriented approach have been demonstrated across several functional domains. Here, we first demonstrate that investigating the relationship between brain and behavior within an individual-oriented framework is particularly important for addressing cognitive control processes and the organization of the frontoparietal domain-general multiple-demand (MD) network. We then emphasize that a key advantage of this approach is its translational potential to clinical applications, in addition to the utility of this approach for addressing fundamental science questions. In a clinical context, diagnosis, treatment and prediction at the individual patient level is a primary goal, rather than prediction at the population level as is commonly studied in the fields of neuroscience and psychology. We will focus on a particular clinical domain as a test case – the investigation of functional organization in patients with brain tumors and advances aimed at improving surgery for

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tumor resection and predicting its outcome. We will highlight challenges and opportunities in this emerging field, focusing on cognitive control processes. Finally, we will propose avenues for integrating multi-modality individual-oriented approaches in clinical practice and research.

2. The multiple-demand frontoparietal network

It has been widely shown that cognitive control across a broad range of domains is supported by a distributed network in frontal and parietal cortical regions. Termed the 'Multiple Demand' network by John Duncan (Duncan and Owen, 2000; Duncan, 2006, 2010), this bilateral network comprises areas in the intraparietal sulcus (IPS) and in the middle frontal gyrus (MFG), the anterior insula (AI) and adjacent frontal operculum, the pre-supplementary motor area (SMA) and the dorsal ACC (Fedorenko et al., 2013; Assem et al., 2020b). Across multiple functional magnetic resonance imaging (fMRI) studies, mounting evidence has shown that regions within the MD network and similar regions in the dorsolateral frontal and parietal cortices are involved in a wide array of cognitive control processes, including working memory, selective attention, goal maintenance, response inhibition, problem solving and set shifting (Cabeza and Nyberg, 2000; Dove et al., 2000; Duncan and Owen, 2000; Dosenbach et al., 2006; Cole and Schneider, 2007; Duncan, 2010; Badre and Nee, 2018; Shashidhara et al., 2019; Braver et al., 2021; Friedman and Robbins, 2022; Reineberg et al., 2022; Saylik et al., 2022). Based on fMRI evidence, it has been demonstrated that regions within this network are recruited with increased demand across diverse cognitive domains such as verbal and spatial working memory, math calculations and response inhibition (Hampshire et al., 2012; Fedorenko et al., 2013; Shashidhara et al., 2020).

3. Group average analysis and individually localized regions in fMRI studies

A common practice in fMRI studies is the use of group-level analysis in which spatial patterns of activity or connectivity are averaged across participants to investigate activity associated with the tested cognitive construct. When a-priori regions of interest (ROIs) are used, typically the same ROIs are defined for all participants based on pre-defined templates, either anatomical or functional. A major advantage of the group template for ROI analysis is that it provides a standard spatial definition of the network or regions under study. This procedure ensures that the same regions are considered for all study participants and allows a straightforward comparison across different studies.

Critically, the underlying assumption of this approach is a high spatial alignment across individuals of anatomo-functional associations. However, along with partial spatial consistency across participants, substantial differences between individuals in functional activity patterns have been demonstrated across multiple domains and brain systems. For example, in the visual cortex, category-selective regions have been robustly identified in individuals in similar though not identical locations (Malach et al., 1995; Kanwisher et al., 1997; Lafer-Sousa et al., 2016; Weiner et al., 2018). Such spatial functional variability is evident in task fMRI and task-related activity as well as in patterns of functional connectivity and brain parcellation into networks and regions. Importantly, large inter-subject variability in brain anatomy and organization may lead to masking detailed patterns of activity, connectivity, and structural features when considered at the group-average level (Saxe et al., 2006; Nieto-Castañón and Fedorenko, 2012; Marek and Dosenbach, 2018) (Fig. 1).

To overcome anatomical and functional variability between participants, designated tasks have been used as functional localizers to define relevant ROIs in each individual participant independently, within which the main task effects were assessed. This localizers approach was initially introduced in the visual domain (Malach et al., 1995; Kanwisher et al., 1997; Epstein and Kanwisher, 1998; Fedorenko, 2021) and has been extensively used, utilizing both univariate and multivariate analyses to reveal information processing and representation in domain-specific regions (e.g., Reddy and Kanwisher, 2007; Julian et al., 2012; Erez and Yovel, 2014; Bracci and Beeck, 2016; for review, see Fedorenko, 2021). The use of functional localizers was further expanded to other domains, such as language (Fedorenko et al., 2010) and theory of mind (Saxe and Powell, 2006).

