



## **UNIVERSITY OF PADUA**

SCHOOL OF MEDICINE AND SURGERY

Neurology Clinic

Director: Prof. Maurizio Corbetta

Department of Neuroscience

Director: Prof. Edoardo Stellini

MASTER'S DEGREE THESIS IN

MEDICINE AND SURGERY

## **ANATOMICAL STUDIES OF EXECUTIVE DYSFUNCTION IN ACUTE STROKE**

Supervisor: Prof. Maurizio Corbetta

Co-supervisor: Sebastiano Cinetto

Graduand: Adam Moryoussef

Academic Year 2025/2026

# TABLE OF CONTENTS

|                                                                                            |                                     |
|--------------------------------------------------------------------------------------------|-------------------------------------|
| <b>TABLE OF FIGURES .....</b>                                                              | <b>II</b>                           |
| <b>TABLES.....</b>                                                                         | <b>II</b>                           |
| <b>ABSTRACT .....</b>                                                                      | <b>ERROR! BOOKMARK NOT DEFINED.</b> |
| <b>GRAPHIC ABSTRACT .....</b>                                                              | <b>ERROR! BOOKMARK NOT DEFINED.</b> |
| <b>1 INTRODUCTION .....</b>                                                                | <b>1</b>                            |
| 1.1 STROKE AND ITS COGNITIVE DEFICITS .....                                                | 1                                   |
| 1.1.1 <i>Pathophysiology and Clinical Context</i> .....                                    | 1                                   |
| 1.1.2 <i>Prevalence and Burden of Post-Stroke Cognitive Impairment</i> .....               | 4                                   |
| 1.2 THE ARCHITECTURE OF EXECUTIVE FUNCTION .....                                           | 7                                   |
| 1.2.1 <i>Defining Executive Function and Its Subdomains</i> .....                          | 7                                   |
| 1.2.2 <i>Neuropsychological Assessment of Executive Domains</i> .....                      | 10                                  |
| 1.3 EXECUTIVE DYSFUNCTION IN THE ACUTE STROKE WINDOW .....                                 | 10                                  |
| 1.3.1 <i>The Acute Window and the Lesion-Deficit Relationship</i> .....                    | 10                                  |
| 1.3.2 <i>Brain and Cognitive Reserve</i> .....                                             | 11                                  |
| 1.4 FROM LOCALIZATION TO NETWORKS .....                                                    | <b>ERROR! BOOKMARK NOT DEFINED.</b> |
| 1.4.1 <i>The Classical Prefrontal Paradigm and Its Limits</i> .....                        | 12                                  |
| 1.4.2 <i>Diaschisis and the Shift to Large-Scale Networks</i> .....                        | 13                                  |
| 1.5 COMPONENTS OF EXECUTIVE FUNCTION.....                                                  | 14                                  |
| 1.5.1 <i>Frontoparietal and Salience Cortical Nodes</i> .....                              | 14                                  |
| 1.5.2 <i>Thalamic and Basal Ganglia Subcortical Relay</i> .....                            | 14                                  |
| 1.5.3 <i>White Matter Tracts and Structural Connectivity</i> .....                         | 16                                  |
| 1.6 METHODOLOGICAL RATIONALE FOR LESION-SYMPTOM MAPPING.....                               | 16                                  |
| 1.6.1 <i>Lesion-Symptom Mapping and Region-Based Parcellation</i> .....                    | 16                                  |
| 1.6.2 <i>Dual-Axis Damage Metrics for Focal Lesions and Structural Disconnection</i> ..... | 17                                  |
| 1.6.3 <i>Cross-Validation, Variance Decomposition and Permutation</i> .....                | 18                                  |
| 1.7 AIMS AND HYPOTHESES .....                                                              | 19                                  |
| <b>2 METHODS.....</b>                                                                      | <b>21</b>                           |
| 2.1 PARTICIPANTS .....                                                                     | 21                                  |
| 2.2 NEUROPSYCHOLOGICAL ASSESSMENT.....                                                     | 21                                  |
| 2.3 MRI ACQUISITION.....                                                                   | 23                                  |
| 2.4 LESION SEGMENTATION AND SPATIAL NORMALIZATION .....                                    | 24                                  |
| 2.5 ATLAS-BASED LESION-LOAD COMPUTATION .....                                              | 24                                  |
| 2.6 STATISTICAL ANALYSES.....                                                              | 26                                  |
| <b>3 RESULTS.....</b>                                                                      | <b>32</b>                           |

|          |                                                                               |           |
|----------|-------------------------------------------------------------------------------|-----------|
| 3.1      | COHORT AND BEHAVIOURAL PERFORMANCE .....                                      | 32        |
| 3.2      | LESION-SYMPTOM MAPPING.....                                                   | 37        |
| 3.3      | THE ANATOMY OF THE FAB SIGNATURE.....                                         | 42        |
| 3.4      | SET-SHIFTING COST .....                                                       | 49        |
| 3.5      | SUPPLEMENTARY ANALYSES .....                                                  | 50        |
| <b>4</b> | <b>DISCUSSION .....</b>                                                       | <b>58</b> |
| 4.1      | SUMMARY OF PRINCIPAL FINDINGS .....                                           | 58        |
| 4.2      | A DISTRIBUTED, MULTI-SUBSTRATE SIGNATURE OF EXECUTIVE<br>DYSFUNCTION.....     | 59        |
| 4.3      | THE SALIENCE NETWORK AND THE CORTICAL SIGNATURE .....                         | 62        |
| 4.4      | SET-SHIFTING, SWITCH-COST PROXY, AND THE LIMITS OF STRUCTURAL<br>MAPPING..... | 65        |
| 4.5      | SUBSCORE COHERENCE AND THE UNITY OF EXECUTIVE FUNCTION.....                   | 67        |
| 4.6      | LIMITATIONS .....                                                             | 68        |
| 4.7      | CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS .....                             | 70        |
|          | <b>BIBLIOGRAPHY .....</b>                                                     | <b>74</b> |

## TABLE OF FIGURES

|                  |                                                                                                |                                     |
|------------------|------------------------------------------------------------------------------------------------|-------------------------------------|
| <b>Figure 1:</b> | Lesion overlap density across the cohort .....                                                 | 33                                  |
| <b>Figure 2:</b> | Latent structure of the FAB.....                                                               | 36                                  |
| <b>Figure 3:</b> | Variance decomposition of executive performance across seven representations .....             | 40                                  |
| <b>Figure 4:</b> | Spatial convergence of cortical focal-damage and structural-disconnection for the FAB<br>..... | <b>Error! Bookmark not defined.</b> |
| <b>Figure 5:</b> | Cortical signature of FAB performance and out-of-sample prediction.....                        | 47                                  |
| <b>Figure 6:</b> | White matter tracts contributing to FAB performance .....                                      | 36                                  |

## TABLES

|                   |                                                                                                                                                           |    |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| <b>Table I:</b>   | Demographic and clinical characteristics of the cohort .....                                                                                              | 33 |
| <b>Table II:</b>  | Executive performance and impairment rates .....                                                                                                          | 34 |
| <b>Table III:</b> | Variance decomposition and permutation testing of the topographic contribution to each<br>executive outcome across seven anatomical representations. .... | 38 |
| <b>Table IV:</b>  | FAB subscore lesion-symptom mapping .....                                                                                                                 | 51 |
| <b>Table V:</b>   | Language-sensitivity analysis of FAB lesion-symptom mapping .....                                                                                         | 54 |

# ABSTRACT

## BACKGROUND

Executive dysfunction is a common, disabling consequence of stroke, frequently undetected and poorly characterized at the level of its neural substrate. Against a network-level understanding in which executive control depends on a distributed circuit of cortical hubs, subcortical relays, and connecting white-matter tracts, this thesis characterizes its structural signature, asking which components of that substrate, when damaged, predict the deficit, and whether the deficit is carried by the location of damage independently of its magnitude and premorbid reserve.

## METHODOLOGY

Sixty patients with acute stroke (mean age 63 years; median 6 days post-stroke) underwent neuropsychological assessment with the Frontal Assessment Battery (FAB) and the Trail Making Test, including the derived TMT B–A set-shifting cost, and the Esame Neuropsicologico per l'Afasia (ENPA), interpreted against Italian normative cutoffs. Lesions were manually segmented on FLAIR and normalized to standard space, then characterized through both focal tissue damage and structural disconnection across cortical (Schaefer 100-region), subcortical (Tian 16-region), and white-matter (Yeh 77-tract) atlases and combined whole-grey-matter representations, yielding seven predictor sets per outcome. Lesion-symptom mapping used ridge regression with leave-one-out cross-validation, adjusting in every model for age, education, lesion volume, and stroke severity. The unique contribution of lesion location was isolated by variance decomposition, tested by permutation, and corrected across the full family of tests by the Benjamini-Hochberg procedure. The FAB's latent structure was examined by principal component analysis, and its subtests analyzed as supplementary outcomes.

## RESULTS AND DISCUSSION

FAB performance was robustly predicted by lesion location beyond all covariates, surviving correction in six of seven anatomical representations, whereas timed trail-making was not: processing speed showed no topographic signal and set-shifting only trend-level signals that did not survive correction. The FAB signature was distributed rather than focal, converging on a single left-lateralized circuit: left peri-Sylvian cortex with salience-network opercular and insular nodes, the left striatal-pallidal-thalamic grey matter, and the left frontal tracts connecting them. Structural disconnection predicted impairment at least as strongly as focal damage, and subcortically survived correction where focal damage did not, indicating that the deficit follows the severing of connections as much as the destruction of tissue. The signature was not attributable to aphasia: after adjustment for language it persisted on the same circuit. Salience-network involvement was consistent with that network's role in executive control, though the structural design cannot test the underlying dynamics and the cortical findings are bounded by the predominance of anterior-circulation stroke; the convergent subcortical and white-matter evidence grounds the distributed-circuit conclusion more securely than the cortical signal alone. Localizable FAB subtests converged on this shared anatomy rather than dissociable substrates, expressing the unity of executive function; the isolated set-shifting cost showed a trend-level, disconnection-weighted signal consistent with, though insufficient to confirm, a disconnection account of shifting deficits.

## CONCLUSION

Executive dysfunction post-stroke has a definable structural signature: a left-lateralized frontal-executive circuit, distributed across cortical, subcortical, and white-matter substrates, disrupted through both destruction of its nodes and disconnection of its pathways, and carried by location of damage independently of its magnitude. These findings establish a structural foundation for understanding the disorder as one of distributed network disruption, and motivate the functional, longitudinal, and larger-cohort studies that would test the network-coordination account.



# 1 INTRODUCTION

## 1.1 STROKE AND ITS COGNITIVE DEFICITS

### 1.1.1 PATHOPHYSIOLOGY AND CLINICAL CONTEXT

Stroke is defined clinically as the acute onset of focal neurological deficit attributable to a vascular cause, persisting beyond 24 hours, or accompanied by imaging evidence of cerebral infarction or hemorrhage (Sacco et al., 2013). Globally, stroke remains the second leading cause of death as well as the third leading cause of combined death and disability, with an estimated 12 million incident cases per year and a lifetime risk of approximately one in four adults (GBD 2019 Stroke Collaborators, 2021). In Italy, stroke affects approximately 100,000 to 150,000 individuals annually and accounts for roughly 10% of all deaths, with a prevalence rising in step with population ageing; it is the leading cause of acquired adult disability nationally and the second-leading cause of dementia after Alzheimer's disease (SPREAD, 2016).

Stroke arises through two principal mechanisms with distinct pathophysiology and clinical course. Ischemic stroke accounts for approximately 85% of cases and occurs through the abrupt occlusion of a cerebral artery, producing a core of irreversibly infarcted tissue surrounded in the acute phase by a metabolically compromised but potentially salvageable penumbra. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system distinguishes five etiological subtypes (Adams et al., 1993): large-artery atherosclerosis, in which an extracranial or intracranial atheromatous plaque produces thrombotic occlusion or distal embolization; cardioembolism, typically from atrial fibrillation, valvular disease, or post-infarction mural thrombus; small-vessel occlusion, producing the lacunar syndromes characteristic of deep penetrating-artery disease; stroke of other determined cause, encompassing dissection, vasculitis, hypercoagulable states, as well as rarer mechanisms; and stroke of undetermined cause, which includes both incomplete

diagnostic evaluations and presumed-embolic strokes in which no source is identified despite thorough workup. Hemorrhagic stroke accounts for the remaining 15%, and arises from rupture of a cerebral vessel, producing intraparenchymal extravasation of blood with associated mass effect and secondary injury. Its principal aetiologies include chronic hypertension and cerebral amyloid angiopathy, with anticoagulation, vascular malformations, and neoplasm as less common causes.

Stroke risk is largely attributable to modifiable cardiovascular risk factors: hypertension, atrial fibrillation, dyslipidemia, diabetes mellitus, tobacco use, physical inactivity, and obesity, together with non-modifiable contributors including age, sex, and genetic predisposition. The INTERSTROKE study identified ten risk factors collectively accounting for approximately 90% of population-attributable stroke risk worldwide (O'Donnell et al., 2016), supporting the notion that a significant proportion of strokes are preventable through population-level and individually targeted secondary prevention. Despite this, residual risk after a first stroke remains substantial, and the cognitive sequelae of the index event compound this risk by impairing adherence to the very secondary-prevention measures that would reduce recurrence.

Anatomically, ischemic strokes follow the territorial distribution of the cerebral vasculature, with the anterior circulation (internal carotid artery and its middle and anterior cerebral artery branches) supplying most of the cerebral hemispheres and the posterior circulation (vertebrobasilar system) supplying the brainstem, cerebellum, and posterior cortical regions. Middle cerebral artery (MCA) territory infarcts dominate clinical stroke cohorts, largely due to its high vascular volume and the embolic preference for its main trunk. The MCA territory encompasses extensive cortical regions of the frontal, temporal, and parietal lobes, deep grey-matter structures including the basal ganglia and thalamus through the lenticulostriate branches, and the long association and projection white-matter tracts that traverse the periventricular and corona radiata regions. The same MCA territory that produces the canonical motor and aphasic syndromes also encompasses cortical, subcortical, and white-matter circuitry serving higher cognitive functions, among them the executive control processes.

The clinical course of stroke unfolds across recognizable phases with implications for both assessment and recovery. The hyperacute phase (0–24 hours) is dominated by core infarct progression, penumbral salvage opportunity, and the window for thrombolytic and endovascular intervention. The acute phase (24 hours to 7 days) is characterized by edema-related secondary injury, evolving diaschisis, and the stabilization of the lesion's structural footprint. The subacute phase (7 days to 6 months) represents the primary window for neurological stabilization, during which acute cytotoxic edema resolves, and perilesional pathways undergo structurally constrained and behaviourally driven remodelling. The chronic phase (beyond 6 months) instead involves a relatively stable residual deficit, modulated by ongoing rehabilitation and the cumulative effects of secondary processes, including white-matter degeneration along damaged tracts and the network-organized grey-matter atrophy that propagates from the lesion to structurally connected regions over the months following stroke (Yang et al., 2026). Across these phases, the severity of the initial deficit shapes the trajectory of recovery and is most indexed at presentation by the National Institutes of Health Stroke Scale (NIHSS; Brott et al., 1989), a 15-item examination scored from 0 to 42 in which higher values denote a more severe deficit.

Stroke, however, produces not only these visible motor and language deficits, but a parallel burden of cognitive impairment which determines functional independence yet receives markedly less systematic attention in acute care. This asymmetry is a persistent feature of stroke management and motivates the present thesis directly. Motor outcomes are tracked closely, quantified by validated scales such as the Fugl-Meyer Assessment and the modified Rankin Scale (Fugl-Meyer et al., 1975; van Swieten et al., 1988), and addressed by structured rehabilitation pathways with measurable goals. Cognitive outcomes, and within them executive outcomes specifically, are quantified less reliably and addressed less systematically, despite being both highly prevalent and strongly predictive of long-term recovery.

### 1.1.2 PREVALENCE AND BURDEN OF POST-STROKE COGNITIVE IMPAIRMENT

The broad cognitive sequelae of stroke affect a wide range of survivors, with prevalence estimates spanning roughly 24% to 70% depending on population, instrument, and diagnostic threshold (Sun et al., 2014). Within this picture, executive dysfunction stands out for both its frequency and its under-recognition, in that estimates vary with cohort and definition, but converging evidence places the prevalence of executive impairment in the acute and subacute phases between 18% and 39% (Nys et al., 2007), establishing it not as one of the most common impairments encountered after a cerebrovascular event.

A central problem in clinical practice is that this prevalence is not matched by an equivalent rate of detection. Routine post-stroke cognitive screening typically relies on global instruments such as the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) or Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), which were not designed to capture the specific construct of executive function and which consistently fail to do so (Sörös et al., 2015). Beyond their limited sensitivity, executive deficits present a deeper challenge: they are intrinsically covert. Unlike hemiparesis or aphasia, executive dysfunction does not announce itself in the clinical encounter. The consultation is, by its nature, a structured environment with externally provided cues, in which a patient with significant impairment in goal-directed behaviour can perform adequately by relying on the scaffolding the clinician unwittingly provides (Owen et al., 2017; Shallice et al., 1991). The deficit instead manifests where structure is absent, in the less constrained organization of daily life. Compounding this, when superimposed on the more visible consequences of stroke, such as motor weakness, dysarthria, or aphasia, executive dysfunction frequently goes unobserved, attributed to or absorbed by the more conspicuous deficits.

The consequences propagate forward through every phase of stroke care. At consultations, patients with executive dysfunction may genuinely overestimate their own capacity to attend to, comprehend, and recall the medical guidance given (Zinn et al., 2007), leaving the encounter with the impression of competent understanding that

does not survive contact with the demands of unsupervised daily life. At home, treatment adherence and rehabilitation engagement suffer in characteristic ways: medications are missed (Jamison et al., 2016), follow-up appointments forgotten, exercise programmes inconsistently performed, and risk-factor management, which is itself central to secondary stroke prevention, neglected (Rohde et al., 2019). At follow-up, deterioration may be misattributed to non-compliance or to a change in personality, when in some cases the underlying mechanism is a neurocognitive deficit that was present from the beginning but never identified. Discharge planning, which in principle bridges hospital and recovery, becomes correspondingly difficult to do well. Without anticipation of the deficit, the fail-safes that would protect the patient, whether caregiver involvement, written instructions, simplified regimens, or structured environmental supports, are not put into place (El Hussein et al, 2023).

The systematic diagnostic gap creates a dual economic and clinical burden. Patients unable to recognize their own deficits cannot effectively advocate for or navigate healthcare access, leading to a profound under-allocation of outpatient recovery resources (Ownsworth et al., 2006; Hartman-Maeir et al., 2002). Conversely, the unrecognized failure of secondary prevention directly drives predictable clinical endpoints, including early hospital readmission and the premature cessation of rehabilitation protocols (Tay, 2021).

Beyond the clinic and ward, executive function provides the internal architecture necessary for independent autonomy. While a highly structured hospital environment naturally cues behaviour, the transition home forces a patient to rely more on internally generated goal representations. When stroke disrupts this capacity, the clinical presentation is characterized by a failure of temporal coordination. Without robust executive oversight, a patient cannot maintain an overarching objective while simultaneously managing immediate micro-distractions (Levine et al., 2011). The resulting fragmentation of behaviour rapidly exhausts the patient's psychological reserves, often causing them to disengage from complex environments entirely (Graaf et al., 2023). Because the patient may retain intact language and memory, this

behavioral retreat is easily misattributed to a sudden loss of motivation or a change in personality, which translates a covert neurocognitive deficit into a chronic interpersonal stressor.

Professional and social consequences follow predictably. Patients attempting to return to previous employment encounter a mismatch between the demands of their pre-stroke role and a now-diminished executive capacity that is not always visible to colleagues, supervisors, or even themselves (Cunningham et al., 2026). Confidence falters, performance suffers, and the affected individual frequently transitions to less demanding work characterized by greater automation and reduced autonomy, when work is retained at all (Balasooriya-Smeekens, 2016). Within the family, role reversals are common, in that a former primary household manager or caregiver may shift involuntarily into a more dependent position, with corresponding strain on relational dynamics that were calibrated to the pre-stroke distribution of responsibility. In the acute phase, this redistribution is often accepted as a temporary sacrifice; sustained over months and years, it produces the well-documented trajectory of caregiver burden, exhaustion, and elevated rates of psychiatric morbidity in the caregiver themselves (Pucciarelli et al., 2017).