Localizing functional regions in individuals is part of a broader approach of individual-oriented neuroimaging, in which a key component is the focus on participant-specific activity patterns. In order to

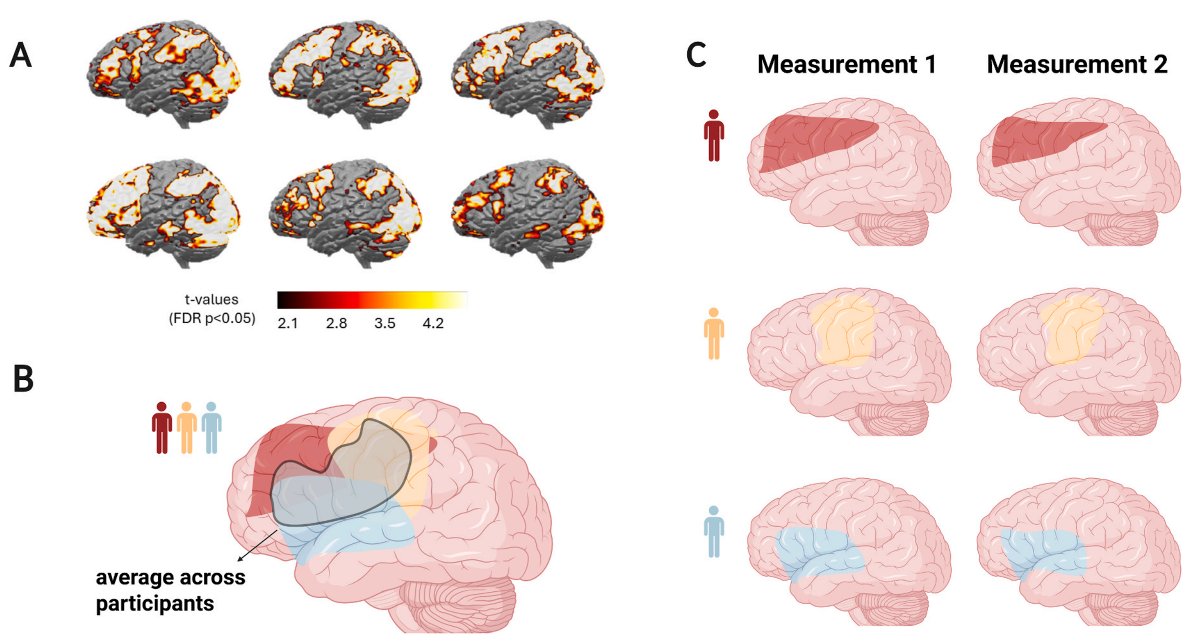

Fig. 1. Individual task-related patterns of activity are obscured in group-averaged analysis. A. Activity maps of six participants, demonstrating the variability of MD activity across individuals. Each map shows activity in a spatial working memory task, contrasting difficult and easy blocks. **B.** An illustration of an average activity across participants (black outlines) that does not capture well individual activity patterns (colored regions). **C.** The individual-specific activity patterns are reproducible across measurements, demonstrating their reliability and stability within each participant.

reduce within-participant variability and increase sensitivity to individual anatomical and functional deviations, an extensive amount of data is collected from individual participants, typically in relatively small sample sizes, often resulting in increased accuracy and larger effect sizes (Gordon et al., 2017; Shashidhara et al., 2020; Fedorenko, 2021; Michon et al., 2022; Mattoni et al., 2025). This family of approaches, termed 'precision', 'high sampling' or 'deep', is increasingly used and has led to several important findings. One prominent example is the Midnight Scan Club dataset (Gordon et al., 2017), in which multiple hours of both resting-state and task fMRI data were collected from 10 participants, revealing highly specific and highly reliable individual-level connectome maps. These maps spatially aligned with task activation patterns, and properties of functional networks were found to be stable within individuals across tasks and states (Gratton et al., 2018a; Seitzman et al., 2019; Kraus et al., 2023). Data from the same dataset were further used to propose a revised organization of the primary motor cortex (Gordon et al., 2023) and reveal plasticity processes in the motor system (Newbold et al., 2020). Other studies along a similar high sampling approach focused on connectome maps (Noble et al., 2017), individual-unique parcellation and topology (Laumann et al., 2015; Poldrack, 2021) and fine-grained details of the cerebellum (Marek et al., 2018) and subcortical areas (Greene et al., 2020). In sum, high sampling of individuals across time, tasks and states has enriched research with new insights into brain organization, with growing evidence for the advantages of this approach in uncovering detailed characteristics of functional networks (For reviews, see Fedorenko, 2021; Michon et al., 2022; Mattoni et al., 2025).

4. Individual-oriented neuroimaging of cognitive control and the MD network

Accumulating findings show that pursuing an individualized high-sampling approach is particularly beneficial for studying the functional organization of association cortices, among them cognitive control regions, because of prominent individual differences in these areas (Tahmasebi et al., 2012; Mueller et al., 2013; Seitzman et al., 2019; Vázquez-Rodríguez et al., 2019; Cui et al., 2020; Dworetsky et al., 2024; for review, see Smith et al., 2021). Therefore, considering inter-participant differences in the spatial arrangement of the MD network and control regions more generally is essential for the study of cognitive control processes. Several variations of high sampling approaches have been used in different studies to reveal fine-grained details of the neural substrates of cognitive control and their relation to cognitive abilities. These include, among others, functional connectivity measures based on extensive resting-state data (e.g., Marek and Dosenbach, 2018; Assem et al., 2020b; Dosenbach et al., 2025) and naturalistic data (e.g., Gal et al., 2022; Rajimehr et al., 2024), multiple tasks for each participant (e.g., Assem et al., 2020b, 2024; Shashidhara et al., 2020; Reineberg et al., 2022; Song et al., 2023), multiple samples over time (Miller et al., 2022), and their combinations.

The MD network was initially proposed by identifying common peaks of activity across participants (Duncan and Owen, 2000; Duncan, 2010). Later on, it has been shown that increased task difficulty across multiple cognitive domains resulted in increased activity in individually-defined frontal and parietal regions (Fedorenko et al., 2013). These patterns of activity in individuals, when averaged across participants, created a delineation of the network that served as a common reference template (Fedorenko et al., 2013; Assem et al., 2020b). Within an individualized approach, this further led to the use of participant-specific MD regions utilizing a task with increased demand manipulation as a functional localizer. It has been shown that patterns of MD activity across several tasks vary considerably across individuals, but are highly reliable within individuals, with larger effect sizes within the individually-localized regions compared to a group-level template (Mineroff et al., 2018; Shashidhara et al., 2020). Using individually-defined MD regions, properties of the network were studied and characterized, revealing its contribution to a variety of cognitive processes, including information representation, reward effects, and limited involvement in linguistic processing under some conditions (Nieto-Castañón and Fedorenko, 2012; Erez and Duncan, 2015; Blank and Fedorenko, 2017; Mineroff et al., 2018; Paunov et al., 2019; Ivanova et al., 2020; Shashidhara et al., 2020; Shashidhara and Erez, 2021). These findings further contributed to a growing body of evidence for the involvement of MD regions and the frontoparietal cortex in a variety of control processes (e.g., Woolgar et al., 2011; Wisniewski et al., 2023; Bhandari et al., 2024; Teng and Postle, 2024).

In another body of work, activity in the MD network was investigated using multiple tasks per participant. Although ample findings showed that different cognitive control tasks engage similar control regions, individualized approaches have revealed fine-scale task-specific variations in activity within the domain-general network and in adjacent areas. For example, Assem et al. showed fine details of activity patterns in domain-general and nearby domain-specific areas evoked by three executive function tasks, thus delineating domain-general and domain-specific regions (Assem et al., 2024). Other studies employing multiple tasks per participant have also reported that different cognitive control tasks evoked different activation patterns in control regions (Lemire-Rodger et al., 2019; Shashidhara et al., 2020; Reineberg et al., 2022; Dengler et al., 2024), supporting a functional and neural distinction between different aspects of cognitive control. For instance, while set-shifting and working memory processes exhibit overlapping activation patterns and associated behavioral measures, interference control (or response inhibition) demonstrates more distinct activation patterns (Shashidhara et al., 2020; Dengler et al., 2024). Supporting this distinction between response inhibition and other cognitive control aspects, additional precision neuroimaging evidence have pinpointed specific areas within the right inferior frontal cortex which are more strongly involved in response inhibition (Suda et al., 2020). The use of multiple tasks for each participant has further uncovered latent states in low-dimensional space, which reflected attentional fluctuations (Song et al., 2023). Furthermore, the individualized approach offers a powerful tool for tracking dynamic network changes and plasticity processes, as exemplified by Miller et al. (2022), who demonstrated that long-term training altered representation of items in the lateral prefrontal cortex during a working memory task.