Compounding these external pressures is a profound internal one, that the persistent failure of self-monitoring can trigger a marked psychological decline. When a patient retains partial awareness of their behavioural errors but lacks the executive capacity to correct them, the resulting erosion of agency often induces social withdrawal (Ownsworth, 2014). Post-stroke depression affects approximately 30% of survivors within the first two years (Hackett & Pickles., 2014) and is itself a strong predictor of poorer functional outcome, reduced rehabilitation participation, and worsened cognitive trajectory, generating a self-reinforcing cycle in which cognitive impairment fuels depression, and depression deepens cognitive impairment.

Together, the systems-level and individual-level cases argue toward the same conclusion, that post-stroke executive dysfunction is prevalent, consequential, and systematically under-detected. Addressing this gap at its root requires not only better

screening instruments but a more precise understanding of which neural structures, when damaged, produce the deficit. Because structural imaging is acquired routinely in acute stroke, knowledge of which lesion patterns predict executive impairment could turn the scan itself into a trigger for targeted cognitive assessment, flagging the patients whose deficits would otherwise pass undetected in the structured clinical encounter before they declare themselves in daily life. The remainder of this thesis is concerned with how the topography of stroke damage across the distributed circuitry supporting executive function maps onto the executive impairments observed at the bedside.

## **1.2 THE ARCHITECTURE OF EXECUTIVE FUNCTION**

### **1.2.1 DEFINING EXECUTIVE FUNCTION AND ITS SUBDOMAINS**

Characterizing the anatomy of executive dysfunction first requires defining the construct itself, and here clinical practice and cognitive neuroscience pull in opposite directions. Clinically, executive dysfunction is approached as a single, unified problem of disordered goal-directed behaviour, codified at the syndrome level by formal diagnostic criteria (Godefroy et al., 2010); theoretically, it resolves into partially separable component processes, no one of which captures the whole. This tension between a unitary clinical presentation and a fractionated cognitive architecture must be resolved before lesion data can be mapped onto the deficit, because how the construct is decomposed determines which behavioural measures are used and how their anatomy is interpreted (Jurado et al., 2007). Early neuropsychological frameworks operating on macro-observations of behavioral changes following penetrating head trauma traditionally treated executive control as a unitary faculty anchored exclusively within the prefrontal cortex (Miller & Cohen, 2001; Goldstein, 1936). This localized model, historically termed the frontal lobe syndrome (Ferrier, 1876), proved insufficient to interpret the empirical realities of cerebrovascular neurology. Lesion data revealed that structurally distinct focal frontal infarctions routinely produced fundamentally dissociable behavioral deficits, dismantling the concept of a singular central executive (Stuss et al., 2007); conversely, identical executive failures often

emerged from focal damage entirely outside the frontal lobe, specifically within the basal ganglia, thalamus, and interconnecting white-matter pathways (Cummings et al., 1993). These double dissociations forced a fundamental paradigm shift, moving the field away from regional phrenology and toward an account of separable cognitive processes supported by distributed neural networks.

The dominant contemporary framework for this architecture is the unity-and-diversity model, which characterizes cognitive control through the statistical intersection of latent variables (Miyake et al., 2000; Friedman & Miyake, 2017). Factor analyses demonstrate that executive performance is best explained by three distinct yet highly correlated vectors: working memory updating, inhibitory control, and set shifting. The model's central claim is a balance between two properties. Its diversity lies in the separability of these three components, each accounting for unique variance and, in principle, dissociable from the others. Its unity lies in their substantial shared covariance, which reflects a domain-general capacity for maintaining internal goal representations in the face of environmental interference. Genetic and longitudinal tracking confirms that these subdomains are both heritable and behaviourally distinct, rather than artifacts of measurement scaling (Friedman et al., 2008). This dual structure carries a direct implication for the anatomy of executive impairment, suggesting that if the components are partly separable, damage might in principle affect them differentially, whereas if they share a common core, damage to that core would degrade executive performance globally.

Working memory updating represents the dynamic mechanism of this system, requiring the continuous revision of information held online to guide immediate behaviour (Miyake et al., 2000). Distinct from the passive retention limits of short-term storage, updating demands active gatekeeping of incoming data, rapid erasure of obsolete task sets, and real-time reordering of operational priorities. This process is captured experimentally by the N-back paradigm (Kirchner, 1958), which forces the system to continuously overwrite its contents, a requirement that scales with fluid

intelligence and indexes a patient's capacity to navigate complex, non-automated environments.

Inhibitory control provides the necessary counterweight, suppressing automated or prepotent behavioral responses when they conflict with the current cognitive objective (Aron et al., 2004). The Stroop task (Stroop, 1935) serves as the classic paradigm for this construct, isolating the reaction-time cost imposed when semantic text conflicts with visual colour perception. This inhibitory gating is increasingly recognized as a multi-layered mechanism involving distinct frontostriatal braking loops (Aron et al., 2014). For the purposes of the present structural analysis, inhibition is treated as a single dimension within the unity-and-diversity framework, without attempting to resolve its finer subcomponents.

Set-shifting, or cognitive flexibility, is the most computationally expensive element of the triad, governing the capacity to disengage from a spent rule set and reconfigure the cognitive apparatus to operate under new parameters (Monsell, 2003). This operation subsumes both inhibitory and updating mechanisms, requiring a patient to deactivate a previously valid response matrix while simultaneously loading a new rule set into working memory. Mechanistically, it is indexed through the calculation of a switch cost (Rogers et al., 1995), the quantifiable degradation of speed or accuracy that accompanies a shifting rule boundary. The Trail Making Test Part B (TMT-B) (Reitan, 1958) provides a clinically accessible proxy for this operation by demanding rapid alternation between numerical and alphabetical sequences; subtracting the baseline visuomotor tracking time of Part A from the alternating performance of Part B yields a difference score that isolates the specific computational cost of cognitive reconfiguration (Sánchez-Cubillo et al., 2009).

### 1.2.2 NEUROPSYCHOLOGICAL ASSESSMENT OF EXECUTIVE DOMAINS

A bedside battery to assess executive function in acute stroke reflects this componential architecture. The Frontal Assessment Battery (FAB; Dubois et al., 2000) serves as a rapid global screen, sampling conceptualization, lexical flexibility, motor sequencing, and inhibitory control through brief, categorical tasks; The executive indices of the Oxford Cognitive Screen (OCS; Demeyere et al., 2015; Mancuso et al., 2018) were additionally administered as part of the broader cognitive assessment of the cohort. Across these instruments, the battery samples the three executive subdomains unevenly: the FAB's Conflicting Instructions and Go-No-Go items probe inhibitory control, its Lexical Fluency and Motor Series items engage flexibility and sequencing, and the Trail Making Test indexes set-shifting through the B-A difference, while working-memory updating, classically assessed with paradigms such as the N-back, is not directly captured by the bedside measures available in the acute setting. The battery thus affords both a global index of executive performance, in the FAB total, and partial coverage of the separable subdomains.

## 1.3 EXECUTIVE DYSFUNCTION IN THE ACUTE STROKE WINDOW

### 1.3.1 THE ACUTE WINDOW AND THE LESION-DEFICIT RELATIONSHIP

The relationship between a lesion and the deficit it produces is clearest in the acute phase. In the weeks and months that follow a stroke, the observed deficit is shaped not only by the structural injury itself but by the brain's response to it. Perilesional reorganization, the recruitment of alternative circuits, behaviourally driven plasticity, and the resolution of acute edema all act progressively to dissociate the deficit from its anatomical origin (Ward et al., 2003). A cognitive assessment performed early, before these compensatory processes have substantially remodelled the relationship between structure and behaviour, therefore offers the most direct window onto the lesion-deficit mapping that this thesis seeks to characterize. Assessment in the acute window carries a cost of its own, in that the transient contributions of edema and diaschisis are still present and inflate the apparent extent of injury (Cramer, 2008); but it avoids the larger

and more intractable confound of compensation, which accumulates over the subacute and chronic phases and increasingly obscures the structural signal (Jones, 2017).

Nonetheless, clinical stakes of that signal are not confined to the acute phase. Executive performance is among the strongest predictors of long-term functional independence after stroke (Laakso et al., 2019), and the association between post-stroke cognitive impairment and functional outcome holds to a similar degree from the early subacute phase out to several years post-stroke (Stolwyk et al., 2021). An executive deficit identified acutely is therefore not a transient epiphenomenon of the injury but an early marker of a clinically consequential trajectory. Characterizing which lesion patterns produce it is what makes this clinically actionable, in that it identifies the patients whose imaging should prompt closer cognitive scrutiny before the deficit has declared itself in the demands of daily life.

### 1.3.2 BRAIN AND COGNITIVE RESERVE

The deficit observed acutely depends not only on the lesion, but on the brain that sustained it. Two patients with structurally identical infarctions, matched in both volume and location, may present with markedly different executive impairment, because the capacity to absorb injury varies with premorbid reserve. As formalized by Stern and colleagues, this reserve operates through two distinct mechanisms (Stern, 2002, 2009; Stern et al., 2020). Brain reserve is the passive structural threshold of the nervous system, set by quantities such as baseline brain volume, neuronal count, or higher/lower integration/segregation of connections which dictates how much physical damage a network can absorb before functional impairment emerges. Cognitive reserve is an active, functional construct, the capacity to maintain performance through the recruitment of alternative circuits or compensatory strategies, for which years of formal education is the most widely validated proxy (Umarova et al., 2019). Advancing age operates against this pool, through subclinical small-vessel change (Pendlebury et al., 2009), which progressively diminish brain reserve and the capacity to reconfigure intact networks, so that older patients sustain more profound executive deficits for any given volume of tissue loss.

These baseline factors are not incidental to the anatomical question; they compete directly with it. Because age, education, and the sheer magnitude of injury each independently shape the acute deficit, any attempt to attribute executive impairment to the location of damage must first account for them. Without such control, an analysis risks rediscovering only the truism that larger, more severe strokes in older, less-educated patients produce worse outcomes (Shin et al., 2020). Isolating a genuinely topographic signal therefore requires statistically separating the location of damage from premorbid reserve and from injury magnitude.

## **1.4 FROM LOCALIZATION TO NETWORKS**

### **1.4.1 THE CLASSICAL PREFRONTAL PARADIGM AND ITS LIMITS**

The componential structure described above is cognitive; the question this thesis asks is anatomical. Where in the brain does damage produce these deficits? The empirical foundation of cognitive neurology historically answered such questions by mapping behaviour onto focal tissue destruction, and for executive control, that tradition began by localizing the function to the prefrontal cortex (Luria, 1964). While this localized model successfully classified elementary sensorimotor deficits, it falters when applied to the complex architecture of executive control (Mesulam, 1998). In clinical practice, three consistent observations undermine strict focal-lesion models. First, patients with anatomically matched frontal lesions frequently exhibit highly divergent executive profiles. Second, identical executive failures routinely emerge from lesions situated in entirely disparate regions of the brain, including the basal ganglia, thalamus, and deep white matter, far from the prefrontal cortex (Fox, 2018; Krause et al 2012). Third, executive deficits frequently arise from purely subcortical or white-matter damage that spares the cortex entirely, implicating structures remote from the prefrontal cortex in the production of the deficit (Grau-Olivares et al., 2007). Together, these inconsistencies give rise to the notion that a model only looking at the frontal lobe cannot account for a substantial proportion of the executive impairment observed after

stroke, because executive dysfunction is not the loss of an isolated regional module but the systemic failure of a distributed circuit.

#### 1.4.2 DIASCHISIS AND THE SHIFT TO LARGE-SCALE NETWORKS

Although stroke originates as a focal vascular event, its consequences are rarely confined to the site of injury. Because the brain operates as a set of interacting distributed networks, damage in one location disrupts the function of structurally connected but anatomically distant regions.

The recognition that local injury exerts remote functional consequences has deep roots in neurological theory, beginning with von Monakow's classical conceptualization of diaschisis, which described the functional silencing of intact tissue remote from, but interconnected with, a primary lesion (Monakow, 1914). This insight was later refined by Geschwind through the framework of disconnection syndromes (Geschwind, 1965), which attributed complex cognitive deficits to the structural severing of white-matter pathways linking specialized cortical zones. Modern network connectomics formalizes these classical principles by defining the brain as an interconnected graph (Sporns, 2011), in which a focal stroke acts as a topographical perturbation that alters the efficiency of long-range systems well beyond the lesion itself. Empirical neuroimaging bears this out; knowing which white-matter connections an infarct severs predicts how brain function is disrupted at sites distant from the lesion, for instance, the breakdown of coordinated activity between regions, more accurately than knowing the location and extent of the grey-matter damage alone (Griffis et al., 2019). In other words, where the lesion disconnects the brain can matter more than where it destroys tissue, establishing structural disconnection as a primary driver of broad cognitive and motor deficits (Kuceyeski et al., 2016). Post-stroke executive dysfunction is, on this account, increasingly characterized as a pathology of circuit disconnection rather than regional destruction.

## **1.5 COMPONENTS OF EXECUTIVE FUNCTION**

### **1.5.1 FRONTOPARIETAL AND SALIENCE CORTICAL NODES**

If executive function is supported by a distributed system rather than a single region, the first question is which cortical regions serve as its principal nodes. Functional neuroimaging has clarified this architecture by identifying three large-scale brain networks that collectively coordinate cognitive control, a framework formalized as the triple-network model (Menon, 2011). The default mode network, centred on the medial prefrontal and posterior cingulate cortices, governs internally directed cognition and typically undergoes suppression during cognitively demanding tasks (Raichle et al., 2001; Andrews-Hanna, 2012). The fronto-parietal network, anchored by the dorsolateral prefrontal and posterior parietal cortices, directly supports externally driven goal pursuit, including planning and rule application, the operations that the unity-and-diversity model identifies as updating and shifting (Seeley et al., 2007). Mediating between them, the salience or cingulo-opercular network unites the anterior insula and the dorsal anterior cingulate cortex to monitor the internal and external environments for behaviourally relevant cues (Menon et al., 2010).

Causal modelling and functional connectivity tracking indicate that the salience network, and specifically the right anterior insula, operates as a dynamic switchboard (Menon & Uddin, 2010; Goulden et al., 2014). It exerts a top-down influence that down-regulates default mode activity while recruiting central executive resources when an environmental shift demands a transition in cognitive mode. These cortical nodes are thus not interchangeable processors but functionally specialized hubs, each contributing a distinct operation to executive control, such that focal cortical damage produces deficits whose character depends on which node is affected.

### **1.5.2 THALAMIC AND BASAL GANGLIA SUBCORTICAL RELAY**

This cortical apparatus does not operate in isolation; it relies on parallel subcortical loops that modulate and gate cortical output. The frontal-subcortical circuit framework identifies distinct, parallel topographies projecting from the cortex through the striatum and globus pallidus to the thalamus, which in turn projects back to the originating

cortical target (Alexander et al., 1986; Cummings, 1993). The dorsolateral prefrontal cortex is a key node within a distributed fronto-parietal network that, while once primarily characterized by its anatomical loops, is now explicitly tied to executive subdomains such as set-shifting and working-memory updating (Alexander et al., 1986; Collette et al., 2005). Because these loops function as integrated processing units, an ischemic lesion located at any point along the circuit can mirror the clinical presentation of direct cortical injury. The cortico-basal ganglia-thalamocortical architecture relies on a hierarchical topological distribution of signal processing. Within this system, the basal ganglia output nuclei serve as a severe computational bottleneck, compressing high-dimensional cortical inputs into a limited-capacity signal (Hwang et al., 2017).

This compressed stream is subsequently routed to subcortical structures, notably the basal ganglia and thalamus. Rather than functioning as uniform global relays, precision functional mapping demonstrates that these structures are highly organized into discrete, network-specific territories and localized multi-network integration zones (Greene et al., 2020). These same subcortical territories participate in broader action-control systems such as the Somato-Cognitive Action Network (SCAN), which integrates goal-directed action with physiological and motor control rather than segregating cognition from movement (Gordon et al., 2023). By acting as structured gatekeepers, the basal ganglia and thalamus help maintain the modular architecture of the cerebral cortex. Consequently, a spatially-restricted subcortical infarction need not uniformly disrupt the entire cortico-thalamic system; an infarct localized to an integration hub can instead induce selective connectomal diaschisis, de-afferenting specific prefrontal association areas and the integrative territories these systems depend on. The resulting disruption of coordinated network activity can produce executive failures whose precise clinical presentation is shaped by individual variation in functional network topology (Gordon et al., 2017; Humphries, 2025).

### 1.5.3 WHITE MATTER TRACTS AND STRUCTURAL CONNECTIVITY

If the cortical nodes are the processors and the subcortical structures their gates, the white-matter tracts are the physical cables that connect them, and on which the synchronization of the whole distributed circuit depends. Structural and lesion evidence has implicated a frontal network of association and projection tracts in executive performance, with lateralization that varies by task demand (Ribeiro et al., 2024). This scaffold includes the superior longitudinal fasciculus, which couples frontal control regions with posterior parietal networks, and the frontal aslant tract, which links the inferior frontal gyrus to supplementary motor zones; the uncinate fasciculus bridges orbitofrontal and anterior temporal regions, while the anterior thalamic radiations carry the ascending projections of the frontostriatal loops (Alexander et al., 1986; Cummings, 1993). Interrupting these tracts degrades the synchronization on which distributed executive processing depends, which positions white-matter injury as a substantial contributor to executive impairment. The consequence is anatomically distinctive, in that a lesion confined to deep white matter may spare every cortical node and subcortical relay yet still produce marked executive deficit, purely by disconnecting intact grey-matter structures from one another.

## 1.6 METHODOLOGICAL RATIONALE FOR LESION-SYMPTOM MAPPING

### 1.6.1 LESION-SYMPTOM MAPPING AND REGION-BASED PARCELLATION

Relating the location of damage to the deficit it produces requires a method capable of doing so across a population of patients, and the clinical-pathological tradition of isolated case observation has been transformed into a quantitative group-level analysis through spatial normalization and in vivo neuroimaging. The earliest computational form of this enterprise, mass-univariate voxel-based lesion-symptom mapping (VLSM), evaluates the behavioural impact of injury at each voxel independently (Bates et al., 2003). For the study of a distributed function such as executive control, this approach carries two disabling limitations. The first is statistical: because the vascular

architecture of stroke produces highly correlated injury across neighbouring voxels, voxelwise analyses suffer severe spatial autocorrelation and a correspondingly heavy multiple-comparison burden (Pustina et al., 2017). The second is conceptual: a mass-univariate framework cannot represent configurations in which a deficit is jointly determined by damage to several structures, none of which is individually sufficient to produce it (Mah et al., 2014). A distributed deficit, in other words, demands a method that can model the joint contribution of multiple regions at once.

This motivates two departures from the classical approach. First, the analysis is multivariate; rather than testing each location in isolation, it models whole-brain lesion configurations simultaneously, an approach for which regularized regression is well suited because the L2 penalty of ridge regression stabilizes coefficient estimation in the high-dimensional, collinear predictor spaces characteristic of stroke data (DeMarco & Turkeltaub, 2018; Pustina et al., 2018; Karnath et al., 2018). Second, the spatial unit shifts from the individual voxel to the anatomically defined region. Aggregating voxels into regions of interest restricts the predictor space to dimensions appropriate for a moderate sample (Kimberg et al., 2007). Crucially, this approach aligns the unit of measurement with current network-level account of executive control, directly mapping onto the cortical nodes, subcortical relays, and white-matter tracts that constitute its structural substrates (Bressler & Menon 2010; Figley et al., 2015). These substrates can be captured by established cortical, subcortical, and white-matter parcellations, aligning the unit of analysis with the level at which the network account makes its claims.

#### 1.6.2 DUAL-AXIS DAMAGE METRICS FOR FOCAL LESIONS AND STRUCTURAL DISCONNECTION

How a region is counted as "damaged" is itself a modelling decision, and the network account of executive function makes a single definition insufficient. The conventional approach defines regional injury by focal overlap, which is the proportion of a region's grey matter directly destroyed by the infarct (Foulon et al., 2018). This accurately indexes the loss of local computational tissue, but, as the preceding sections

established, it is blind to a distinct mechanism of injury. A lesion confined to white matter may leave a grey-matter region structurally intact while severing the connections through which it communicates, functionally isolating it without destroying it. Characterizing injury by direct overlap alone would therefore misattribute the mechanism of such deficits and underestimate the true network-level footprint of the stroke.

The analysis consequently evaluates injury along two parallel axes. The first is focal damage, the direct destruction of grey matter at a region. The second is structural disconnection. By projecting each patient's lesion onto a normative tractography template derived from healthy population data, the white-matter streamlines passing through the lesion can be identified, and each grey-matter region assigned a disconnection load reflecting the proportion of its normal structural connectivity lost to the injury (Foulon et al., 2018). Treating focal damage and structural disconnection as separate predictors allows for analysis of whether a given executive deficit tracks the destruction of specialized regions or the disconnection of the circuits that link them.

### 1.6.3 CROSS-VALIDATION, VARIANCE DECOMPOSITION AND PERMUTATION

Modelling whole-brain lesion configurations in a moderately sized cohort raises a genuine risk of overfitting, and a valid topographic claim must therefore satisfy three requirements. First, predictive accuracy must be assessed out-of-sample, so that it reflects generalization to unseen patients rather than fit to the sample at hand (Varoquaux, 2018). Second, and central to the thesis question, the unique contribution of lesion location must be isolated from the demographic and severity factors that independently predict the deficit, since predictive accuracy alone would otherwise risk rediscovering only that larger, more severe strokes in older patients produce worse outcomes (Corbetta et al., 2015). Third, because regularized, cross-validated models do not admit a closed-form significance test, inference must be established non-parametrically.

## 1.7 AIMS AND HYPOTHESES

The preceding sections have established the clinical importance of post-stroke executive dysfunction, the componential structure of executive function, the network-level architecture that supports it across cortical, subcortical, and white-matter substrates, the baseline factors that modulate the relationship between brain damage and cognitive outcome, and the methodological rationale through which that relationship can be characterized. The present thesis brings these together in a single question: which components of the distributed executive system, when damaged by acute stroke, predict the executive deficit observed at the bedside, each fitted separately of the magnitude of that damage? The aim is to characterize the distributed pattern of damage that predicts executive impairment, with explicit separation of lesion location from the injury-magnitude and reserve factors with which it is otherwise confounded. Pursuing this aim begins with a behavioural characterization of executive impairment in the cohort, its prevalence, the relationships among measures, and their dependence on stroke severity, which grounds the anatomical analysis that follows. This aim is addressed through four hypotheses.

### *Hypothesis 1*

Measures of executive function will demonstrate shared covariance with one another and with baseline stroke severity, as both measures index the common cognitive demands and diffuse pathophysiological consequences of acute vascular injury. Critically, however, the executive measures will retain shared variance after adjustment for stroke severity and demographic factors.

### *Hypothesis 2*

Lesion location will predict executive performance beyond the variance explained by lesion volume, stroke severity, age, and education. The structural signature of executive dysfunction is therefore predicted to be topographic, and not merely about how much tissue is destroyed or how clinically severe the stroke is. This is the central hypothesis of the thesis, and the variance-decomposition approach set out above is how it is tested,

since only the unique contribution of lesion location, isolated from the magnitude and reserve confounds, constitutes evidence for a genuinely topographic account.

### *Hypothesis 3*

The topographic signature of executive dysfunction will span multiple anatomical substrates rather than localizing to any single one. Specifically, white-matter disconnection is predicted to contribute to the prediction of executive performance alongside focal grey-matter damage, consistent with a network-level account in which the deficit arises not only from the destruction of computational tissue but from the interruption of the connections through which preserved tissue communicates. The structural-disconnection characterization is predicted to capture variance not fully accounted for by focal lesion overlap, supporting the inclusion of disconnection as a distinct and informative axis of damage.

### *Hypothesis 4*

Insofar as the cortical signature of executive impairment proves localizable, it is predicted to implicate the cortical nodes of the salience network, the anterior insula, frontal operculum, and dorsal anterior cingulate cortex, prominently among cortical regions. This prediction follows from the network's established role as the cortical coordinator of executive control, detecting behaviourally relevant events and governing transitions between internally and externally directed cognition. The present structural design can test whether damage to these regions predicts executive impairment, but cannot observe the coordinating dynamics that the functional literature proposes as the underlying mechanism.

## **2 METHODS**

### **2.1 PARTICIPANTS**

Participants were drawn from an ongoing prospective cohort of acute stroke patients enrolled at the Neurology Clinic of the University of Padova between May 2021 and October 2024. The full baseline (T0) dataset comprised 124 patients assessed within the first weeks following stroke. Inclusion criteria for the present analysis were: (i) absence of post-enrolment exclusion; (ii) availability of a manually segmented lesion mask; and (iii) complete neuropsychological data on the Frontal Assessment Battery (FAB), Trail Making Test parts A and B (TMT-A, TMT-B), and the Oxford Cognitive Screen executive subtests. Both ischemic and hemorrhagic strokes were retained, the single hemorrhagic case on the rationale that perilesional edema in the acute phase produces functional disconnection with cognitive consequences captured by the lesion mask. Application of these criteria yielded a final analyzable cohort of 60 patients.

Healthy control data collected under the same protocol were available but were not analyzed here, the present lesion-symptom mapping design requiring lesion-bearing patients only. The study was approved by the local Ethics Committee of the University Hospital of Padova (Study AOP1995 code CESC 4996/AO/21, approval protocol 22903/2021), and all participants or their legal representatives provided written informed consent in accordance with the Declaration of Helsinki.

### **2.2 NEUROPSYCHOLOGICAL ASSESSMENT**

All patients underwent a standardized neuropsychological assessment at baseline (T0), administered at a median of 6 days post-stroke (IQR 4 to 9). The present analysis draws on two instruments of executive function, the FAB, the TMT, together with a measure of language function, the Esame Neuropsicologico per l'Afasia (ENPA), used to characterize the relationship between executive and language performance in the cohort. For each measure, performance was interpreted against Italian normative data providing age- and education-adjusted cutoffs, ensuring that classification of

impairment reflected deviation from demographically matched expectations rather than raw performance alone.

The Frontal Assessment Battery (Dubois et al., 2000) is a brief bedside instrument yielding a total score from 0 to 18 across six subtests, each scored from 0 to 3: Similarities, assessing conceptualization; Lexical Fluency, assessing mental flexibility; Motor Series, assessing motor programming; Conflicting Instructions, assessing sensitivity to interference; Go-No-Go, assessing inhibitory control; and Prehension Behaviour, assessing environmental autonomy. The FAB total served as the principal measure of global executive function in the analyses that follow. In addition, because the six subtests index partially distinct executive processes, each was examined individually, permitting the global score to be decomposed into its component demands. The Prehension Behaviour subtest was excluded from these subscore analyses owing to a pronounced ceiling effect, with 58 of 60 patients scoring at maximum, leaving no usable variance; the remaining five subtests were retained. Impairment on the FAB total was defined by the Italian normative cutoff of Aiello and colleagues (2022), with an adjusted score at or below 12.02 indicating impairment.

The Trail Making Test (Reitan, 1958) was administered in its standard two-part form. Part A requires the sequential connection of numbered targets and indexes visuomotor processing speed and visual scanning; Part B requires alternation between numerical and alphabetical sequences and additionally taxes set-shifting and cognitive flexibility (Sánchez-Cubillo et al., 2009). Completion times in seconds were recorded, with administration capped at a ceiling of 420 seconds. A derived difference score, TMT B minus A (TMT B-A), was computed to isolate the set-shifting component by subtracting the processing-speed demand common to both parts; this difference score provides the closest available approximation to a switch-cost index within the battery, although as a difference between two timed and partially ceiling-bounded measures it is necessarily noisier than its constituents. Impairment was defined using the Italian normative cutoffs of Siciliano and colleagues (2019): adjusted completion times at or

above 127 seconds for TMT-A, at or above 294 seconds for TMT-B, and at or above 163 seconds for the TMT B-A difference score.

The executive subtests of the Oxford Cognitive Screen (OCS; Demeyere et al., 2015), a stroke-specific cognitive screening instrument, were administered as part of the cohort's broader cognitive characterization. Owing to pronounced ceiling effects that left insufficient variance for multivariate modelling at the present sample size, the OCS executive subtests were not used as an outcome in the lesion-symptom mapping analyses and are not analyzed further here.

Language function was assessed with the Esame Neuropsicologico per l'Afasia (Capasso & Miceli, 2001), a standardized Italian aphasia battery. Eleven ENPA subscores were combined into a single language composite, spanning repetition (of words, non-words, and sentences), reading (of words, non-words, and sentences), naming (nouns), and auditory and visual comprehension (of words and sentences). Because the ENPA provides a graded, multi-domain assessment of language rather than the brief screening afforded by the executive instruments, it was selected as the cohort's primary language measure to quantify the association between language and executive performance. In addition, the severity of aphasia at presentation was indexed by the Best Language item of the baseline NIHSS, scored from 0 (no aphasia) to 3 (mute or global aphasia).

## **2.3 MRI ACQUISITION**

All patients underwent structural magnetic resonance imaging at a median of 6 days post-stroke, acquired on a 3-Tesla scanner using the standard stroke imaging protocol of the Neurology Clinic of the University of Padova. The protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), fMRI, and diffusion-weighted sequences.

## 2.4 LESION SEGMENTATION AND SPATIAL NORMALIZATION

Lesion segmentation was performed manually on each patient's FLAIR sequence, on which acute and subacute lesions appear as regions of hyperintensity, using ITK-SNAP (Yushkevich et al., 2006). The T1-weighted and remaining sequences were available to support anatomical localization where required. Hyperintense regions corresponding to acute or subacute infarction, or to acute haemorrhage in the single hemorrhagic case, were delineated voxel by voxel in native space. Imaging was reviewed for quality and adequacy of coverage prior to inclusion. Each patient's native-space structural image was registered to MNI152 1mm standard space using ANTs with rigid, affine, and deformable transformations and enantiomorphic lesion filling for more accurate registration (Nachev, 2008); the resulting transformation was then applied to the binary lesion mask. All masks were inspected for adequate registration prior to inclusion.

## 2.5 ATLAS-BASED LESION-LOAD COMPUTATION

Lesion effects were characterized at the level of anatomically and functionally defined regions, rather than at the level of individual voxels, for the reasons set out in Section 1.61, where region-based predictors reduce the dimensionality of the lesion data to a tractable scale, yield estimates at the level at which the network account makes its claims and are better suited than mass-univariate voxelwise testing to a sample of moderate size. Three established atlases were used, spanning the cortical, subcortical, and white-matter substrates of the distributed executive system, and each lesion was characterized through two complementary metrics: focal damage, quantifying the tissue a lesion destroys, and structural disconnection, quantifying the connectivity a lesion severs.

### *Atlases*

Cortical parcellation was provided by the Schaefer 2018 atlas at the 100-region, 7-network resolution (Schaefer et al., 2018), in MNI152 1mm space. Subcortical parcellation was provided by the Tian 2020 atlas at Scale 1 (Tian et al., 2020), comprising 16 bilateral regions spanning the thalamus, caudate, putamen, globus

pallidus, nucleus accumbens, hippocampus, and amygdala. White-matter tracts were defined by the Yeh 2022 HCP1065 population-averaged tractography atlas (Yeh, 2022); of the available tracts, the peripheral cranial nerve tracts were excluded as not relevant to cerebral cognition, leaving 77 cerebral tracts. The 100-region cortical and Scale 1 subcortical resolutions were selected as a deliberate balance between anatomical specificity and predictor count, coarser parcellations concentrating rather than dispersing lesion-related signal at the present sample size.

#### *Focal Lesion Load*

For each grey-matter region in the cortical and subcortical atlases, focal lesion load was computed as the proportion of that region's voxels intersecting the patient's binary lesion mask, expressed as a value between zero and one. For each white-matter tract, the analogous focal metric was the proportion of the tract's streamlines passing through the lesion, computed by intersecting each tract's streamlines, drawn from the normative HCP1065 tractography, with the patient's lesion mask in MNI152 1mm space and dividing the number of intersecting streamlines by the tract's total streamline count.

#### *Structural Disconnection*

Structural disconnection maps were generated for each patient using the Disconnectome procedure of the BCBtoolkit (Foulon et al., 2018). In this procedure, the patient's lesion is projected onto a normative tractography dataset to estimate, at each voxel, the probability that it is structurally disconnected because of the lesion; the resulting probabilistic map is thresholded at the toolbox's standard value of 0.5 to yield a binary disconnection map. These maps were provided in MNI152 1mm space. From them, a regional structural-disconnection load was computed for each cortical and subcortical region as the proportion of that region's voxels flagged as disconnected, paralleling the focal-overlap metric but reflecting severed connectivity rather than direct tissue damage. Structural disconnection was computed at the cortical and subcortical levels only; the white-matter tract analysis, being itself a measure of disconnection, was not duplicated in this form.

### *Predictor Set*

Combining the three atlases with the two–damage metrics yielded seven predictor sets through which the anatomy of each behavioural outcome was examined. Five were anatomically specific: cortical focal and cortical disconnection (each a 100-region matrix), subcortical focal and subcortical disconnection (each a 16-region matrix), and white-matter focal (a 77-tract matrix). Two were composite, formed by linking the cortical and subcortical regions into a single 116-region grey-matter matrix in each of its focal and disconnection versions, providing a whole-grey-matter characterization alongside the substrate-specific sets. Each predictor set, for each outcome, was carried forward to the statistical analysis described in the following section, where its capacity to predict executive performance was assessed and the unique contribution of lesion location isolated from demographic and severity confounds.

## **2.6 STATISTICAL ANALYSES**

All analyses were conducted in Python using NumPy, pandas, scikit-learn, nibabel, Nilearn, and DIPY (Harris et al., 2020; McKinney, 2010; Pedregosa 2012; Brett et al., 2024; Abraham et al., 2014; Garyfallidis et al., 2014). The analysis proceeded in three stages: a behavioural characterization of executive performance and its relationship to clinical and demographic variables; a principal component analysis of the FAB subscores to establish their latent structure; and the lesion-symptom mapping itself, in which the contribution of lesion location to each executive outcome was estimated, isolated from confounds, and tested for significance.

### *Behavioural Analyses*

The behavioural analyses tested Hypothesis 1, that the executive measures share variance not reducible to injury severity or premorbid factors. Relationships among the executive measures, and between each measure and stroke severity, were quantified by Pearson correlation. To establish whether the executive measures shared variance beyond what was attributable to overall injury and premorbid factors, partial correlations were computed with adjustment for age, education, and log-transformed

lesion volume, and separately with the additional inclusion of baseline NIHSS. The unique contribution of stroke severity to each executive measure was assessed by the change in explained variance when NIHSS was added to a model already containing age, education, and log lesion volume.

#### *Principal Component Analysis*

To characterize the latent structure of the FAB and to determine whether its subscores indexed separable processes or a single dominant dimension, a principal component analysis was performed on the five retained FAB subscores (Similarities, Lexical Fluency, Motor Series, Conflicting Instructions, and Go-No-Go; the Prehension subtest having been excluded for ceiling, as described in Section 2.2). Also serving Hypothesis 1, the analysis was characterizational rather than a primary mapping outcome: its purpose was to establish whether the FAB total could be interpreted as a unitary index of executive impairment, justifying its use as the principal outcome in the tests that follow, and to identify any secondary axis of variation among the subscores.

#### *Lesion-symptom Mapping Model*

The lesion-symptom mapping provided the test of Hypotheses 2 to 4, which concern whether and how lesion location predicts executive performance; the modelling choices described in this and the following three subsections apply to all three. Lesion-symptom mapping was conducted separately for each behavioural outcome and each of the seven predictor sets defined in Section 2.5, using ridge regression (L2-regularized linear regression). Ridge was selected over sparse alternatives such as the LASSO because, in a predictor space of spatially correlated anatomical regions in which signal is expected to be distributed rather than concentrated at a single locus, the L2 penalty shrinks coefficients smoothly while retaining all predictors, rather than arbitrarily selecting one of several collinear regions. Each model comprised the anatomical predictor matrix together with four covariates: age, years of education, log-transformed lesion volume, and baseline NIHSS. All predictors and covariates were standardized to zero mean and unit variance prior to fitting. The ridge regularization

parameter was selected within each model by internal cross-validation across a logarithmically spaced range of candidate values.

#### *Out-of-sample Performance*

The predictive performance of each model was estimated by leave-one-out cross-validation (LOOCV): the model was fitted on all patients but one and used to predict the held-out patient, the procedure repeated across all sixty patients, and the predictions aggregated into a cross-validated coefficient of determination (LOOCV  $R^2$ ). LOOCV was preferred to k-fold cross-validation at this sample size because partitioning sixty patients into a small number of folds yields unstable performance estimates dominated by the composition of individual folds, whereas leave-one-out uses the maximum available training set at each step and tests on every patient in turn. Out-of-sample LOOCV  $R^2$ , rather than in-sample fit, was treated throughout as the measure of whether a lesion-deficit relationship generalized.

#### *Variance Decomposition*

The variance decomposition operationalized Hypothesis 2 directly: the central question was not whether a model predicted an outcome, but whether lesion location predicted it beyond the variance already explained by the demographic and severity covariates. The topography-unique  $R^2$  is therefore the quantity by which Hypothesis 2 stands or falls. This was addressed by a drop-one-out decomposition of the cross-validated explained variance. For each outcome and predictor set, a full model containing the anatomical predictors together with all four covariates was compared against a reduced model containing the covariates alone; both models were estimated under identical leave-one-out cross-validation. Comparing the topography-unique variance across the seven predictor sets, and between focal and disconnection metrics within each substrate, provided the test of Hypothesis 3, that the signature spans multiple substrates and that disconnection contributes alongside focal grey-matter damage. The topography-unique  $R^2$ , defined as the difference between the full-model LOOCV  $R^2$  and the covariates-only LOOCV  $R^2$ , quantified the variance in the outcome attributable to lesion location over and above age, education, lesion volume, and severity. The same

procedure, removing each covariate in turn from the full model, quantified the unique contributions of the individual covariates, permitting the topographic signal to be compared directly against the contributions of severity and age.

#### *Permutation Testing*

Significance for the tests of Hypotheses 2 and 3 was established non-parametrically. Because ridge regression yields biased coefficients without an analytic significance test, and because the cross-validated performance metric has no closed-form null distribution, the significance of the topography-unique contribution was established by permutation. For each outcome and predictor set, the outcome values were randomly shuffled across patients, breaking any true association between lesion pattern and behaviour while preserving the structure of the predictor matrix, and the full fitting, cross-validation, and variance-decomposition procedure was repeated on the permuted data. This was performed across 1000 permutations to construct an empirical null distribution of the topography-unique  $R^2$  under the hypothesis of no lesion-deficit relationship. The permutation p-value was the proportion of permuted topography-unique values equaling or exceeding the observed value. This test was deliberately framed at the level of the whole predictor set rather than the individual region, asking whether the multivariate lesion pattern as a whole carried information about the outcome beyond the covariates; given that regularization distributes signal across correlated predictors by design, inference at the level of the model is the appropriate frame, and the coefficients of individual regions are accordingly interpreted as descriptions of where signal concentrates within a significant model rather than as independently significant regional localizations.

#### *Regional Coefficient Interpretation*

To address Hypothesis 4, that the cortical signature, where localizable, implicates salience-network nodes, the standardized ridge coefficients within each significant cortical model were ranked by magnitude, and the anatomical identity of the most heavily weighted regions examined. Consistent with the model-level framing of the permutation test, these rankings were interpreted descriptively, as indicating where

predictive signal concentrates within a significant model, rather than as independently tested regional localizations.

#### *Correction for Multiple Comparisons*

The topography-unique permutation test was applied across the full factorial combination of four outcomes (FAB total, TMT-A, TMT-B, and the TMT B-A difference score) and seven predictor sets, yielding a family of 28 tests. To control the false discovery rate across this family, Benjamini-Hochberg correction was applied to the 28 permutation p-values, and significance was evaluated at a corrected threshold of  $q < 0.05$ . No outcome or predictor set was excluded from this correction; the full family was corrected as a single set, such that the reported significance of any individual result reflects its standing among all tests performed.

#### *Confirmatory Analysis of FAB Component Structure*

As a robustness check on the unitary-FAB interpretation underlying Hypothesis 1, the first two principal components of the FAB were additionally submitted to the same lesion-symptom mapping procedure as a confirmatory analysis. This examined whether the dominant general component reproduced the anatomical signature of the FAB total, and whether the secondary component, capturing variation among the subscores, carried any unique anatomical signal of its own.

#### *ENPA Language Composite*

To characterize the relationship between executive and language performance, an ENPA language composite was formed as the mean of eleven z-standardized ENPA subscores (spanning repetition, reading, naming, and comprehension), each standardized across the cohort to zero mean and unit variance. This composite was correlated with FAB total, with a FAB sub-total recomputed after removing the Lexical Fluency subtest, and with TMT-B, using Spearman correlation as the primary statistic given the skewed distribution of language scores in a predominantly non-aphasic cohort, with Pearson correlations additionally reported. These analyses were restricted to the 50 of 60 patients with available ENPA data; the missing cases reflected incomplete administration unrelated to language status.