The individualized approach has further advanced the understanding of functional organization in the associative cortex by distinguishing networks and uncovering previously unrecognized sub-networks. In an early example of an individualized-localizer study, Fedorenko et al. (2012) differentiated language-specific regions from the closely juxtaposed MD regions. Subsequent research has demonstrated that sensory-related areas are intertwined within frontal domain-general regions (Michalka et al., 2015; Noyce et al., 2017; Lefco et al., 2020; Assem et al., 2022). Leveraging the multimodal dataset and parcellation from the Human Connectome Project (HCP) (Glasser et al., 2016), Assem et al. (2020b) refined the functional organization of the MD network, identifying its core and penumbra regions, as well as subcortical and cerebellar components. Braga and Buckner (2017) further showed that the Default Mode Network (DMN) is composed of the functionally distinct frontoparietal and dorsal attention networks, and a close juxtaposition of the language network and adjacent networks has been demonstrated (Braga et al., 2020). These findings complement previous evidence for a division of control regions into frontoparietal and cingulo-opercular networks (e.g., Dosenbach et al., 2006, 2007, 2008; Power et al., 2011; Wallis et al., 2015; see Gratton et al., 2018b for a review).

Several studies have demonstrated that individual variations in associative networks, and in the frontoparietal network in particular, are predictors of behavioral performance related to executive functions and general intelligence (Woolgar et al., 2018; Li et al., 2019; Assem et al., 2020a; Cui et al., 2020; Kong et al., 2021). For instance, a study involving hundreds of youth subjects found that individual differences in the topographic structure of the associative cortex predicted variations in executive function performance across a range of cognitive tests (Cui et al., 2020). Specifically, larger representations of lateral and medial frontoparietal networks were associated with better executive functions. Another study found that activation levels within individually-localized MD regions, disentangled from adjacent language regions, were associated with fluid intelligence scores (Assem et al., 2020a).

Altogether, accumulating findings show how individualized approaches uncovered detailed functional organization of control regions. These findings have implications for theories and models of cognitive control and more generally for the understanding of organizational principles of cortical processing.

5. Individual-oriented neuroimaging and functional mapping in patients with brain tumors

Alongside the advantages of individual-oriented neuroimaging approach from a fundamental science perspective, this approach may have far-reaching implications for clinical applications. In translational research, in addition to addressing questions at the population level, a primary goal is to make accurate predictions and characterize neural substrates at the individual level. In addition to the variability in neurotypical individuals, brain disorders are often widely heterogeneous, and each case is unique. The need for reliable and accurate methodologies to address brain-behavior associations at the individual level in patients is therefore a necessity. Furthermore, individual-level inference can be facilitated by integrating data from multiple modalities and scales, including neuroimaging, electrophysiology, metabolic, cellular and molecular markers.

An increased range of neuroimaging tools has been used in recent years in translational research within an individualized approach. Developments in this direction have a vast potential to enhance diagnosis, prognosis, treatment, and outcome prediction across a wide range of neurological and psychiatric disorders. Some examples from the psychiatric disorders domain include the identification of biomarkers for diagnostic purposes (e.g., Niznikiewicz, 2019), classification of diseases into sub-groups (Drysdale et al., 2017; Xia et al., 2018) and diseases prognosis and prediction of symptoms in schizophrenia (Fan et al., 2021), obsessive-compulsive disorder (Brennan et al., 2019) and major depression (Zhao et al., 2023). The potential utility of precision imaging has been also demonstrated for mapping targets for neuromodulation therapies, such as transcranial magnetic stimulation (TMS) or deep stimulation (Lynch et al., 2019; Greene et al., 2020; Medaglia et al., 2020) and for neurofeedback (Thibault et al., 2018; Tursic et al., 2020. For reviews see Gratton et al., 2020; Kraus et al., 2023; Demeter and Greene, 2024).

One emerging clinical field in which functional brain organization at the individual level is essential is the diagnosis and treatment of patients with a brain tumor. We use this domain as a test case and focus in particular on functional mapping before surgery for tumor removal, during surgery, and outcome prediction following surgery, with an emphasis on cognitive control. Through this lens we illustrate the importance of individualized functional neuroimaging, highlighting the need to integrate data across multiple neuroimaging modalities to better connect brain function and cognition in clinical research (Fig. 2).

For certain tumor types, and in particular diffuse low-grade gliomas (DLGGs), a primary surgical aim is to remove as much as possible of the tumor while preserving function and preventing cognitive impairments. DLGGs are slow-growing primary brain tumors that infiltrate nearby tissue with no clear boundary between the tumor and healthy tissue around it (Santarius et al., 2019). In many cases, surgery is the first treatment that is offered to patients. To achieve an optimal balance between tumor removal and function preservation, and to provide good quality of life for patients following surgery, it is required to identify critical regions involved in different functions, as well as white matter tracts which subserve these functions. While canonical group-average data provides initial information about functional regions and networks, individual-level mapping is critical. A range of methodologies and neuroimaging tools is increasingly used in recent years before and during surgery to obtain a comprehensive picture of functional brain organization at the individual level and guide clinical decision-making (Duffau, 2010; Mitchell et al., 2013; Hacker et al., 2019; Mandal et al., 2023; Yamamoto et al., 2024). In addition to the surgical

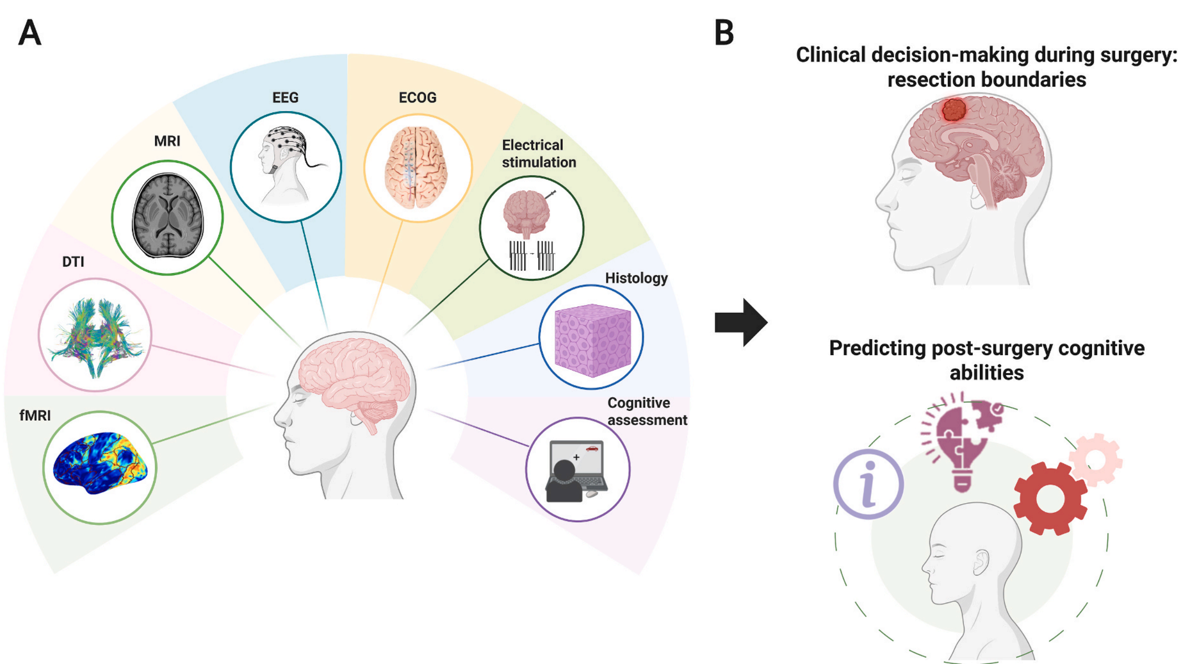

Fig. 2. Individual-oriented multi-modality approach in clinical applications. A. Integration of data from multiple neuroimaging and functional mapping modalities across multiple scales, combined with molecular markers and cognitive assessments, will facilitate fundamental and clinical research, and the development of novel personalized therapeutic and diagnostic tools. **B.** Examples of how multi-modality data might be integrated in clinical practice. Top: Functional mapping for optimizing resection boundaries during surgery for tumor removal. Bottom: Predicting post-surgery profile of cognitive abilities.

intervention, neuroimaging is used to predict long-term prognosis and cognitive outcome, and deepen the understanding of the disease progression and its effects on brain networks at multiple scales (for reviews, see Verburg and de Witt Hamer, 2021; Tiefenbach et al., 2024). While individual variability is common in many diseases, brain tumors present specific challenges related to functional brain organization. The infiltrating nature of DLGGs may alter functionality in the vicinity of the tumor. In addition, the tumor's mass and growth over an unknown period of time before diagnosis reduces the ability to rely on neuro-typical anatomical and spatial landmarks for inferring functionality. Furthermore, gliomas are most frequent in association cortices (Mandal et al., 2020), where multiple adjacent networks are juxtaposed, and heterogeneity is large. At the cellular and molecular levels, recent evidence demonstrated interactions between the tumor and the neural tissue around it (Venkatesh et al., 2019; Krishna et al., 2023), further convoluting potential effects of the tumor on brain organization and functionality at multiple scales.