### *Sensitivity Analyses for Language*

Two sensitivity analyses tested whether the FAB topographic signal was attributable to co-occurring language impairment. In the first, the FAB total was residualized on the ENPA language composite, regressing language out of the outcome within each cross-validation fold to avoid leakage, and the full variance decomposition was repeated on the language-residualized scores across all seven predictor sets ( $n = 50$ , the patients with complete ENPA data). In the second, the same procedure was applied using the NIHSS Best Language item in place of the ENPA composite, retaining all 60 patients. For each analysis, the topography-unique  $R^2$  and its FDR-corrected significance were compared against the primary FAB result, and the ridge coefficient vectors were correlated (Spearman) with the primary-FAB coefficient vectors to test whether any residual signal localized to the same structures.

### 3 RESULTS

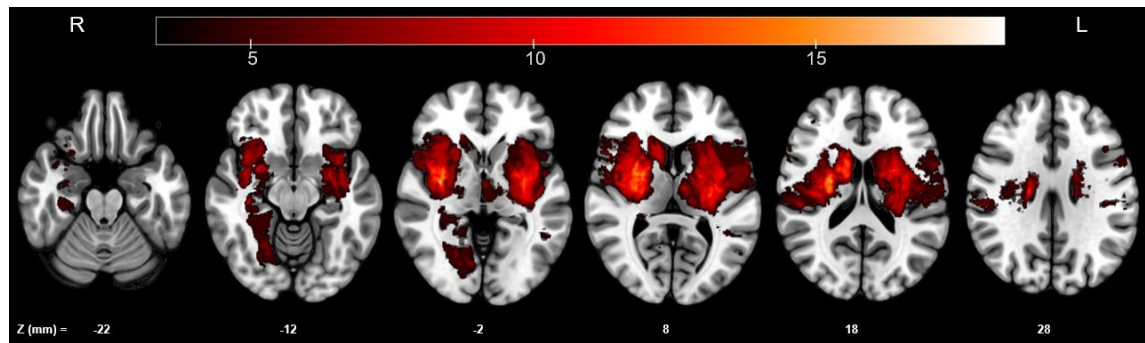
#### 3.1 COHORT AND BEHAVIOURAL PERFORMANCE

The final cohort comprised 60 patients with acute stroke (37 men, 23 women), with a mean age of 63.1 years (SD 14.6, range 25 to 85) and a median of 11 years of formal education. Stroke severity at presentation was predominantly mild to moderate, with a median baseline NIHSS of 4 (IQR 2 to 7) and a mean of 6.0 (SD 5.9), though the range extended to 23, capturing a tail of more severely affected patients. At neuropsychological evaluation, 47 of 60 patients (78.3%) showed no language impairment on the NIHSS Best Language item; 7 (11.7%) showed mild-to-moderate aphasia, 2 (3.3%) severe aphasia, and (6.7%) were mute or globally aphasic. Lesions were distributed across the left hemisphere ( $n = 26$ ), the right hemisphere ( $n = 23$ ), and bilaterally ( $n = 11$ ), and lesion volume was strongly right-skewed (median 11,909 mm<sup>3</sup>, range 46 to 166,988). Of the 60 patients, 59 had ischemic strokes and one had an intraparenchymal hemorrhage (a left temporo-occipital bleed). The ischemic strokes were classified by TOAST criteria as undetermined cause ( $n = 21$ ), cardioembolic ( $n = 20$ ), large-artery atherosclerosis ( $n = 9$ ), other determined cause ( $n = 7$ ; comprising three cases with an identified but atypical mechanism, two internal carotid artery dissections, one vertebral artery dissection, and one pulmonary arteriovenous malformation), and small-artery occlusion ( $n = 2$ ). Neuropsychological evaluation was performed at a median of 6 days post-stroke (IQR 4 to 9), and structural MRI within a comparable acute window (median 6 days). The voxel-wise distribution of lesions across the cohort is shown in Figure 1. Of the 60 strokes, 59 were ischemic and one was an intraparenchymal hemorrhage; the ischemic subtypes and the full demographic profile are detailed in Section 2.1 and Table 1. Neuropsychological assessment and structural imaging were both performed at a median of 6 days post-stroke.

**Table I:** Demographic and clinical characteristics of the cohort

| Characteristic                                 | Value                    |
|------------------------------------------------|--------------------------|
| N                                              | 60                       |
| Age, years - mean (SD); range                  | 63.1 (14.6); 25–85       |
| Education, years - median                      | 11                       |
| Sex - n men / n women                          | 37 / 23                  |
| Hemisphere - left / right / bilateral, n       | 26 / 23 / 11             |
| Stroke type - ischemic / hemorrhagic, n        | 59 / 1                   |
| NIHSS - mean (SD); median (IQR); range         | 6.0 (5.9); 4 (2–7); 0–23 |
| Lesion volume, mm <sup>3</sup> - median; range | 11,909; 46–166,988       |
| Time to assessment, days - median              | 6                        |

*Note.* NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range. Lesion volume is reported as median given its right-skewed distribution; it was log-transformed for all analyses.

**Figure 1:** Lesion overlap density across the cohort.

*Note.* Lesion overlap density across the cohort. Voxel-wise overlap of all 60 binary lesion masks in MNI152 1mm standard space, shown in neurological convention (image left = patient left) on representative axial slices ( $z = -22$  to 28 mm). Colour indicates the percentage of patients with a lesion at each voxel, from 3.3% (dark red) to a maximum of 18.3% (bright yellow); Coverage was concentrated in peri-Sylvian, insular, and deep middle-cerebral-artery territory of both hemispheres.

Performance on the executive measures showed the distributional features characteristic of an acute mild-to-moderate stroke cohort assessed with these

instruments (Table 2). FAB total scores were ceiling-weighted, with a median of 16 out of 18, but the distribution extended downward to a minimum of 3, identifying a subgroup of substantially impaired patients; the mean was 14.4 (SD 4.4). Applying the Italian age- and education-adjusted cutoff (Aiello et al., 2022), 13 of 60 patients (21.7%) were classified as impaired on the FAB. The Trail Making Test showed the expected separation between its two parts: TMT-A had a median completion time of 43 seconds (range 16 to 240), while TMT-B was substantially slower at a median of 148.5 seconds, with 18 of 60 patients (30.0%) reaching the 420-second administration ceiling, reflecting the greater cognitive demand of the alternating condition. By the Italian normative cutoffs (Siciliano et al., 2019), 7 of 60 patients (11.7%) were impaired on TMT-A and 18 of 60 (30.0%) on TMT-B, with 14 of 60 (23.3%) impaired on the derived TMT B-A difference score (cutoff  $\geq 163$  s).

**Table II:** Executive performance and impairment rates

| Measure    | Central Tendency           | Range  | Impaired, n (%) |
|------------|----------------------------|--------|-----------------|
| FAB total  | Mean 14.4<br>Median 16.0   | 3–18   | 13 (21.7)       |
| TMT-A, s   | Mean 66.1<br>Median 43     | 16–240 | 7 (11.7)        |
| TMT-B, s   | Mean 210.8<br>Median 148.5 | 41–420 | 18 (30.0)       |
| TMT B-A, s | Mean 114.7<br>Median 105   | 16–372 | 14 (23.3)       |

*Note.* FAB, Frontal Assessment Battery; TMT, Trail Making Test. Impairment classified against Italian age- and education-adjusted normative cutoffs (FAB, Aiello et al., 2022; TMT, Siciliano et al., 2019). TMT-B administration was capped at a 420-second ceiling, reached by 18 of 60 patients.

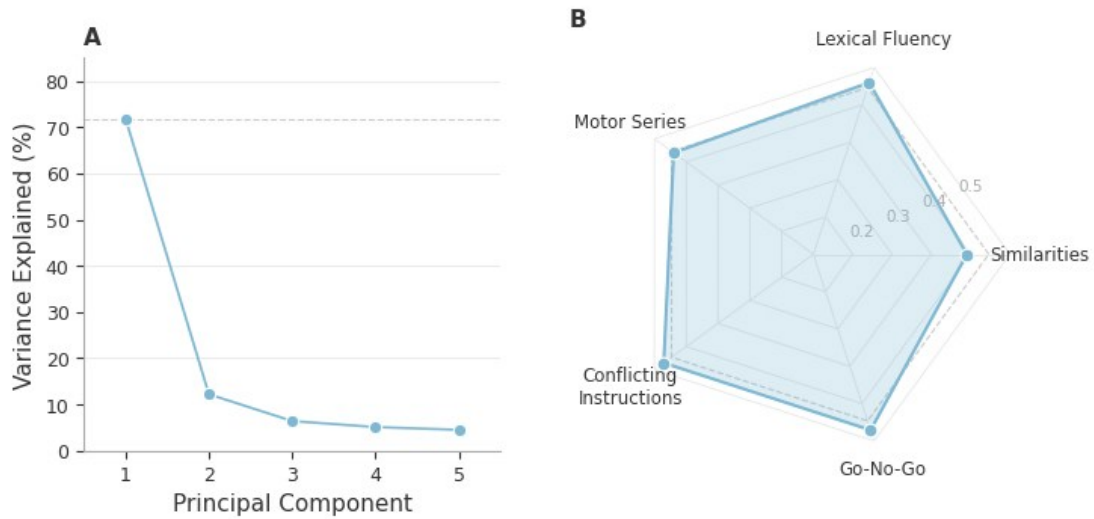
The executive measures were substantially intercorrelated, consistent with their shared dependence on common executive demands. FAB total correlated strongly and

negatively with both Trail Making measures (TMT-A,  $r = -0.784$ ; TMT-B,  $r = -0.709$ ), worse global frontal performance corresponding to slower completion times. Critically for the interpretation that executive impairment is not merely a reflection of overall stroke severity, these relationships were only modestly attenuated by adjustment for age, education, and lesion volume (partial  $r = -0.730$  and  $-0.664$  respectively), and remained substantial after the further inclusion of stroke severity (partial  $r = -0.713$  and  $-0.605$  with NIHSS added). The shared executive variance among these measures therefore persisted after demographic and severity adjustment.

Stroke severity was itself related to executive performance but did not account for the bulk of the variance. Baseline NIHSS correlated with FAB total ( $r = -0.545$ ) and with TMT-B ( $r = +0.415$ ), greater clinical severity corresponding to worse performance on both. However, the unique contribution of severity was partial: adding NIHSS to a model already containing age, education, and lesion volume raised the explained variance in FAB by 14.7% and in TMT-B by 7.9%, leaving the majority of executive variance unexplained by injury magnitude alone.

This pattern has a specific implication for the analyses that follow. If executive impairment were simply a by-product of how severe the stroke was, then stroke severity should account for most of the variance in executive performance, but it does not: most of that variance remains after severity, age, education, and lesion volume are taken into account. Executive impairment is therefore not reducible to a generalized consequence of injury magnitude; it carries information of its own, which is what justifies asking, as the anatomical analyses now do, whether that residual variance is explained by where the damage falls.

**Figure 2:** Latent structure of the FAB.



*Note:* Principal component analysis of the five retained FAB subscores (Similarities, Lexical Fluency, Motor Series, Conflicting Instructions, and Go-No-Go; Prehension excluded for a ceiling effect). (A) Scree plot of the variance explained by each principal component. A single dominant component accounted for 71.8% of the total variance, the second for 12.2%, and each of the remaining three for less than 7%. (B) Loadings of the five subscores on the first principal component, shown on a common radial axis spanning 0 to 0.5. All five subscores loaded positively and within a narrow range (0.39-0.47); the dashed reference circle marks the mean loading (0.43). This uniform loading structure supports interpretation of the FAB total as a unitary index of global executive function, as treated throughout the primary analyses.

The latent structure of the FAB (Figure 2) was examined by principal component analysis of its five retained subscores (Similarities, Lexical Fluency, Motor Series, Conflicting Instructions, and Go-No-Go; Prehension excluded for ceiling). A single dominant component emerged, accounting for 71.8% of the variance, on which all five subscores loaded positively and comparably (loadings 0.39 to 0.47). This pattern, a single large general factor with uniform positive loadings, indicates that the FAB total score is dominated by a general dimension of executive impairment rather than reflecting a heterogeneous aggregate of separable abilities, and supports its interpretation and use as a unitary index of global executive function in the analyses that follow. The second component accounted for only 12.2% of the variance and distinguished the Similarities subtest (loading +0.82) from the motor and inhibitory

subtests; the remaining three components each accounted for less than 7% and were not interpreted.

Within this subsample, a composite of the ENPA language subscores correlated strongly with FAB total (Spearman  $\rho = 0.68$ ; Pearson  $r = 0.74$ ,  $p < .001$ ). This association was only modestly reduced when Lexical Fluency was removed from the FAB total ( $\rho = 0.65$ ), positing that the relationship between executive and language performance was not confined to the FAB's single verbal-fluency item but was distributed across the battery. A weaker association was present for TMT-B ( $\rho = -0.72$ ;  $r = -0.53$ ), the non-verbal set-shifting measure.

### **3.2 LESION-SYMPTOM MAPPING**

Correcting for multiple comparisons across the entire family of 28 regularized models, which mapped the four behavioural outcomes across each of the seven anatomical matrices, revealed a selective distribution of topographic signals. Following the Benjamini-Hochberg procedure to control the false discovery rate, the Frontal Assessment Battery emerged as the sole executive metric where the unique contribution of lesion location survived model-level significance testing. The variance decomposition and permutation results for all outcomes and predictor sets are reported in Table 3; the central finding is a dissociation between the global frontal screener, whose relationship to lesion location was robust, and the timed trail-making measures: for pure processing speed (TMT-A) the topographic signal was effectively absent (a true null, with unique variance at or below zero), whereas for the set-shifting measures (TMT-B, TMT B-A) a weak signal was present but did not survive correction for multiple comparisons.

**Table III:** Variance decomposition and permutation testing of the topographic contribution to each executive outcome across seven anatomical representations.

| Outcome   | Predictor set     | Full R <sup>2</sup> | Cov. R <sup>2</sup> | Topo-<br>unique R <sup>2</sup> | p     | q            |   |
|-----------|-------------------|---------------------|---------------------|--------------------------------|-------|--------------|---|
| FAB total | Cortical SDC      | 0.426               | 0.282               | <b>0.144</b>                   | 0.004 | <b>0.033</b> | * |
|           | Subcortical SDC   | 0.405               | 0.282               | <b>0.122</b>                   | 0.002 | <b>0.028</b> | * |
|           | WM focal          | 0.432               | 0.282               | <b>0.150</b>                   | 0.006 | <b>0.033</b> | * |
|           | Grey matter focal | 0.430               | 0.282               | <b>0.148</b>                   | 0.005 | <b>0.033</b> | * |
|           | Grey matter SDC   | 0.441               | 0.282               | <b>0.159</b>                   | 0.002 | <b>0.028</b> | * |
|           | Cortical focal    | 0.410               | 0.282               | <b>0.128</b>                   | 0.007 | <b>0.033</b> | * |
|           | Subcortical focal | 0.359               | 0.282               | 0.077                          | 0.026 | 0.077        | . |
| TMT-A     | Cortical focal    | 0.257               | 0.257               | -0.000                         | 0.913 | 0.927        |   |
|           | Cortical SDC      | 0.257               | 0.257               | -0.000                         | 0.917 | 0.927        |   |
|           | Subcortical focal | 0.257               | 0.257               | -0.000                         | 0.927 | 0.927        |   |
|           | Subcortical SDC   | 0.257               | 0.257               | -0.000                         | 0.918 | 0.927        |   |
|           | WM focal          | 0.253               | 0.257               | -0.003                         | 0.886 | 0.927        |   |
|           | Grey matter focal | 0.257               | 0.257               | -0.000                         | 0.922 | 0.927        |   |
|           | Grey matter SDC   | 0.257               | 0.257               | -0.000                         | 0.922 | 0.927        |   |
| TMT-B     | Cortical focal    | 0.385               | 0.384               | 0.001                          | 0.132 | 0.176        |   |
|           | Cortical SDC      | 0.409               | 0.384               | 0.025                          | 0.067 | 0.114        |   |
|           | Subcortical focal | 0.399               | 0.384               | 0.015                          | 0.073 | 0.114        |   |
|           | Subcortical SDC   | 0.421               | 0.384               | 0.037                          | 0.033 | 0.077        | . |
|           | WM focal          | 0.437               | 0.384               | 0.053                          | 0.031 | 0.077        | . |
|           | Grey matter focal | 0.394               | 0.384               | 0.010                          | 0.110 | 0.147        |   |
|           | Grey matter SDC   | 0.431               | 0.384               | 0.047                          | 0.036 | 0.078        | . |
| TMT B-A   | Cortical focal    | 0.274               | 0.267               | 0.007                          | 0.039 | 0.078        | . |
|           | Cortical SDC      | 0.297               | 0.267               | 0.030                          | 0.047 | 0.088        | . |
|           | Subcortical focal | 0.280               | 0.267               | 0.013                          | 0.082 | 0.121        |   |

|                   |       |       |       |       |       |   |
|-------------------|-------|-------|-------|-------|-------|---|
| Subcortical SDC   | 0.309 | 0.267 | 0.042 | 0.029 | 0.077 | · |
| WM focal          | 0.329 | 0.267 | 0.062 | 0.022 | 0.077 | · |
| Grey matter focal | 0.278 | 0.267 | 0.011 | 0.069 | 0.114 |   |
| Grey matter SDC   | 0.318 | 0.267 | 0.051 | 0.032 | 0.077 | · |

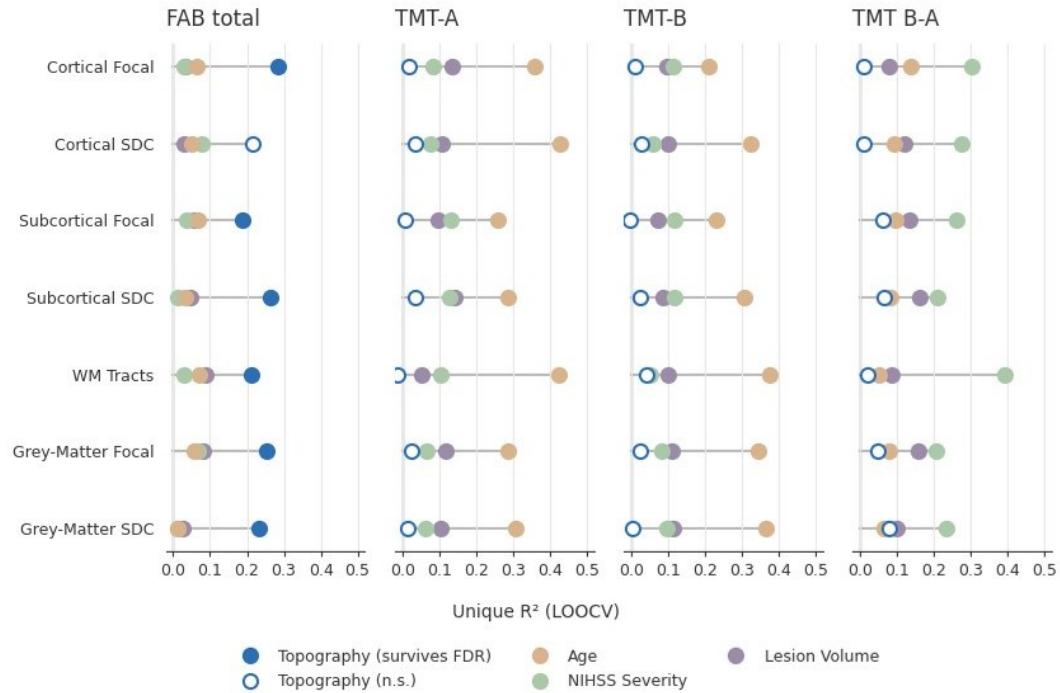
---

*Note.* Each row reports a ridge model containing the anatomical predictor set together with four covariates (age, education, log lesion volume, NIHSS). Full  $R^2$  and Cov.  $R^2$  are leave-one-out cross-validated coefficients of determination for the full model and the covariates-only model, respectively; topographic-unique  $R^2$  is their difference.  $p$  is the permutation  $p$ -value for the topographic contribution (1000 permutations);  $q$  is the Benjamini-Hochberg false-discovery-rate value across the full family of 28 tests. \*  $q < 0.05$  (survives correction); ·  $0.05 \leq q < 0.10$  (trend). SDC, structural disconnection; WM, white matter; Grey matter, combined cortical-plus-subcortical grey-matter matrix.