During surgery, a primary aim is to identify eloquent regions and tracts at the vicinity of the tumor to determine resection boundaries and prevent post-surgery functional impairment. This is commonly achieved using an intraoperative functional mapping procedure, typically conducted using Direct Electrical Stimulation (DES). In this procedure, functionally critical regions and tracts are identified in the craniotomy area near and around the tumor using brief pulses of electrical stimulation during the surgery, often while the patient is awake. A site that exhibits (reversible) functional impairment in response to stimulation is considered as a functionally critical area. Mapping with DES is commonly conducted for motor and language-related areas and pathways, with the latter being typically done using a picture naming task (Duffau et al., 2002; Bello et al., 2008, 2021; Verst et al., 2022). Despite the coarse nature of this mapping procedure, it has been consistently shown to lead to increased extent of resection while preserving function (Duffau et al., 2002, 2008; Gerritsen et al., 2019). There are multiple efforts in the field to expand the range of tasks and cognitive functions used for mapping, aiming to improve patients' post-operative quality of life and functioning. These include visuospatial processing, verbal memory, calculation, dual tasking and a wider array of aspects related to language processing (Duffau, 2010; Coello et al., 2013; Mandonnet et al., 2020a; Schiavolin et al., 2021; Van Dyk et al., 2022; Collée et al., 2023; Ekert et al., 2024). The use of DES is the gold standard in clinical practice to guide resection, as it provides a causal indication for the potential effect of lesion on functionality and therefore ensures maximum tumor removal while preserving cognitive functions. Nevertheless, some of the limitations of DES include the risk of intraoperative seizure as a result of stimulation (Roca et al., 2020) and the procedure being time-consuming with multiple stimulations required across the craniotomy area for a single cognitive task (Catalino et al., 2020; Mandonnet et al., 2020a).

Importantly, mapping cognitive control regions in patients with gliomas has been challenging, primarily because of the complex and diverse nature of executive functions and the distributed regions that support them. Accumulating evidence reported cognitive deficits in patients following surgery (Habets et al., 2014; Lang et al., 2017; Campanella et al., 2018; Incekara et al., 2018; Ng et al., 2019; Cochereau et al., 2020; Acevedo-Vergara et al., 2022), demonstrating the need to efficiently and accurately map these functions as part of the surgical procedure. Furthermore, executive functions play a crucial role in patients' quality of life. For some individuals, the ability to think flexibly may be as important, if not more so, than the ability to control movement, for example. Nevertheless, evidence for the use of intraoperative DES to map executive functions is sparse (for review, see Ekert et al., 2024). For example, several previous studies used mostly the Stroop task to identify cortical and subcortical regions associated with executive function. Identified areas include the anterior cingulate cortex (ACC) (Wager et al., 2013) and subcortical areas medial to the inferior and middle frontal gyrus (Puglisi et al., 2018, 2019). In a test case report, a network approach with a set-shifting paradigm was used to map areas around the middle frontal gyrus associated with executive function (Mandonnet et al., 2020b).

Complementary to DES, the use of electrocorticography (ECOG) has been suggested in order to obtain an individual-level functional map and guide DES. Using ECOG data while the patients perform a designated task, functionally-relevant sites in the craniotomy area can be identified in real-time and be used to guide DES in these specific sites, thus making the overall mapping procedure more efficient and safer. Leveraging previous evidence for the role of broadband high gamma activity (typically 70–200 Hz) in neural processing (Crone et al., 2006; Lachaux et al., 2012), we have proposed ECOG for mapping executive function intraoperatively (Erez et al., 2021). Using a task with an increased demand level, similar to what has been used in fMRI to recruit control MD regions, we showed that a functional signature based HG activity in ECOG data spatially overlapped with frontal control regions, disentangling them from adjacent functional networks (Assem et al., 2023). These findings establish the foundation for mapping cognitive control during surgeries using ECOG, further expanding such mapping beyond motor and language functions (Brunner et al., 2009; Vansteensel et al., 2013; Tamura et al., 2016; Ogawa et al., 2017).

In addition to intraoperative monitoring, pre-operative non-invasive mapping is used with a variety of neuroimaging tools for surgery planning purposes, to reduce operative time, and to provide functional localization when awake mapping is not feasible, e.g., in children. Diffusion weighted imaging (DWI) is used to delineate primary neural tracts in the tumor area such as the superior and inferior longitudinal fasciculus (SLF and ILF, respectively) and the frontal aslant tract (Zacà et al., 2018; Sierpowska et al., 2019; Muir et al., 2024). In addition, network analysis of resting-state fMRI (rs-fMRI) is used to mark individual-level canonical distributed networks (Mitchell et al., 2013; Tie et al., 2014; Hart et al., 2016; Ghinda et al., 2018; Moretto et al., 2024). Task fMRI and functional localizers are used in some medical centers, primarily to identify language and motor regions and determine the language-dominant hemisphere (Bizzi et al., 2008). TMS has been proposed to determine effects of reversible lesions on functionality (Krieg et al., 2015). Importantly, by integrating multiple modalities, the primary goal is to provide a comprehensive picture of functional brain organization for each patient and achieve precise, individualized mapping for improved treatment and outcome (Puglisi et al., 2019; Mandonnet et al., 2020b; Romero-Garcia et al., 2020; Ius et al., 2021; Verburg and de Witt Hamer, 2021).

Another key aim beyond optimizing the onco-functional balance is to predict survival and functional outcomes following surgery and other treatment options (e.g., radiotherapy and chemotherapy), as well as to deepen the understanding of the effects of the disease on functional organization (Keunen et al., 2014; Zangrossi et al., 2022; Herbet et al., 2024). It has been demonstrated that specific neural substrates and biomarkers, together with pre-surgery cognitive assessments, may predict post-surgery outcome. For example, resection cavities in varied locations were associated with post-surgery decline across several cognitive domains (Hendriks et al., 2018; Zangrossi et al., 2022), and memory recovery following surgery was associated with pre-operative neurite density and tumor overlap with the DMN (Romero-Garcia et al., 2021). In addition to such associations between neural substrates and cognitive function, alterations in functional organization in patients with gliomas have been reported, spanning multiple scales (Maas and Douw, 2023; Mandal et al., 2023). These include synaptic signalling that increases glioma growth with a positive feedback that further increases neuronal activity (Venkatesh et al., 2019), tumor interactions with functional circuits (Krishna et al., 2023; Aznarez-Sanado et al., 2024; Mandal et al., 2024), local changes in neural language-related processing in tumour-infiltrated areas (Aabedi et al., 2021; Nakajima et al., 2024), and activity and connectivity at the whole brain level (Liu et al., 2019; Derks et al., 2021; Numan et al., 2022; Semmel et al., 2022) (For reviews, see Maas and Douw, 2023; Mandal et al., 2023). This wide range of molecular, cellular, structural and functional alterations reflects the complexity of the disease, and together with the heterogeneity across patients further underscores the need for an individualized multi-modality multi-scale approach.

Predicting outcomes specifically related to executive functions and their associated networks has been the focus of multiple recent efforts. Following surgery, impairments in executive functions were reported by multiple studies (Marin et al., 2017; Barzilai et al., 2018; Hendriks et al., 2018; Ng et al., 2019, 2020; Romero-Garcia et al., 2022; De Roeck et al., 2023) although in some domains, such as attention, improvement was reported (Barzilai et al., 2018; Ng et al., 2019, 2020; Lemaitre et al., 2022; See Ng et al., 2019; De Roeck et al., 2023 for meta-analyses). Post-surgery impairments were not conclusively related to extent of resection, tumor size, location, and overlap with functional networks (e.g., Hendriks et al., 2018; Ng et al., 2020; Lemaitre et al., 2022; Zangrossi et al., 2022), and in one of the studies were reported to be related mostly to pre-surgery impairments (Zangrossi et al., 2022). At the neural level, impairments in executive function have been associated with several diffusion imaging biomarkers, such as disruption to white matter tracts in frontoparietal and cortico-subcortical pathways (Puglisi et al., 2019; Tringale et al., 2019; Cochereau et al., 2020; Mandonnet et al., 2020b). Abnormal patterns of rs-fMRI functional connectivity were associated with lower performance on executive function tasks (Lang et al., 2017; Mandonnet et al., 2020b), and pre-operative connectivity of the tumor with the dorsal attention network was positively associated with better performance in an attention task post-surgery (Mandal et al., 2024).