For the FAB, lesion location contributed unique variance beyond age, education, lesion volume, and stroke severity in six of the seven anatomical representations, all surviving Benjamini-Hochberg correction across the 28-test family. The topography-unique variance for FAB outcomes ranged from 0.122 to 0.159 across the six surviving representations (all  $q \leq 0.033$ ) and spanned every substrate of the analysis: cortical (focal  $q = 0.033$ , disconnection  $q = 0.033$ ), subcortical disconnection ( $q = 0.028$ ), white-matter ( $q = 0.033$ ), and the two combined whole-grey-matter representations (focal  $q = 0.033$ , disconnection  $q = 0.028$ ). The single FAB representation that did not survive correction was subcortical focal damage (topography-unique 0.077,  $q = 0.078$ ), which reached only trend level; notably, the subcortical contribution did survive in its disconnection form, suggesting that the subcortical involvement in FAB performance was better captured by the connectivity a lesion severed than by the grey matter it directly destroyed. The full-model cross-validated performance for the surviving FAB representations ranged from an LOOCV  $R^2$  of 0.405 to 0.441, against a covariates-only baseline of 0.282, so that lesion location raised the explained variance by roughly half above what demographic and severity factors alone achieved. The fact that this topographic contribution was significant across focal, disconnection, and combined representations, and across all three anatomical substrates, establishes that FAB

performance after stroke is robustly predicted by where damage falls, and not only by its magnitude or by the patient’s demographic profile.

**Figure 3:** Variance decomposition of executive performance across seven representations



*Note:* For each behavioural outcome (FAB total, TMT-A, TMT-B, and the TMT B–A difference score) and each of seven anatomical predictor sets (rows), dots show the unique cross-validated variance (LOOCV R<sup>2</sup>) attributable to

lesion topography and to the covariates age, NIHSS stroke severity, and lesion volume; a stem connects each row to the zero line. Topography dots are filled where the topographic contribution survived Benjamini–Hochberg FDR correction across the full 28-test family ( $q < 0.05$ ) and open where it did not. Education was included as a covariate in all models but contributed negligible unique variance throughout and is omitted here for visual clarity. All four panels share a common x-axis. Topography contributed significant unique variance for FAB total in six of seven representations (topography-unique R<sup>2</sup> = 0.122–0.159, all  $q < 0.05$ ), spanning cortical, subcortical, white-matter, and combined grey-matter substrates; only subcortical focal damage fell short of correction. No representation survived correction for any timed trail-making measure: TMT-A showed no topographic contribution in any representation, while TMT-B and TMT B–A reached only trend level ( $q \geq 0.077$ ), concentrated in the white-matter and disconnection representations.

The contrast with pure processing speed was complete. For TMT-A, lesion location contributed essentially no unique variance in any representation: topography-unique values were at or below zero throughout (range  $-0.003$  to  $-0.000$ ), and none approached significance (all  $q = 0.927$ ). The full models for TMT-A predicted performance at an LOOCV  $R^2$  of approximately 0.257, almost entirely attributable to the covariates, with age the dominant contributor. This comprehensive null is itself informative, in that a measure of visuomotor processing speed, which has no strong a priori reason to depend on the specific location of damage, showed no topographic signal whatsoever.

The two set-shifting-related measures occupied an intermediate position, showing topographic signals that were detectable but did not survive correction. For raw TMT-B, topography-unique variance was near zero in the focal grey-matter representations (cortical focal 0.001; subcortical focal 0.015) but reached 0.037 to 0.053 in the disconnection and white-matter representations (subcortical disconnection  $q = 0.077$ , white-matter  $q = 0.077$ , grey matter disconnection  $q = 0.078$ ), clustering at trend level. The isolated set-shifting cost, TMT B-A, showed the same pattern slightly more consistently: its strongest topographic contribution was in the white-matter representation (topography-unique 0.062,  $q = 0.077$ ), with further trend-level signals in subcortical and grey matter disconnection (both  $q = 0.077$ ). In both measures, the topographic signal appeared specifically in the white-matter and disconnection representations and was absent or negligible in focal grey-matter terms, and in neither case did any representation survive correction. The full TMT-B and TMT B-A models were, like TMT-A, dominated by age (see Figure 3). These results indicate at most a weak, disconnection-associated topographic contribution to set-shifting performance, insufficient at the present sample size to be distinguished from chance after correction.

Taken together, the variance decomposition establishes a clear dissociation. Global executive performance, as captured by the FAB, is anatomically localizable: lesion location predicts it robustly, across every substrate and every form of damage characterization, and survives stringent correction. Timed set-shifting and processing-

speed performance, as captured by the Trail Making Test, is not: TMT-A shows no topographic signal at all, and the set-shifting measures show only trend-level signals concentrated in disconnection space that do not survive correction. The anatomy of this localizable FAB signal, which structures and tracts carry it, is the subject of the next section.

### **3.3 THE ANATOMY OF THE FAB SIGNATURE**

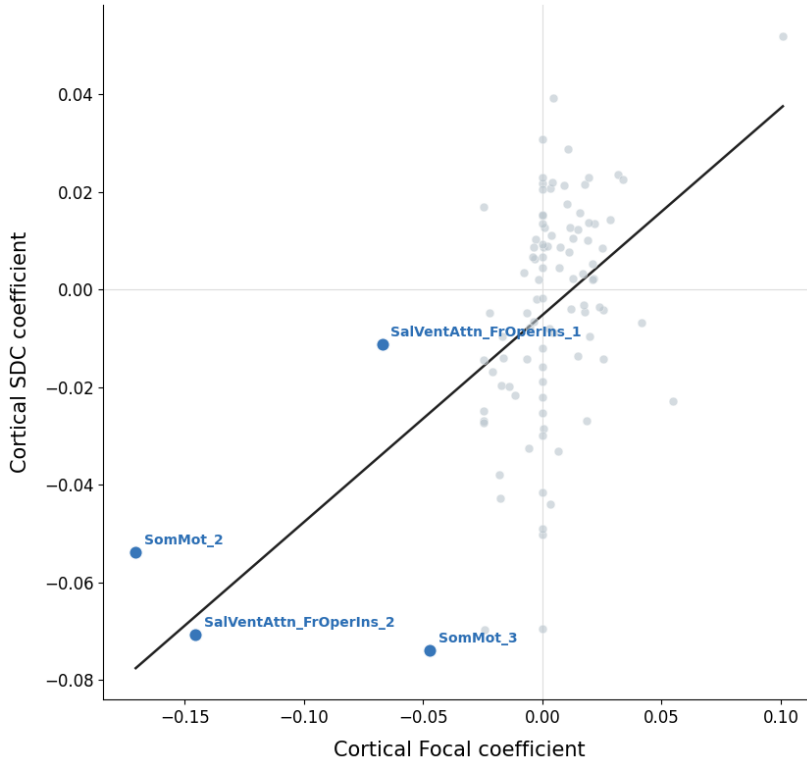
The six FAB representations that survived correction localize the executive signal to a consistent set of structures. Before describing them, a methodological qualification governs their interpretation. The permutation test established significance at the level of the whole predictor set, not the individual region; ridge regression, moreover, distributes weight across correlated predictors and shrinks individual coefficients. The regional coefficients reported below are therefore to be read as a description of where the predictive signal concentrates within each significant model, rather than as a set of independently significant regional localizations. With that qualification, one feature is common to every surviving model and is the most robust anatomical observation of the analysis: the FAB signal is overwhelmingly left-lateralized. Across cortical, subcortical, white-matter, and combined representations, the predictors carrying the largest weight in the direction of worse performance were almost exclusively in the left hemisphere, with right-hemisphere regions contributing little or, where they appeared, in the opposite direction.

In the cortical models, the FAB signal concentrated in left peri-Sylvian cortex. The most heavily weighted regions were the left somatomotor cortex and the left salience-network nodes of the frontal operculum and anterior insula, all loading in the direction of worse FAB performance with greater damage. This pattern was consistent across the focal and disconnection representations: in the cortical disconnection model, the same left somatomotor regions and the FrOperIns\_2 frontal-opercular parcel appeared among the top predictors (see the cortical convergence analysis in this section for the divergent behavior of the two frontal-opercular parcels), alongside left prefrontal

default-network and cingulate-control regions. The prominence of the salience-network frontal-opercular and insular nodes is consistent with the hypothesized involvement of this network in executive control (Hypothesis 4), and these regions were reliably among the top cortical predictors across models. They did not, however, stand alone: the left somatomotor cortex was weighted comparably or more heavily, rather suggesting that the cortical signature is better described as a left peri-Sylvian territory encompassing both salience-network and adjacent sensorimotor cortex than as a salience-network locus in isolation.

To quantify this convergence, the standardized ridge coefficients of the Cortical Focal and Cortical SDC models were correlated across all 100 Schaefer parcels (Pearson  $r = 0.53$ , Spearman  $\rho = 0.45$ ; both  $p < .001$ ), indicating substantial spatial agreement between the two damage metrics' cortical patterns. This correlation was materially unchanged when restricted to regions meeting the coverage-adequacy criteria on either metric ( $r = 0.53$ ,  $\rho = 0.46$ ), indicating the association is not driven by agreement among poorly-sampled regions. Because focal damage and structural disconnection are derived from the same underlying lesion masks, they are not statistically independent measures; this analysis is accordingly interpreted as evidence of spatial coincidence consistent with a shared anatomical circuit, rather than as convergence between independent methods. The reported p-values assume spatial independence across parcels, an assumption violated by cortical adjacency effects, and should be treated as indicative rather than exact; the correlation coefficients themselves are the more robust summary statistic.

**Figure 4:** Spatial convergence of cortical focal-damage and structural-disconnection for the FAB.



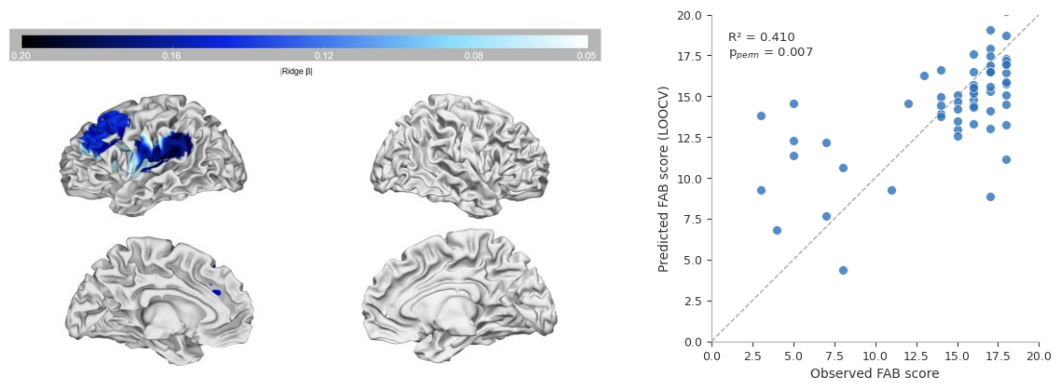
*Note:* Region-wise comparison of standardized ridge-regression coefficients from the Cortical Focal model (x-axis) and the Cortical SDC model (y-axis), one point per Schaefer 100-region parcel ( $N = 100$ ). The fitted regression line indicates the spatial association between the two damage metrics' coefficient patterns (Pearson  $r = 0.53$ , Spearman  $\rho = 0.45$ ). The four regions carrying the largest coefficients in the focal model are labelled: left somatomotor parcels (SomMot\_2, SomMot\_3) and left frontal-opercular parcels (FrOperIns\_1, FrOperIns\_2). Note that FrOperIns\_2, despite its salience-network label, was anatomically localised to dorsolateral prefrontal territory (Section 3.3). Because focal damage and structural disconnection are derived from the same lesion masks, the correlation reflects spatial coincidence consistent with a shared circuit rather than agreement between independent measures.

The four cortical regions carrying the largest coefficients in the focal model — left somatomotor cortex (SomMot\_2, SomMot\_3) and the left salience-network frontal-opercular parcels (FrOperIns\_1, FrOperIns\_2) — were examined for their ranking within the disconnection model. Three of the four ranked among the five most heavily weighted regions in the disconnection model (SomMot\_3, rank 1 of 28; FrOperIns\_2,

rank 2 of 28; SomMot\_2, rank 5 of 28), supporting convergence at the level of individual regions as well as the aggregate correlation. The fourth region, FrOperIns\_1, the anatomically-verified insula/operculum parcel, as distinct from FrOperIns\_2, which despite its salience-network label was independently confirmed via centroid coordinates to lie in dorsolateral prefrontal territory, ranked 22nd of 28 in the disconnection model despite meeting coverage-adequacy criteria in both analyses. This indicates that the salience-network convergence between focal and disconnection metrics is carried primarily by the DLPFC-territory parcel rather than the anatomically verified insula/operculum node, a distinction the present data cannot further resolve.

This cortical signature must be read against the coverage of the cohort, in that adequate lesion sampling was concentrated in peri-Sylvian, insular, and sensorimotor territory, with posterior and dorsomedial regions sparsely represented. The cortical findings therefore identify where the signal falls among the regions this cohort can interrogate, and do not exclude contributions from regions it could not adequately sample.

**Figure 5:** Cortical signature of FAB performance and out-of-sample prediction.



*Note:* (A) Ridge-regression coefficients for the cortical focal-damage model of FAB total, projected onto the cortical surface (Schaefer 100-region parcellation). Colour encodes standardised coefficient magnitude (single-hue blue,  $|\beta|$  range (0.05-0.20); All displayed coefficients were negative (greater focal damage associated with worse FAB performance). The signal is left-lateralised, concentrated in left frontal-opercular and insular salience-network cortex and adjacent left somatomotor cortex. Coefficients describe where predictive signal concentrates within a significant multivariate model and are not separately fitted at the level of individual regions. (B) Leave-one-out cross-validated predicted FAB score plotted against observed FAB score for the same cortical focal-damage model.

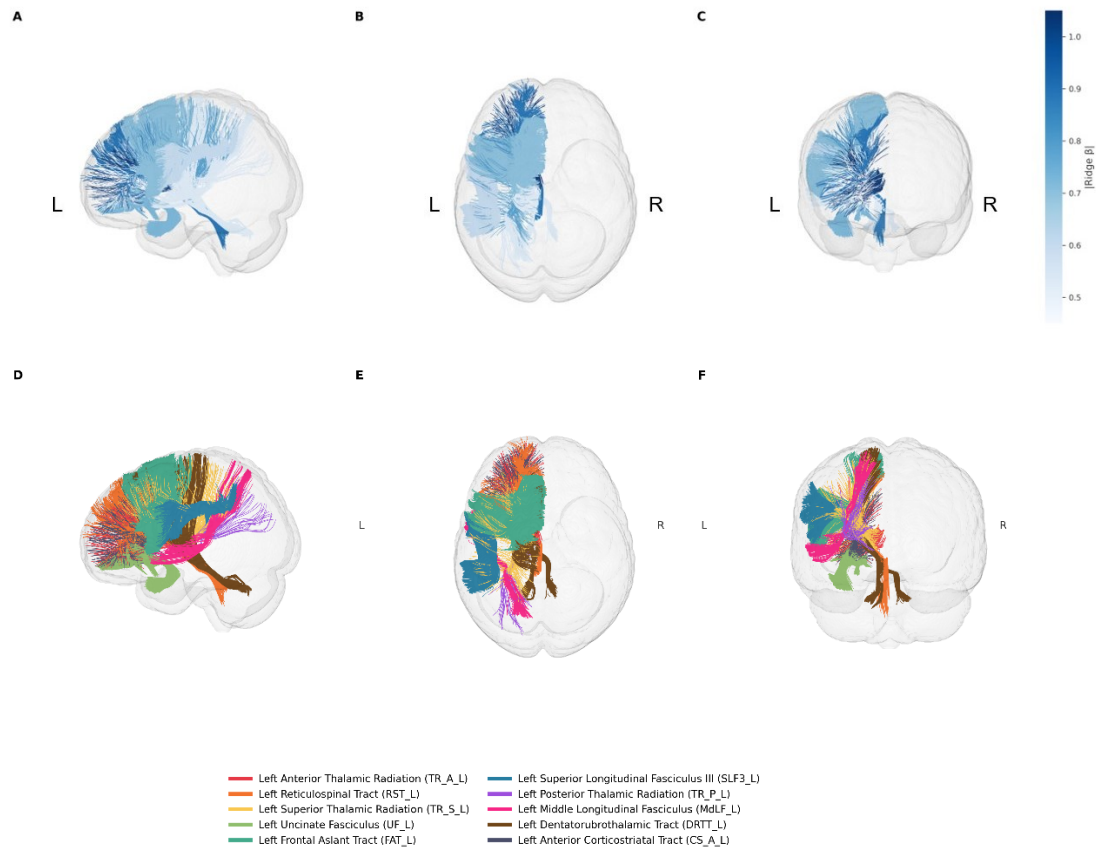
Each point is one patient; the dashed line is identity. The model explained significant variance out-of-sample beyond demographic and severity covariates (full-model LOOCV  $R^2 = 0.410$ ; topography-unique  $R^2 = 0.128$ ,  $p_{\text{perm}} = 0.007$ ,  $q = 0.033$ ).

The subcortical model, significant in its disconnection form, localized the FAB signal to the left basal ganglia and thalamus. The most heavily weighted regions, all in the direction of worse performance with greater disconnection, were the left globus pallidus, nucleus accumbens, putamen, anterior thalamus, and caudate, a contiguous left striatal-pallidal-thalamic set. Right-hemisphere subcortical regions contributed negligibly. This signature corresponds closely to the frontostriatal-thalamic circuitry described in Section 1.52, in which the striatum, pallidum, and thalamus form the subcortical limb of the loops supporting executive control, and it indicates that disconnection of these left subcortical structures from their cortical partners is associated with worse global executive performance. That the subcortical contribution was significant in its disconnection form but only trend-level in its focal form (Section 3.2) reinforces a narrative: the executive consequence of subcortical damage tracked the connectivity disrupted more closely than the grey matter destroyed.

The white-matter model localized the FAB signal to a set of left-hemisphere association and projection tracts (Figure 6). The most heavily weighted, all loading toward worse performance with greater disconnection, comprised left frontal association tracts, the superior longitudinal (SLF3 and SLF2) and frontal aslant tracts, the uncinate, and the middle longitudinal fasciculus, together with projection tracts, the anterior and superior thalamic radiations and the reticulospinal and dentatorubrothalamic tracts. The association tracts correspond closely to the left-lateralized frontal network that recent synthesis has identified as central to executive function (Section 1.53): the superior longitudinal and frontal aslant tracts connecting frontal control regions to parietal and premotor cortex, and the uncinate linking orbitofrontal and anterior temporal cortex. The prominence of the thalamic radiations and of the reticulospinal and dentatorubrothalamic projection tracts alongside these association pathways indicates

that the white-matter signal was not confined to classical executive tracts but extended to the projection systems linking frontal, motor, and subcortical nodes, consistent with the somatomotor involvement seen in the cortical signature. The convergence of the white-matter signature on this left frontomotor-thalamic system, independently of the grey-matter analyses, indicates that disruption of the long-range connections of the left peri-Sylvian–frontostriatal–thalamic circuit is itself a substantial correlate of global executive impairment.

**Figure 6:** White matter tracts contributing to FAB performance.



*Note:* The ten highest-ranked tracts of the white-matter focal model, which survived false-discovery-rate correction (topographic-unique  $R^2 = 0.150$ ,  $q = 0.033$ ;  $N = 60$ ), rendered as streamline bundles on a semi-transparent MNI152 glass brain. Three views are shown: left sagittal (A), superior axial (B), and anterior coronal (C). Tracts are coloured by the magnitude of their standardized ridge coefficient (single-hue blue,  $|\beta|$  range 0.45–1.05; darker indicates greater magnitude); all coefficients were negative (greater tract damage associated with worse FAB performance). The signal was carried by left frontal association tracts (superior longitudinal fasciculus III, frontal aslant tract,

uncinate fasciculus, middle longitudinal fasciculus) together with projection tracts (anterior, superior, and posterior thalamic radiations, anterior corticostriatal tract, reticulospinal tract, dentatorubrothalamic tract), a consistently left-lateralized frontomotor and thalamic distribution evident in the superior and coronal views. Coefficients describe where signal concentrates within a significant multivariate model and are not separately fitted at the level of individual tracts. For anatomical identification, the same ten tracts and viewing angles are reproduced in panels D-F below with each tract assigned a distinct, non-magnitude colour and labelled individually.