Altogether, these findings point at a variety of structural and functional alterations in patients with gliomas that may be predictive of cognitive outcome, hence impact overall patients' quality of life. Integrating data across multiple modalities combined with multivariate statistical models have a promising potential to advance the prediction of survival and detailed cognitive profile for individual patients.

6. Challenges and avenues to advance translational utility of individual-oriented multi-modality neuroimaging

Despite the immense prospect of personalized individual-oriented neuroimaging for clinical applications, the implementation and use of such approaches in patient populations present several challenges. One primary challenge is the testing and scan duration that is required to obtain high quality data that will allow the separation of signal and noise and yield reliable and replicable measures at the individual level. In healthy participants, signal to noise ratio of fMRI data is improved by using within-individual high sampling with long scanning time. In patients, however, scanning time is limited for several reasons, including difficulty of patients to remain within the scanner for prolonged periods of time; patients with neurological disorders being more prone to movement during scans, leading to degraded data quality; funding and cost-effective requirements of clinical scans; and limited availability of clinical scanners and personnel resources. When multiple neuroimaging modalities are combined, scanning time is even longer. Another challenge concerns spatial alignment or comparison to brain atlases which are an integral part of many neuroimaging analysis pipelines, e.g., when using resting-state fMRI data to identify canonical networks in individuals. In patients, such comparisons are often disrupted by the clinical conditions, e.g., a tumor. The heterogeneity of many disorders also results in lack of normative relevant databases that can potentially be used as benchmarks for comparison. Beyond scanning in an MRI facility, testing patients in other clinical settings such as an operating room, often under strict time constraints, requires special preparations and designated protocols. Importantly, studies of clinical populations in general, and using an individualized multi-modality approach in particular, often include relatively small cohorts, limiting the ability to generalize findings across patients. Nevertheless, the contribution of neuroimaging tools to diagnosis and treatment is invaluable. For patients with brain tumors, as well as for other disorders such as epilepsy and vascular malformations, neuroimaging and functional mapping more generally provide an opportunity to *prevent* cognitive impairments resulting from the surgical intervention.

Several avenues may promote the integration of multi-modality individual-oriented approaches in clinical practice and research, applicable to a wide range of neurological disorders. Developments of advanced imaging protocols such as shorter multi-echo fMRI sequences (Lynch et al., 2020) may shorten scanning time, improve signal quality, and reduce costs, which are particularly critical for patient populations. Developments of automated or semi-automated analysis pipelines will be key for streamlining with clinical protocols and workflows. Improved tools that integrate data from multiple modalities to guide clinical decision-making, both extra- and intra-operatively, will be required to make the data accessible for clinicians. Open-access data and multi-center collaborations will be critical to increase study sample sizes, build normative datasets and to benchmark the clinical utility of individualized neuroimaging. Such studies may be facilitated by improved harmonization pipelines, development of data sharing platforms (Lefort-Besnard et al., 2025), and standardized protocols, assessments and data formats such as the Brain Imaging Data Structure (BIDS) (Gorgolewski et al., 2016). Importantly, increasingly formed collaborative teams of clinicians and scientists will be pivotal in driving the field forward.

7. Summary and conclusions

An individual-oriented approach to neuroimaging holds great promise for uncovering fine-grained organization of functional networks and for applying these insights in clinical contexts. By leveraging individualized neuroimaging, studies have revealed detailed properties of the neural substrates of cognitive control, including the disentanglement of adjacent, functionally distinct regions and networks, the contribution of domain-general and domain-specific areas, division into sub-networks, and underlying cortical gradients. Importantly, we emphasize the unique benefits of an individualized, multi-modality approach for clinical research and practice, where precise patient-specific mapping is essential for accurate diagnosis and effective treatment. In patients with brain tumors, specifically gliomas, studies in recent years have employed diverse neuroimaging modalities to advance multiple aspects of patient care such as surgical mapping and prediction of cognitive outcome, for cognitive control and other cognitive abilities. Future methodological developments will facilitate the integration of data across modalities while balancing scientific rigor with clinical practicality, thereby promoting more precise and personalized diagnosis and interventions for a wide range of neurological disorders.

CRediT authorship contribution statement

Shir Hartman: Writing – original draft, Visualization, Investigation. **Tamar Arnon:** Writing – review & editing, Writing – original draft, Investigation. **Yaara Erez:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used chatGPT in order to enhance clarity and improve wording and grammar. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declarations of competing interests

The authors have no conflicts to disclose.

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Data availability

No data was used for the research described in the article.

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