To characterize where these tracts reach the cortical surface, their endpoints were projected onto the fsaverage cortex (Figure 5b). The endpoint clusters fell on left precentral and superior frontal cortex, with further contributions to left inferior frontal, temporal, and medial frontal (supplementary motor) regions. These cortical territories overlap with the regions independently implicated by the Schaefer-based cortical lesion analysis. This overlap should be read as anatomical grounding rather than as a second, independent result: the endpoint projection and the cortical lesion analysis share an underlying anatomical substrate, since a tract necessarily terminates near the cortex it connects, and the convergence therefore reflects the coherence of a single distributed circuit characterized through two complementary windows rather than two statistically independent findings.

The three substrate-specific signatures describe a single coherent picture. The cortical, subcortical, and white-matter analyses, each conducted separately, converged on the same left-lateralized frontomotor-thalamic circuit: peri-Sylvian cortex including salience-network frontal-opercular and insular nodes, the left striatal-pallidal-thalamic grey matter, and the left frontal association and projection tracts that connect them. The two combined whole-grey-matter models, which were the strongest of the surviving representations (Section 3.2), reproduced this same pattern, their top predictors integrating the left subcortical and left peri-Sylvian cortical regions identified separately, and adding no structure not already implicated in the substrate-specific analyses. This convergence is the central anatomical result of the thesis. It supports the hypothesis that the structural signature of post-stroke executive dysfunction spans multiple anatomical substrates rather than localizing to any one (Hypothesis 3), with

disconnection contributing alongside, and at the subcortical level more strongly than, focal grey-matter damage. It supports, more specifically, the prediction that the cortical component would implicate salience-network nodes (Hypothesis 4), while qualifying that prediction: the salience-network frontal operculum and insula are prominent and consistent contributors, but they form part of a broader left peri-Sylvian and frontostriatal circuit rather than constituting the signature on their own.

### **3.4 SET-SHIFTING COST**

The Trail Making Test results in Section 3.2 showed that timed set-shifting performance, unlike global FAB performance, was not robustly localizable. A more targeted question concerns the set-shifting cost in isolation. Raw TMT-B completion time confounds set-shifting with the visuomotor processing speed also required by TMT-A, and TMT-A in this cohort carried no topographic signal whatever. The derived difference score, TMT B-A, removes the shared processing-speed demand and isolates the additional cost of alternating between sequences, providing the closest approximation in the battery to a pure index of shifting. Examining its anatomy therefore offers the most direct structural test of set-shifting that the present data allow.

Isolating the shifting cost in this way produced a topographic signal that, while modest, was both stronger and more consistent than that of raw TMT-B. Where TMT-B's topographic contribution had been negligible in focal grey-matter terms and reached only trend level in the disconnection representations, TMT B-A showed its clearest signal in the white-matter representation (topography-unique  $R^2 = 0.062$ ), with further trend-level contributions in the subcortical and combined disconnection representations. The signal was, in every case, a feature of the white-matter and disconnection representations rather than of focal grey-matter damage: subtracting the processing-speed component revealed a contribution expressed through disrupted connectivity. In this respect the shifting cost patterned with the disconnection-weighted profile already seen, weaker, in raw TMT-B, and stood in contrast to the focally-expressed and far stronger FAB signal.

Notwithstanding this internal consistency, none of the TMT B-A representations survived correction for multiple comparisons. The strongest, in the white-matter representation, reached a corrected  $q$  of 0.078, within the trend band but short of the  $q < 0.05$  threshold, as did its subcortical and combined disconnection counterparts (Table 3). The shifting-cost signal is therefore best characterized as a consistent but statistically unconfirmed trend: detectable, concentrated specifically in disconnection space, and more coherent than that of the raw measure, but not of a magnitude that can be distinguished from chance at the present sample size once the full family of tests is accounted for.

### 3.5 SUPPLEMENTARY ANALYSES

#### *Confirmatory Analysis of the FAB Component Structure*

To verify that the FAB total result was not an artifact of aggregating heterogeneous subtests, the first two principal components of the FAB were submitted to the same lesion-symptom mapping procedure as the primary outcomes, corrected within their own family of 14 tests (two components across the seven representations). The first component, the general impairment factor accounting for 71.8% of the subtest variance, behaved almost identically to the FAB total. Its topographic signal survived correction in six of seven representations, the same six that survived for the FAB total, with closely matching topography-unique variance (0.123 to 0.153). More directly, the region-wise correlation between the PC1 ridge coefficients and the FAB-total ridge coefficients was near-unity in every predictor set ( $r = 0.992$  to  $0.999$ ), establishing that the general component and the total score recover not merely comparable performance but essentially the same anatomical pattern. The second component, which accounted for 12.2% of the variance and captured the axis distinguishing the Similarities subtest from the motor and inhibitory subtests, showed no reliable topographic signal: it failed correction in six of seven representations ( $q = 0.115$  to  $0.954$ ), with a single marginal exception in the subcortical focal representation ( $q = 0.036$ ) that was isolated and not reproduced in any other. The FAB total can therefore be interpreted, as the primary

analyses have treated it, as a unitary index of executive impairment whose anatomical signature is carried by its dominant general dimension, while the residual variance that distinguishes the subtests from one another carries essentially no anatomical signal of its own.

#### *Subscore-level Lesion-symptom Mapping*

Although the FAB total is dominated by a single general factor, the individual subtests were additionally examined as outcomes, within a separate 35-test correction family (five subscores  $\times$  seven representations), to characterize their relationship to lesion topography (Table S1). Four of the five subscores carried a topographic signal that survived correction. Lexical Fluency was the strongest, reaching a topography-unique  $R^2$  of 0.283 in the white-matter representation exceeding even the FAB total in magnitude and constituting the single most robust topographic effect in the analysis; Conflicting Instructions localized across all seven representations, and Similarities and Motor Series each survived in several, while Go-No-Go survived in none. Critically, as the coefficient rankings below show, the subscores that localized did so to the same left-lateralized anatomy, not to dissociable substrates.

**Table IV:** FAB subscore lesion-symptom mapping

|                             | Cortical<br>Focal | Cortical<br>SDC | Subcortical<br>Focal | Subcortical<br>SDC | WM<br>Tracts | Whole<br>Grey<br>Focal | Whole<br>Grey<br>SDC |
|-----------------------------|-------------------|-----------------|----------------------|--------------------|--------------|------------------------|----------------------|
| Lexical<br>Fluency          | 0.209****         | 0.264****       | 0.069**              | 0.191**            | 0.283****    | 0.194****              | 0.260****            |
| Similarities                | 0.001*            | 0.041*          | 0.106**              | 0.115**            | 0.145**      | 0.056*                 | 0.137**              |
| Motor Series                | 0.026*            | 0.015*          | 0.134**              | 0.069**            | 0.031*       | 0.076**                | 0.053*               |
| Conflicting<br>Instructions | 0.086**           | 0.171**         | 0.061**              | 0.089**            | 0.122**      | 0.096**                | 0.099**              |
| Go-No-Go                    | 0.029*            | 0.019*          | 0.000                | 0.002*             | 0.008        | 0.019*                 | 0.004                |

*Note:* Subscore-level lesion-symptom mapping: topographic contribution across seven anatomical representations. Topography-unique  $R^2$  for each of the five retained FAB subscores across the seven predictor sets, from ridge models adjusted for age, education, log lesion volume, and NIHSS. Significance reflects Benjamini-Hochberg

correction within the 35-test subscore family (five subscores  $\times$  seven representations). \*\*\*\*  $q < 0.001$ ; \*\*\*  $q < 0.01$ ; \*\*  $q < 0.05$ ; \*  $0.05 \leq q < 0.10$ ; unmarked, not significant. SDC, structural disconnection; WM, white matter; Whole, combined cortical-plus-subcortical grey-matter matrix.

Examination of the coefficient rankings showed that the surviving subscores concentrated their signal on the same left-lateralized structures that carried the FAB-total and PC1 signatures: the left frontal-opercular and insular salience-network cortex and the left somatomotor cortex among cortical regions; the left putamen, pallidum, caudate, and anterior thalamus among subcortical regions; and the left thalamic radiations, frontal aslant tract, uncinate, and superior longitudinal fasciculus among white-matter tracts. Lexical Fluency, the strongest subscore, drew on precisely this left peri-Sylvian–frontostriatal–thalamic circuit, differing from the other subscores in the magnitude of its loadings rather than in their location. This convergence is consistent with the principal component result, where the subtests localize because they share the general executive factor that carries the anatomical signal, and the variance that distinguishes them from one another, isolated in the second principal component, does not localize. The subscore-level deficits in this cohort are therefore best understood as graded expressions of a common distributed substrate rather than as evidence of anatomically dissociable executive component processes.

Two cautions qualify the subscore findings. First, the FAB subtests differed substantially in their ceiling rates, from 22 of 60 at maximum for Similarities to 47 of 60 for Conflicting Instructions, and Go-No-Go, the one subtest with no surviving topographic signal, was among the more ceiling-bound. The amount of usable variance available to each subscore analysis therefore differed, and the pattern of which subscores localized cannot be fully separated from this distributional constraint. Second, the subscore analyses share the cortical coverage limitations described below. These results are accordingly reported as a characterization of the subtests' shared anatomy.

### *Lesion Coverage*

The interpretability of the regional findings depends on how adequately each atlas region was sampled by the lesions in the cohort. Coverage was quantified by counting, for each region, the number of patients with any lesion involvement and the number with substantial involvement (at least 10% of the region), a region being considered adequately covered when at least five patients had any involvement and at least three had substantial involvement. The three atlases differed markedly. Subcortical and white-matter coverage was good: 11 of 16 subcortical regions (69%) and 58 of 77 white-matter tracts (75%) were adequately covered, with no subcortical region and only three tracts entirely unsampled, and with balanced left–right representation. Cortical coverage, by contrast, was sparse: only 16 of 100 cortical regions (16%) met the adequacy threshold, 63 were sparsely sampled, and 21 were not lesioned in any patient. This cortical sparsity is an expected feature of an unselected acute stroke cohort, as the deep middle-cerebral-artery territory most often involved delivers lesions preferentially to subcortical grey matter and the white-matter tracts of the corona radiata, so that any given cortical parcel is lesioned in comparatively few patients even when overall cortical involvement is common. Importantly, the adequately-covered cortical regions were concentrated in the same peri-Sylvian, insular, and sensorimotor territory that carried the FAB and subscore signals, so that the cortical signal did not arise from unstable estimates in poorly-sampled regions but from among the best-sampled parcels in the cohort.

### *Sensitivity of the FAB Signature to Language*

The strong association between FAB and language performance (Section 3.1) raises the possibility that the left-lateralized FAB signature reflects co-occurring aphasia rather than executive dysfunction. Two sensitivity analyses addressed this by removing language variance from the FAB total and repeating the variance decomposition (Table S2). When the FAB was residualized on the ENPA language composite, the topographic signal was attenuated but persisted: it survived FDR correction in five of the seven representations (topography-unique  $R^2 = 0.090\text{--}0.106$ ), against six of seven in the primary analysis. When instead the cruder NIHSS Best Language item was used,

the residualized signal no longer survived correction in any representation, the topography-unique variance falling close to zero.

**Table V:** Language-sensitivity analysis of FAB lesion-symptom mapping

| Predictor set     | Primary FAB    |        | ENPA-residualized (n = 50) |        |      | NIHSS-residualized (n = 60) |        |      |
|-------------------|----------------|--------|----------------------------|--------|------|-----------------------------|--------|------|
|                   | R <sup>2</sup> | q      | R <sup>2</sup>             | q      | ρ    | R <sup>2</sup>              | q      | ρ    |
| Cortical Focal    | 0.128          | 0.033* | 0.100                      | 0.047* | 0.58 | -0.000                      | 0.539  | 0.78 |
| Cortical SDC      | 0.144          | 0.033* | -0.000                     | 0.763  | —    | -0.000                      | 0.691  | 0.78 |
| Subcortical Focal | 0.077          | 0.077· | 0.000                      | 0.181  | —    | 0.000                       | 0.161  | 0.82 |
| Subcortical SDC   | 0.122          | 0.028* | 0.106                      | 0.047* | 0.51 | 0.090                       | 0.081· | 0.85 |
| WM Tracts         | 0.150          | 0.033* | 0.098                      | 0.048* | 0.54 | 0.073                       | 0.093  | 0.66 |
| Whole Grey Focal  | 0.148          | 0.033* | 0.095                      | 0.047* | 0.43 | 0.000                       | 0.297  | 0.72 |
| Whole Grey SDC    | 0.159          | 0.028* | 0.101                      | 0.047* | 0.56 | 0.085                       | 0.081· | 0.78 |

*Note.* Topography-unique R<sup>2</sup>, FDR q-value, and the Spearman correlation (ρ) between each residualized model's ridge coefficient vector and the corresponding primary-FAB vector. \* q < 0.05; · 0.05 ≤ q < 0.10. ρ shown for ENPA-residualized representations that survived correction, and for all NIHSS-residualized representations for completeness despite non-survival. ENPA-residualized restricted to the 50 patients with complete ENPA data; NIHSS-residualized retains all 60. Language was residualized within each cross-validation fold. SDC, structural disconnection; WM, white matter; Whole Grey, combined cortical-plus-subcortical matrix.

Decisive, however, was not the survival count but the anatomy of the residual signal. In both analyses, the coefficient vectors of the language-residualized models remained positively correlated with those of the primary FAB models (ENPA-residualized, Spearman ρ = 0.43–0.58 across the surviving representations; NIHSS-residualized, ρ = 0.66–0.85), and their most heavily weighted predictors were the same left-lateralized

structures that carried the primary signature: the left nucleus accumbens, caudate, anterior thalamus, globus pallidus, and putamen among subcortical regions; the left thalamic radiations, frontal aslant tract, and uncinate among white-matter tracts; and the left frontal- opercular, insular, and salience-network nodes among cortical regions. Removing language variance therefore attenuated the magnitude of the topographic signal without relocating it. The residual executive signal occupied the same circuit, rather than being replaced by a distinct anatomy. This indicates that the FAB signature is not reducible to an aphasia signature, while confirming that the executive and language contributions cannot be fully separated in this cohort.

The divergence between the two residualizations, survival under ENPA adjustment, non- survival under NIHSS adjustment, may be due to the small magnitude of the language-independent signal, which sits near the threshold of detectability at this sample size, rather than a difference in what the two measures capture; both indexed language specifically (the NIHSS Best Language item correlated with the ENPA composite at  $\rho = -0.62$ , far exceeding its correlation with overall stroke severity,  $\rho = 0.35$ ).

#### *Specificity of the FAB Signature to Executive Impairment*

Because lesions in this cohort concentrate in middle cerebral artery territory, and the identified circuit itself lies substantially within that territory, the association between circuit damage and FAB impairment could in principle reflect the general topography of stroke occurrence in this cohort rather than a relationship specific to executive impairment. To address this, patients were dichotomized by FAB total score (impaired,  $n = 12$ , FAB total  $\leq 12.02$ , unadjusted for age and education; unimpaired,  $n = 48$ ; this classification differs by one patient from the age- and education-adjusted prevalence reported in Table 2, as the full normative adjustment equation was not reproduced for this supplementary analysis, and does not affect the primary lesion-symptom mapping results, which used the continuous FAB score throughout) and compared on a composite circuit-damage score, computed by standardizing and averaging lesion or disconnection load across the cortical (focal damage: left SomMot\_2, SomMot\_3, and

FrOperIns\_1) and subcortical (structural disconnection: left putamen, pallidum, caudate, anterior thalamus, and nucleus accumbens) regions identified in the primary FAB signature. White-matter tracts were not included in this composite, as tract-level lesion-load data were unavailable for this analysis. FAB-impaired patients showed substantially greater circuit damage than unimpaired patients (Mann-Whitney  $U = 493.0$ ,  $p < .001$ , rank-biserial  $r = -0.71$ ). Total lesion volume also differed significantly between groups ( $U = 467.0$ ,  $p = .001$ ), confirming that the topographic confound this analysis was designed to address is genuinely present in the cohort. To isolate circuit involvement independent of overall lesion burden, the circuit-damage score was residualized on log-transformed lesion volume; the resulting volume-independent measure continued to discriminate the groups ( $U = 431.0$ ,  $p = .0085$ ,  $r = -0.50$ ). A logistic regression predicting group membership from circuit-damage score and log lesion volume simultaneously found circuit score to be an independent predictor (OR = 5.48, 95% CI 1.63–18.38,  $p = .006$ ), while lesion volume alone was no longer significant once circuit involvement was accounted for ( $p = .079$ ). Given the modest size of the impaired group (events-per-variable  $\approx 6$ , below conventional guidelines for stable logistic regression estimates), the volume-residualized comparison is treated as the primary evidence for specificity, with the logistic regression as supportive; both indicate that circuit involvement carries information about FAB impairment beyond what overall lesion burden explains. A voxelwise lesion-subtraction analysis directly contrasting lesion frequency between groups showed modest spatial concentration of group differences within the pre-specified circuit, relative to the circuit's share of the coverage-adequate lesioned field (55% of the strongest group differences falling within the circuit, against a 39% baseline expected from the circuit's size alone). An attempt to replicate the volume-residualization approach at the voxel level produced a map nearly identical to the unadjusted difference map (spatial correlation = .99), indicating this correction could not be reliably estimated given the sparsity of lesion coverage at individual voxels in this sample. The aggregated circuit-damage score analysis above, which benefits from substantially greater statistical power through cross-region

aggregation, is accordingly treated as the primary spatial-specificity evidence, with the voxelwise result presented as a consistent but exploratory descriptive observation.

## 4 DISCUSSION

### 4.1 SUMMARY OF PRINCIPAL FINDINGS

This thesis set out to characterize the structural signature of executive dysfunction in acute stroke, asking not where executive function resides but which components of its distributed neural substrate, when damaged, predict the executive impairment observed at the bedside. The analyses support four principal conclusions. **First**, executive performance as captured by the Frontal Assessment Battery is anatomically localizable: lesion location predicted FAB performance beyond age, education, lesion volume, and stroke severity, robustly and across every anatomical substrate examined, surviving correction for multiple comparisons in six of seven representations. This extends the one prior lesion-symptom mapping of the FAB in stroke (Kopp et al., 2013), which used mass-univariate voxel-based mapping in a right-hemisphere cohort and localized the FAB to focal cortical foci, principally the anterior insula and lateral frontal gyri. The present analysis differs by employing multivariate, atlas-based mapping rather than mass-univariate voxelwise testing; it examines multiple anatomical substrates and both focal damage and structural disconnection rather than focal cortical damage alone; and it characterizes a predominantly left-hemisphere cohort. Where the earlier work identified discrete cortical foci, the present findings indicate that FAB performance is predicted by damage distributed across a multi-substrate circuit, a characterization not accessible to the univariate, single-substrate approach. Second, this localizability did not extend to timed trail-making. Pure processing speed showed no topographic signal whatever, and the set-shifting measures showed only trend-level signals that did not survive correction, which established a dissociation between the two classes of executive measure under identical analytic conditions. Third, the FAB signature was distributed across multiple anatomical substrates rather than localized to anyone, in that cortical, subcortical, and white-matter representations each carried significant signal, and at the subcortical level the disconnection of structures from their cortical partners predicted impairment more strongly than focal damage to those structures, insinuating that the deficit follows the severing of connections as much as the destruction of tissue.

Fourth, the signature was consistently left-lateralized: across all three substrates, separately analyzed, it converged on a single left peri-Sylvian–frontostriatal–thalamic circuit.

Two further findings refine this picture. The decomposition of the FAB into its component subtests showed that four of five subscores were separately localizable, with lexical fluency producing the strongest topographic signal in the entire analysis, but that these subscores localized to the same shared left frontal-subcortical anatomy rather than to dissociable substrates, a convergence corroborated by the finding that the latent dimension distinguishing the subtests from one another carried no reliable anatomical signal. And the interpretation of all cortical findings is bounded by the coverage of the cohort, in which only a sixth of cortical regions were adequately sampled, concentrated in the same peri-Sylvian territory in which the signal appeared.

## **4.2 A DISTRIBUTED, MULTI-SUBSTRATE SIGNATURE OF EXECUTIVE DYSFUNCTION**

The central anatomical finding of this thesis is that the structural signature of executive impairment is distributed rather than focal. The involvement of a frontal-subcortical circuit in executive performance is itself consistent with a long-standing literature linking frontal-subcortical loops to executive control (Alexander et al., 1986; Cummings, 1993), and earlier stroke work had associated FAB performance broadly with frontal-subcortical territory. The contribution of the present analysis is not the identification of this circuit in principle, but its quantitative characterization: the demonstration, using multivariate multi-substrate lesion-symptom mapping, that the signature is distributed across cortical, subcortical, and white-matter compartments; that structural disconnection contributes alongside focal damage, and at the subcortical level more strongly than focal damage; and that independently-fitted analyses of the three substrates converge on the same left-lateralized circuit. The disconnection contribution and the cross-substrate convergence are, to our knowledge, novel to the lesion-mapping literature on the FAB. Executive performance was predicted by a

pattern spanning cortical, subcortical, and white-matter compartments, each of which carried unique variance beyond the covariates and survived correction. This result is the empirical realization of the network-level account developed in the introduction, in which executive function is supported by a distributed circuit whose disruption, at any of its nodes or connections, degrades performance. The convergence is striking precisely because the three substrates were analyzed separately: the cortical, subcortical, and white-matter models were fitted independently of one another, yet each implicated the same left peri-Sylvian–frontostriatal–thalamic circuit, the cortical analysis identifying its peri-Sylvian and frontal-opercular nodes, the subcortical analysis its striatal-pallidal-thalamic relays, and the white-matter analysis the association and projection tracts that bind these together. That three separate analyses recover the components of a single recognizable circuit is stronger evidence for the distributed account than any one substrate could provide alone. It should be noted that these three substrates are not statistically separable from one another. Because they are derived from the same lesions in the same brains, a single infarct contributes to cortical, subcortical, and white-matter damage simultaneously, so their signals necessarily share lesion-driven variance. The spatial correlation between the cortical focal and disconnection coefficient patterns ( $r = 0.53$ ; Section 3.3) provides quantitative support for this convergence at the cortical level, though because the two damage metrics derive from the same lesions, it reflects spatial coincidence within a shared circuit rather than agreement between independent measures. The claim then is therefore that each, considered separately and adjusted for the same covariates, carries a topographic signal, and that the three converge on one anatomically coherent circuit.

A further concern is that, because lesions in this cohort concentrate in middle cerebral artery territory and the identified circuit lies substantially within it, the circuit's association with FAB impairment might reflect the general topography of stroke occurrence rather than a relationship specific to executive dysfunction. A supplementary group comparison (Section 3.5) addressed this directly: FAB-impaired patients showed disproportionate damage to the cortical–subcortical circuit even after

adjustment for overall lesion volume, indicating that circuit involvement carries information about executive impairment beyond what general lesion burden explains. This converges with the behavioural dissociation reported earlier: had the circuit merely reflected where lesions fall, it would be expected to predict the timed trail-making measures as well, yet it does not. Together these provide two independent lines of evidence that the signature is specific to executive impairment rather than an artifact of lesion distribution.

The comparison between focal damage and structural disconnection sharpens this interpretation. For the FAB, disconnection-based representations predicted performance at least as well as focal representations, and at the subcortical level the dissociation was explicit. The disconnection of subcortical structures from their cortical partners survived correction, whereas focal damage to those same structures reached only trend level. The executive consequence of a subcortical lesion, in other words, tracked the connectivity it severed more closely than the grey matter it destroyed. This is consistent with the principle, central to the disconnection tradition from which the structural-disconnection method derives, that the functional cost of a lesion is often determined less by the tissue lost than by the network the loss disconnects. For a cognitive function as dependent on the integration of distributed processing as executive control, this is the expected pattern, and its observation here, in a measure that survived stringent correction, provides direct support for treating disconnection as a substrate of post-stroke executive dysfunction in its own right rather than as a secondary correlate of grey-matter damage.

The white-matter findings reinforce this reading from the third substrate. The tracts whose disconnection predicted FAB performance, the left superior longitudinal fasciculus, frontal aslant tract, uncinate fasciculus, and thalamic radiations, are precisely the association and projection pathways that the literature implicates in executive control, and that physically instantiate the long-range connections of the left peri-Sylvian–frontostriatal–thalamic circuit (Ribeiro et al 2024). Their appearance as separable predictors, converging with the grey-matter findings on the same circuit,

suggests that the integrity of the connections within this system is itself a determinant of executive performance, separable from and additional to the integrity of the regions they connect (Dick et al., 2019). Taken together, the cortical, subcortical, and white-matter results compose a coherent account in which post-stroke executive dysfunction arises from damage distributed across a left-lateralized peri-Sylvian–frontostriatal–thalamic circuit, expressed through both the destruction of its computational nodes and the disconnection of its constituent pathways.

#### **4.3 THE SALIENCE NETWORK AND THE CORTICAL SIGNATURE**

Among the cortical regions implicated in the FAB signature, the salience-network nodes of the left frontal operculum and anterior insula were prominent and consistent, appearing among the highest-weighted predictors across the focal and disconnection cortical representations and across the combined whole-grey-matter models. This convergence on insular and opercular cortex echoes a prior lesion-symptom mapping of the FAB in stroke, which localized the FAB global composite score to the anterior insula, albeit in the right hemisphere and through focal cortical damage rather than the distributed, disconnection-weighted pattern seen here (Kopp et al., 2013). This is the pattern anticipated in the fourth hypothesis, which predicted that insofar as the cortical signature proved localizable, it would preferentially implicate salience-network cortex. The prediction followed from a substantial and replicated functional literature assigning the salience network, and the anterior insula in particular, a coordinating role in executive control, which is the detection of behaviourally relevant events and the initiation of transitions between the brain’s internally and externally directed modes. That damage to these same regions predicts global executive impairment is consistent with this account, and provides a structural complement to a body of evidence that has been, to date, overwhelmingly functional.

This interpretation must be advanced with two explicit constraints, the first concerning what the present design can observe and the second concerning what the cohort can sample. The structural design of this study can establish that damage to salience-network cortex predicts executive impairment; it cannot observe the network dynamics,

the switching between large-scale networks, that the functional literature proposes as the mechanism by which that cortex supports executive control. The finding is therefore consistent with the proposed coordinating role of the salience network, but does not test it. To move from the structural observation made here to the functional claim it is consistent with would require the resting-state and dynamic-connectivity measurements.

The second constraint, lesion coverage, bears most heavily on the salience-network finding specifically. The frontal-opercular and insular regions carrying the cortical signal were not only among the strongest predictors but also among the best-sampled cortical regions in the cohort, a coincidence following directly from the predominance of anterior-circulation stroke. Their prominence cannot, in consequence, be cleanly separated from the fact that they were among the few cortical territories this cohort could interrogate at all. Nonetheless, the salience-network finding is the most provisional of the thesis's anatomical results, and the distributed-circuit conclusion rests more securely on the better-sampled subcortical and white-matter substrates than on the cortical signature alone.

A further interpretive caution concerns the nature of the cortical and white-matter signal itself. The left somatomotor cortex was weighted as heavily as the salience-network nodes, and the white-matter signature included projection tracts, the reticulospinal and dentatorubrothalamic pathways, whose primary affiliations are motor rather than executive. This raises the possibility that part of the FAB signal reflects motor-execution demand rather than executive control per se. Several FAB items (Motor Series, Go/No-Go) and the broader bedside setting require intact motor output, and patients with motor-strip or projection-tract damage may score worse for reasons partly independent of executive function. Adjustment for stroke severity (NIHSS) partially controls for this, since motor impairment is a major contributor to the NIHSS, but it cannot fully separate motor- execution demand from executive demand on a brief bedside instrument. The somatomotor and motor-projection

involvement in the signature should therefore be read as consistent with, but not specific to, executive control.

A parallel and arguably more consequential ambiguity concerns language. The FAB correlated strongly with performance on a dedicated aphasia battery, and this association persisted with little attenuation when the FAB's overt verbal-fluency item was removed, suggesting that the entanglement of executive and language performance pervaded the instrument rather than residing in a single subscore. The clinical implication is that in patients with post-stroke language impairment, a battery such as the FAB cannot be assumed to index executive function in isolation, and a low score may reflect compromised language as much as compromised executive control. Standard bedside executive instruments that carry verbal demands may therefore be poorly suited to assessing executive function in left-hemisphere stroke with aphasia, a limitation avoided only by excluding left-hemisphere patients altogether (Kopp et al., 2013).

The present cohort, being left-lateralized, cannot apply that exclusion, and so the question of whether the FAB signature reflects executive dysfunction or co-occurring aphasia was addressed directly, by removing language variance from the FAB and re-examining its anatomy (Section 3.5, Table S2). Removing language variance attenuated the topographic signal, surviving correction in five of seven representations when a graded language composite was regressed out, and in none when a coarser aphasia-severity item was used, confirming that a substantial portion of the FAB signal is shared with language and cannot be separated from it. Yet in every case the residual signal localized to the same left frontostriatal-thalamic circuit as the full FAB signature, with its strongest weights on the same subcortical, white-matter, and frontal-opercular structures; the language adjustment reduced the magnitude of the signal without relocating it. The executive signature is therefore best understood as entangled with language but not reducible to it: in a left-hemisphere-predominant cohort assessed with a partly verbal battery, the executive and language contributions share variance and cannot be fully disentangled, but the anatomy that remains once language is removed

is the left peri-Sylvian–frontostriatal–thalamic circuit, not a distinct language network. This aligns with the broader observation that, where executive and language functions share variance, an analysis that removes the language component interrogates only the language-independent portion of executive function, a necessarily smaller signal, whose preserved localization here argues that what the FAB captures in this cohort is genuinely anatomical and executive, even as its separation from language remains, at the behavioural level, incomplete.

#### **4.4 SET-SHIFTING, SWITCH-COST PROXY, AND THE LIMITS OF STRUCTURAL MAPPING**

The dissociation between the FAB and timed trail-making in itself poses questions, namely what it reveals about the measures themselves, and what it reveals about the limits of the structural approach. The Frontal Assessment Battery, a global screen of executive function, was robustly localizable; the Trail Making Test, and the set-shifting cost derived from it, were not. Part of this difference is likely attributable to the measurement properties of timed trail-making in an acute stroke cohort. Completion times are heavily influenced by visuomotor processing speed, itself dominated in these data by age and carrying no topographic signal, and TMT-B performance was further compressed by a substantial ceiling effect, with nearly a third of patients reaching the administration limit. A measure whose variance is dominated by age and truncated by a ceiling offers little residual signal for lesion location to explain, and the comprehensive null for pure processing speed (TMT-A) indicates that the timed component contributes nothing localizable. The FAB, by contrast, samples executive function more broadly and is scored categorically rather than against a clock, and it is this broader, speed-independent sampling that appears to render its variance anatomically tractable where the timed measures are not.

Against this background, the analysis of the isolated set-shifting cost takes on particular interest, because it bears most directly on the account of executive dysfunction that motivated this work. Subtracting the processing-speed component from TMT-B, to isolate the additional cost of alternating between sequences, produced a topographic

signal that, though it did not survive correction, was stronger and more consistent than that of the raw measure, and was expressed specifically through white-matter and subcortical disconnection rather than focal grey-matter damage. The direction of this trend is notable. If set-shifting depends, as the functional literature proposes, on the coordinated reconfiguration of large-scale networks, and if that coordination is implemented through the long-range connectivity of a distributed frontal system, then a disconnection-weighted signal for the isolated shifting cost is precisely what one would expect to find. The observation that the shifting cost, once separated from processing speed, points toward disrupted connectivity rather than focal damage is consistent with the hypothesis that set-shifting deficits after stroke arise from the disconnection of the circuits that coordinate cognitive transitions, the same circuits whose cortical anchor, the salience network, featured in the FAB signature.

This is an interpretation that exceeds what the data establishes, and it must be labelled as such. The set-shifting signal was a trend that did not survive correction for multiple comparisons; at the present sample size it cannot be distinguished from chance. On the other hand, the isolated shifting cost showed a consistent, disconnection-concentrated trend in the direction the network account predicts, insufficient in this cohort to constitute confirmation but sufficient to motivate the analyses that would constitute a test. The convergence of three separable strands, the prominence of salience-network cortex in the robustly-localized FAB signature, the dominance of disconnection over focal damage in the subcortical findings, and the disconnection-weighted trend for the isolated shifting cost, points consistently toward an account of post-stroke executive dysfunction in which the coordination of distributed networks, and its disruption by disconnection, is central. The structural findings of this thesis are consistent with that account and motivate it; they do not, and given the structural-only design cannot, confirm it.

#### **4.5 SUBSCORE COHERENCE AND THE UNITY OF EXECUTIVE FUNCTION**

The decomposition of the FAB into its component subtests produced a result that initially appears to complicate the thesis's account but in fact clarifies it. Four of the five subtests were separately localizable, surviving correction within their own family, and lexical fluency produced the strongest topographic signal of any measure in the analysis, exceeding even the FAB total. Taken at face value, a set of separately-localizable subtests might suggest that the components of executive function occupy distinct anatomical substrates, the dissociation that a strong reading of the componential model would predict. The coefficient rankings show that this is not what occurred. The subtests that localized did so to the same left peri-Sylvian–frontostriatal–thalamic anatomy: the same left frontal-opercular and somatomotor cortex, the same left striatal-pallidal-thalamic structures, the same left frontal tracts. They differed in the magnitude of their loadings, lexical fluency expressing the shared substrate most strongly, but not in its location. The subtests localize because each draws on a common substrate.

The prominence of lexical fluency within this shared signature merits a specific comment. That fluency produced the strongest topographic signal is consistent with its standing as the most demanding and most frontally-dependent of the FAB subtests, requiring strategic retrieval, self-monitoring, and the suppression of repetition, operations that draw heavily on the left peri-Sylvian–frontostriatal–thalamic circuit and its white-matter connections. Its strength is therefore plausibly read not as evidence of a fluency-specific substrate distinct from the others, but as the subtest that most fully engages, and is therefore most sensitive to damage in, the common substrate that the analysis as a whole implicates. This reading coheres with the white-matter findings, in which fluency's signal, like the FAB total's, concentrated in the left frontal association and projection tracts. This executive reading must, however, be tempered by fluency's verbal nature. Lexical fluency is also the most language-dependent of the FAB subtests, and in a left-hemisphere-predominant cohort its strong signal in peri-Sylvian territory is consistent with its lexical-retrieval demands as much as its executive ones. That

lexical fluency reflects both a left-lateralized verbal component and a frontal executive component is long recognized (Kopp et al., 2013, after Ramier & Hécaen, 1970); as the analysis of language performance indicates (Section 4.3), the present data cannot fully separate the two.

This interpretation finally is corroborated directly by the principal component analysis. The first component, capturing the variance shared across all subtests, reproduced the FAB-total anatomy almost exactly and carried the localizable signal; the second component, capturing the variance that distinguishes the subtests from one another, carried essentially no anatomical signal. The structural data thus speaks to the architecture of executive function in a specific way. The dimension along which the subtests covary, the general factor, has a definite and distributed neural signature; the dimensions along which they diverge do not, at least not one detectable in this cohort. In the terms of the unity-and-diversity framework introduced earlier, the present findings are a structural expression of unity: the shared, general component of executive function maps onto a coherent distributed circuit, while the diversity among its components, real at the behavioural and psychometric level, does not resolve into separable anatomical substrates here. Whether this reflects a genuine anatomical convergence of the executive subdomains, or the limits of what a moderately-sized acute-stroke cohort with these measures can resolve, cannot be settled by the present data, and the ceiling effects that differentially constrained the subtests counsel particular caution. But the direction of the finding is clear and consistent. At the level of structure, post-stroke executive impairment presents as the disruption of a shared frontal-subcortical system expressed across multiple tasks.

#### **4.6 LIMITATIONS**

The decomposition of the FAB into its component subtests produced a result that initially appears to complicate the thesis's account but in fact clarifies it. Four of the five subtests were separately localizable, surviving correction within their own family, and lexical fluency produced the strongest topographic signal of any measure in the

analysis, exceeding even the FAB total. Taken at face value, a set of separately-localizable subtests might suggest that the components of executive function occupy distinct anatomical substrates, the dissociation that a strong reading of the componential model would predict. The coefficient rankings show that this is not what occurred. The subtests that localized did so to the same left peri-Sylvian–frontostriatal–thalamic anatomy: the same left frontal-opercular and somatomotor cortex, the same left striatal-pallidal-thalamic structures, the same left frontal tracts. They differed in the magnitude of their loadings, lexical fluency expressing the shared substrate most strongly, but not in its location. The subtests localize not because each occupies its own territory but because each draws on a common substrate.

The prominence of lexical fluency within this shared signature merits a specific comment. That fluency produced the strongest topographic signal is consistent with its standing as the most demanding and most frontally-dependent of the FAB subtests, requiring strategic retrieval, self-monitoring, and the suppression of repetition, operations that draw heavily on the left peri-Sylvian–frontostriatal–thalamic circuit and its white-matter connections. Its strength is therefore plausibly read not as evidence of a fluency-specific substrate distinct from the others, but as the subtest that most fully engages, and is therefore most sensitive to damage in, the common substrate that the analysis as a whole implicates. This reading coheres with the white-matter findings, in which fluency’s signal, like the FAB total’s, concentrated in the left frontal association and projection tracts. This executive reading must, however, be tempered by fluency’s verbal nature. Lexical fluency is also the most language-dependent of the FAB subtests, and in a left-hemisphere-predominant cohort its strong signal in peri-Sylvian territory is consistent with its lexical-retrieval demands as much as its executive ones. That lexical fluency reflects both a left-lateralized verbal component and a frontal executive component is long recognized (Kopp et al., 2013, after Ramier & Hécaen, 1970); as the analysis of language performance indicates (Section 4.3), the present data cannot fully separate the two.

This interpretation finally is corroborated directly by the principal component analysis. The first component, capturing the variance shared across all subtests, reproduced the FAB-total anatomy almost exactly and carried the localizable signal; the second component, capturing the variance that distinguishes the subtests from one another, carried essentially no anatomical signal. The structural data thus speak to the architecture of executive function in a specific way. The dimension along which the subtests covary, the general factor, has a definite and distributed neural signature; the dimensions along which they diverge do not, at least not one detectable in this cohort. In the terms of the unity-and-diversity framework introduced earlier, the present findings are a structural expression of unity: the shared, general component of executive function maps onto a coherent distributed circuit, while the diversity among its components, real at the behavioural and psychometric level, does not resolve into separable anatomical substrates here. Whether this reflects a genuine anatomical convergence of the executive subdomains, or the limits of what a moderately-sized acute-stroke cohort with these measures can resolve, cannot be settled by the present data, and the ceiling effects that differentially constrained the subtests counsel particular caution. But the direction of the finding is clear and consistent. At the level of structure, post-stroke executive impairment presents as the disruption of a shared frontal-subcortical system expressed across multiple tasks.

#### **4.7 CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS**

The clinical motivation for this work was the under-recognition of executive dysfunction after stroke and the consequent gap between its prevalence and its detection. The present findings are foundational rather than directly clinical, in that they characterize the structural basis of the deficit rather than proposing a tool for its management. Nonetheless, two implications follow. First, the robust localizability of the FAB, against the comprehensive failure of timed trail-making to localize, suggests that brief, speed-independent global screening of executive function captures a signal more closely tied to lesion anatomy than timed measures do, a consideration potentially

relevant to the choice of screening instrument in acute settings, though one that would require direct validation before any clinical recommendation could follow. Second, the prominence of white-matter and subcortical disconnection in the signature reinforces a broader clinical point, which is that executive deficits may follow from lesions that spare the cortex entirely, arising through the disconnection of subcortical and white-matter pathways, and that their anatomical basis will be missed by any assessment of grey-matter damage alone.

The clearest implications, however, are for future research, and they follow directly from the limitations of the present design. The interpretations advanced in this thesis, that the executive signature reflects the disruption of a distributed frontal system, and that set-shifting deficits in particular may arise from the disconnection of the circuits coordinating cognitive transitions, are consistent with the structural findings but cannot be confirmed by them. They are, however, directly testable. The structural convergence identified here, on a left peri-Sylvian–frontostriatal–thalamic circuit with the salience network among its cortical nodes, generates a specific functional prediction. Patients with executive impairment should show altered functional connectivity within and between the large-scale networks this circuit subserves and altered dynamics of the transitions between them. The resting-state and dynamic functional connectivity measurements that would test this prediction were beyond the scope of the present structural study, but the cohort and the framework are in place to pursue them. A study comparing functional network organization between stroke patients with and without executive impairment, and against healthy controls, would establish whether the structural signature identified here is accompanied by the functional disruption that the interpretation predicts, and would move the account from one consistent with the structural evidence to one tested against functional evidence. Beyond this, longitudinal assessment extending from the acute into the chronic phase would determine whether the acute anatomical associations identified here persist as the deficit stabilizes, and larger multi-centre cohorts with more complete cortical coverage would permit the

contributions of regions beyond the anterior-circulation territory, the dorsolateral prefrontal cortex foremost among them, to be assessed directly.

Beyond confirming the mechanism, the anatomical specificity of the signature has implications for treatment. If executive impairment is carried by a definable left peri-Sylvian–frontostriatal–thalamic circuit, then the cortical nodes of that circuit constitute candidate targets for circuit-directed neuromodulation. Lesion-network and disconnection-based mapping is increasingly used to derive individualized targets for non-invasive brain stimulation (Siddiqi et al., 2020; 2022; Fox et al 2018), and a network-guided approach to executive rehabilitation would represent a departure from stimulating a single, anatomically generic prefrontal site. Rather than treating "the frontal lobe," stimulation could be directed at the preserved, accessible nodes of the specific circuit a given patient's lesion implicates. Two constraints define what such an approach could realistically achieve. First, standard focal transcranial magnetic stimulation acts on superficial cortex and cannot reach the subcortical and white-matter structures that carried much of the present signature (Wagner et al., 2009; Deng et al., 2013); its plausible role is therefore to modulate the surviving cortical entry points of the circuit, the left frontal-opercular and peri-Sylvian nodes, and through them the deeper network transsynaptically (Di Pino et al., 2014). Second, and more fundamentally, stimulation cannot restore a severed tract (Stinear et al., 2007); where the deficit follows structural disconnection, the realistic therapeutic goal is driving the re-emergence and normalization of large-scale modular networks, enhancing the coordinated activity of the nodes that remain connected (Siegel et al., 2018; Di Pino et al., 2014). Within these limits, the framework developed here, which identifies, for a given lesion, both the damaged connections and the preserved cortical nodes of the left peri-Sylvian–frontostriatal–thalamic circuit, is precisely the information such a targeting strategy would require, and whether network-guided stimulation improves executive outcomes is a question the present structural characterization is positioned to inform.

The present thesis characterizes the structural signature of post-stroke executive dysfunction; the functional, longitudinal, and more fully sampled studies it motivates would complete the account.

## BIBLIOGRAPHY

Abraham, A., Pedregosa, F., Eickenberg, M., Gervais, P., Mueller, A., Kossaifi, J., Gramfort, A., Thirion, B., & Varoquaux, G. (2014). Machine learning for neuroimaging with scikit-learn. *Frontiers in Neuroinformatics*, 8. <https://doi.org/10.3389/fninf.2014.00014>

Adams, H. P., Bendixen, B. H., Kappelle, L. J., Biller, J., Love, B. B., Gordon, D. L., & Marsh, E. E. (1993). Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*, 24(1), 35–41. <https://doi.org/10.1161/01.STR.24.1.35>

Aiello, E. N., Esposito, A., Gramegna, C., Gazzaniga, V., Zago, S., Difonzo, T., Appollonio, I. M., & Bolognini, N. (2022). The Frontal Assessment Battery (FAB) and its sub-scales: Validation and updated normative data in an Italian population sample. *Neurological Sciences*, 43(2), 979–984. <https://doi.org/10.1007/s10072-021-05392-y>

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, 9, 357–381. <https://doi.org/10.1146/annurev.ne.09.030186.002041>

Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, 18(3), 251–270. <https://doi.org/10.1177/1073858411403316>

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2014). Inhibition and the right inferior frontal cortex: One decade on. *Trends in Cognitive Sciences*, 18(4), 177–185. <https://doi.org/10.1016/j.tics.2013.12.003>

Balasoorya-Smeekens, C., Bateman, A., Mant, J., & De Simoni, A. (2016). Barriers and facilitators to staying in work after stroke: Insight from an online forum. *BMJ Open*, 6(4), e009974. <https://doi.org/10.1136/bmjopen-2015-009974>

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., & Dronkers, N. F. (2003). Voxel-based lesion-symptom mapping. *Nature Neuroscience*, 6(5), 448–450. <https://doi.org/10.1038/nn1050>

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: Emerging methods and principles. *Trends in Cognitive Sciences*, 14(6), 277–290. <https://doi.org/10.1016/j.tics.2010.04.004>

Brett, M., Markiewicz, C. J., Hanke, M., Côté, M.-A., Cipollini, B., Papadopoulos Orfanos, D., McCarthy, P., Jarecka, D., Cheng, C. P., Larson, E., Halchenko, Y. O., Cottaar, M., Ghosh, S., Wassermann, D., Gerhard, S., Lee, G. R., Baratz, Z., Moloney, B., Wang, H.-T., ... freec84. (2024). *nipy/nibabel: 5.3.1* [Computer software]. <https://doi.org/10.5281/ZENODO.13936989>

Brott, T., Adams, H. P., Olinger, C. P., Marler, J. R., Barsan, W. G., Biller, J., Spilker, J., Holleran, R., Eberle, R., & Hertzberg, V. (1989). Measurements of acute cerebral infarction: A clinical examination scale. *Stroke*, 20(7), 864–870. <https://doi.org/10.1161/01.str.20.7.864>

Capasso, R., & Miceli, G. (2001). *Esame neuropsicologico per l'afasia: E.N.P.A.* Springer.

Carrera, E., & Bogousslavsky, J. (2006). The thalamus and behavior: Effects of anatomically distinct strokes. *Neurology*, 66(12), 1817–1823. <https://doi.org/10.1212/01.wnl.0000219679.95223.4c>

Collette, F., Van der Linden, M., Laureys, S., Delfiore, G., Degueldre, C., Luxen, A., & Salmon, E. (2005). Exploring the unity and diversity of the neural substrates of executive functioning. *Human Brain Mapping*, 25(4), 409–423. <https://doi.org/10.1002/hbm.20118>

Corbetta, M., Ramsey, L., Callejas, A., Baldassarre, A., Hacker, C. D., Siegel, J. S., Astafiev, S. V., Rengachary, J., Zinn, K., Lang, C. E., Connor, L. T., Fucetola, R., Strube, M., Carter, A. R., & Shulman, G. L. (2015). Common behavioral clusters and subcortical anatomy in stroke. *Neuron*, 85(5), 927–941. <https://doi.org/10.1016/j.neuron.2015.02.027>

Cramer, S. C. (2008). Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Annals of Neurology*, 63(3), 272–287. <https://doi.org/10.1002/ana.21393>

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology*, 50(8), 873–880. <https://doi.org/10.1001/archneur.1993.00540080076020>

Cunningham, L. J., Stapleton, T., Walsh, K., & Horgan, F. (2026). Post-stroke cognitive impairment is associated with poorer return-to-work outcomes in working-aged stroke survivors: A systematic review. *Clinical Rehabilitation*, 2692155261420770. <https://doi.org/10.1177/02692155261420770>

DeMarco, A. T., & Turkeltaub, P. E. (2018). A multivariate lesion symptom mapping toolbox and examination of lesion-volume biases and correction methods in lesion-

symptom mapping. *Human Brain Mapping*, 39(11), 4169–4182. <https://doi.org/10.1002/hbm.24289>

Demeyere, N., Riddoch, M. J., Slavkova, E. D., Bickerton, W.-L., & Humphreys, G. W. (2015). The Oxford Cognitive Screen (OCS): Validation of a stroke-specific short cognitive screening tool. *Psychological Assessment*, 27(3), 883–894. <https://doi.org/10.1037/pas0000082>

Deng, Z.-D., Lisanby, S. H., & Peterchev, A. V. (2013). Electric field depth-focality tradeoff in transcranial magnetic stimulation: Simulation comparison of 50 coil designs. *Brain Stimulation*, 6(1), 1–13. <https://doi.org/10.1016/j.brs.2012.02.005>

Di Pino, G., Pellegrino, G., Assenza, G., Capone, F., Ferreri, F., Formica, D., Ranieri, F., Tombini, M., Ziemann, U., Rothwell, J. C., & Di Lazzaro, V. (2014). Modulation of brain plasticity in stroke: A novel model for neurorehabilitation. *Nature Reviews. Neurology*, 10(10), 597–608. <https://doi.org/10.1038/nrneurol.2014.162>

Dick, A. S., Garic, D., Graziano, P., & Tremblay, P. (2019). The frontal aslant tract (FAT) and its role in speech, language and executive function. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, 111, 148–163. <https://doi.org/10.1016/j.cortex.2018.10.015>

Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. (2000). The FAB: A Frontal Assessment Battery at bedside. *Neurology*, 55(11), 1621–1626. <https://doi.org/10.1212/wnl.55.11.1621>

El Hussein, N., Katzan, I. L., Rost, N. S., Blake, M. L., Byun, E., Pendlebury, S. T., Aparicio, H. J., Marquine, M. J., Gottesman, R. F., Smith, E. E., & American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Radiology and Intervention; Council on Hypertension; and Council on Lifestyle and Cardiometabolic Health. (2023). Cognitive Impairment After Ischemic and Hemorrhagic Stroke: A Scientific Statement From the American Heart Association/American Stroke Association. *Stroke*, 54(6), e272–e291. <https://doi.org/10.1161/STR.0000000000000430>

Feigin, V. L., Stark, B. A., Johnson, C. O., Roth, G. A., Bisignano, C., Abady, G. G., Abbasifard, M., Abbasi-Kangevari, M., Abd-Allah, F., Abedi, V., Abualhasan, A., Abu-Rmeileh, N. M., Abushouk, A. I., Adebayo, O. M., Agarwal, G., Agasthi, P., Ahinkorah, B. O., Ahmad, S., Ahmadi, S., ... Murray, C. J. L. (2021). Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Neurology*, 20(10), 795–820. [https://doi.org/10.1016/S1474-4422\(21\)00252-0](https://doi.org/10.1016/S1474-4422(21)00252-0)

- Figley, T. D., Bhullar, N., Courtney, S. M., & Figley, C. R. (2015). Probabilistic atlases of default mode, executive control and salience network white matter tracts: An fMRI-guided diffusion tensor imaging and tractography study. *Frontiers in Human Neuroscience*, 9, 585. <https://doi.org/10.3389/fnhum.2015.00585>
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189–198. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
- Foulon, C., Cerliani, L., Kinkingnéhun, S., Levy, R., Rosso, C., Urbanski, M., Volle, E., & Thiebaut De Schotten, M. (2018). Advanced lesion symptom mapping analyses and implementation as *BCBtoolkit*. *GigaScience*, 7(3), giy004. <https://doi.org/10.1093/gigascience/giy004>
- Fox, M. D. (2018a). Mapping Symptoms to Brain Networks with the Human Connectome. *The New England Journal of Medicine*, 379(23), 2237–2245. <https://doi.org/10.1056/NEJMr1706158>
- Fox, M. D. (2018b). Mapping Symptoms to Brain Networks with the Human Connectome. *The New England Journal of Medicine*, 379(23), 2237–2245. <https://doi.org/10.1056/NEJMr1706158>
- Friedman, N. P., & Miyake, A. (2017). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, 86, 186–204. <https://doi.org/10.1016/j.cortex.2016.04.023>
- Friedman, N. P., Miyake, A., Young, S. E., DeFries, J. C., Corley, R. P., & Hewitt, J. K. (2008). Individual differences in executive functions are almost entirely genetic in origin. *Journal of Experimental Psychology. General*, 137(2), 201–225. <https://doi.org/10.1037/0096-3445.137.2.201>
- Fugl-Meyer, A. R., Jääskö, L., Leyman, I., Olsson, S., & Steglind, S. (1975). The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scandinavian Journal of Rehabilitation Medicine*, 7(1), 13–31.
- Garyfallidis, E., Brett, M., Amirbekian, B., Rokem, A., van der Walt, S., Descoteaux, M., Nimmo-Smith, I., & Dipy Contributors. (2014). Dipy, a library for the analysis of diffusion MRI data. *Frontiers in Neuroinformatics*, 8, 8. <https://doi.org/10.3389/fninf.2014.00008>
- Geschwind, N. (1965). Disconnexion syndromes in animals and man. I. *Brain: A Journal of Neurology*, 88(2), 237–294. <https://doi.org/10.1093/brain/88.2.237>

- Godefroy, O., Azouvi, P., Robert, P., Roussel, M., LeGall, D., Meulemans, T., & Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives Study Group. (2010). Dysexecutive syndrome: Diagnostic criteria and validation study. *Annals of Neurology*, 68(6), 855–864. <https://doi.org/10.1002/ana.22117>
- Goldstein, K. (1936). The Significance of the Frontal Lobes for Mental Performances. *The Journal of Neurology and Psychopathology*, 17(65), 27–40. <https://doi.org/10.1136/jnnp.s1-17.65.27>
- Gordon, E. M., Chauvin, R. J., Van, A. N., Rajesh, A., Nielsen, A., Newbold, D. J., ... & Dosenbach, N. U. F. (2023). A somato-cognitive action network alternates with effector regions in motor cortex. *Nature*, 617(7960), 351–359. <https://doi.org/10.1038/s41586-023-05964-2>
- Gordon, E. M., Laumann, T. O., Gilmore, A. W., Newbold, D. J., Greene, D. J., Berg, J. J., ... & Dosenbach, N. U. F. (2017). Precision functional mapping of individual human brains. *Neuron*, 95(4), 791–807. <https://doi.org/10.1016/j.neuron.2017.07.011>
- Goulden, N., Khusnulina, A., Davis, N. J., Bracewell, R. M., Bokde, A. L., McNulty, J. P., & Mullins, P. G. (2014). The salience network is responsible for switching between the default mode network and the central executive network: Replication from DCM. *NeuroImage*, 99, 180–190. <https://doi.org/10.1016/j.neuroimage.2014.05.052>
- Grau-Olivares, M., Arboix, A., Bartrés-Faz, D., & Junqué, C. (2007). Neuropsychological abnormalities associated with lacunar infarction. *Journal of the Neurological Sciences*, 257(1–2), 160–165. <https://doi.org/10.1016/j.jns.2007.01.022>
- Greene, D. J., Marek, S., Gordon, E. M., Barch, D. M., & Dosenbach, N. U. F. (2020). Integrative and network-specific connectivity of the basal ganglia and thalamus defined in individuals. *Neuron*, 105(4), 742–758. <https://doi.org/10.1016/j.neuron.2019.11.012>
- Griffis, J. C., Metcalf, N. V., Corbetta, M., & Shulman, G. L. (2019). Structural Disconnections Explain Brain Network Dysfunction after Stroke. *Cell Reports*, 28(10), 2527–2540.e9. <https://doi.org/10.1016/j.celrep.2019.07.100>
- Hackett, M. L., & Pickles, K. (2014). Part I: Frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *International Journal of Stroke: Official Journal of the International Stroke Society*, 9(8), 1017–1025. <https://doi.org/10.1111/ijs.12357>
- Harris, C. R., Millman, K. J., Van Der Walt, S. J., Gommers, R., Virtanen, P., Cournapeau, D., Wieser, E., Taylor, J., Berg, S., Smith, N. J., Kern, R., Picus, M., Hoyer, S., Van Kerkwijk, M. H., Brett, M., Haldane, A., Del Río, J. F., Wiebe, M.,

Peterson, P., ... Oliphant, T. E. (2020). Array programming with NumPy. *Nature*, 585(7825), 357–362. <https://doi.org/10.1038/s41586-020-2649-2>

Hartman-Maeir, A., Soroker, N., Ring, H., & Katz, N. (2002). Awareness of deficits in stroke rehabilitation. *Journal of Rehabilitation Medicine*, 34(4), 158–164. <https://doi.org/10.1080/16501970213236>

Humphries, M. D. (2025). The Computational Bottleneck of Basal Ganglia Output (and What to Do About it). *eNeuro*, 12(4), ENEURO.0431-23.2024. <https://doi.org/10.1523/ENEURO.0431-23.2024>

Hwang, K., Bertolero, M. A., Liu, W. B., & D’Esposito, M. (2017). The Human Thalamus Is an Integrative Hub for Functional Brain Networks. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 37(23), 5594–5607. <https://doi.org/10.1523/JNEUROSCI.0067-17.2017>

Jamison, J., Graffy, J., Mullis, R., Mant, J., & Sutton, S. (2016). Barriers to medication adherence for the secondary prevention of stroke: A qualitative interview study in primary care. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners*, 66(649), e568-576. <https://doi.org/10.3399/bjgp16X685609>

Jones, T. A. (2017). Motor compensation and its effects on neural reorganization after stroke. *Nature Reviews. Neuroscience*, 18(5), 267–280. <https://doi.org/10.1038/nrn.2017.26>

Jurado, M. B., & Rosselli, M. (2007). The elusive nature of executive functions: A review of our current understanding. *Neuropsychology Review*, 17(3), 213–233. <https://doi.org/10.1007/s11065-007-9040-z>

Karnath, H.-O., Sperber, C., & Rorden, C. (2018). Mapping human brain lesions and their functional consequences. *NeuroImage*, 165, 180–189. <https://doi.org/10.1016/j.neuroimage.2017.10.028>

Kimberg, D. Y., Coslett, H. B., & Schwartz, M. F. (2007). Power in Voxel-based lesion-symptom mapping. *Journal of Cognitive Neuroscience*, 19(7), 1067–1080. <https://doi.org/10.1162/jocn.2007.19.7.1067>

Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology*, 55(4), 352–358. <https://doi.org/10.1037/h0043688>

Kopp, B., Rösler, N., Tabeing, S., Stürenburg, H. J., de Haan, B., Karnath, H.-O., & Wessel, K. (2013). Performance on the Frontal Assessment Battery is sensitive to

frontal lobe damage in stroke patients. *BMC Neurology*, 13, 179. <https://doi.org/10.1186/1471-2377-13-179>

Krause, M., Mahant, N., Kotschet, K., Fung, V. S., Vagg, D., Wong, C. H., & Morris, J. G. L. (2012). Dysexecutive behaviour following deep brain lesions—A different type of disconnection syndrome? *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, 48(1), 97–119. <https://doi.org/10.1016/j.cortex.2011.03.014>

Kuceyeski, A., Navi, B. B., Kamel, H., Raj, A., Relkin, N., Togli, J., Iadecola, C., & O'Dell, M. (2016). Structural connectome disruption at baseline predicts 6-months post-stroke outcome. *Human Brain Mapping*, 37(7), 2587–2601. <https://doi.org/10.1002/hbm.23198>

Laakso, H. M., Hietanen, M., Melkas, S., Sibolt, G., Curtze, S., Virta, M., Ylikoski, R., Pohjasvaara, T., Kaste, M., Erkinjuntti, T., & Jokinen, H. (2019). Executive function subdomains are associated with post-stroke functional outcome and permanent institutionalization. *European Journal of Neurology*, 26(3), 546–552. <https://doi.org/10.1111/ene.13854>

Levine, B., Schweizer, T. A., O'Connor, C., Turner, G., Gillingham, S., Stuss, D. T., Manly, T., & Robertson, I. H. (2011). Rehabilitation of executive functioning in patients with frontal lobe brain damage with goal management training. *Frontiers in Human Neuroscience*, 5, 9. <https://doi.org/10.3389/fnhum.2011.00009>

Luriya, A. R. (1966). Brain and Mind. *Soviet Psychology and Psychiatry*, 4(3–4), 62–69. <https://doi.org/10.2753/RPO1061-040504030462>

Mah, Y.-H., Husain, M., Rees, G., & Nachev, P. (2014). Human brain lesion-deficit inference remapped. *Brain: A Journal of Neurology*, 137(Pt 9), 2522–2531. <https://doi.org/10.1093/brain/awu164>

Mancuso, M., Demeyere, N., Abbruzzese, L., Damora, A., Varalta, V., Pirrotta, F., Antonucci, G., Matano, A., Caputo, M., Caruso, M. G., Pontiggia, G. T., Coccia, M., Ciancarelli, I., Zoccolotti, P., & Italian OCS Group. (2018). Using the Oxford Cognitive Screen to Detect Cognitive Impairment in Stroke Patients: A Comparison with the Mini-Mental State Examination. *Frontiers in Neurology*, 9, 101. <https://doi.org/10.3389/fneur.2018.00101>

McKinney, W. (2010). *Data Structures for Statistical Computing in Python*. 56–61. <https://doi.org/10.25080/Majora-92bf1922-00a>

Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, 15(10), 483–506. <https://doi.org/10.1016/j.tics.2011.08.003>

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure & Function*, 214(5–6), 655–667. <https://doi.org/10.1007/s00429-010-0262-0>

Mesulam, M. M. (1998). From sensation to cognition. *Brain: A Journal of Neurology*, 121 ( Pt 6), 1013–1052. <https://doi.org/10.1093/brain/121.6.1013>

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, 24, 167–202. <https://doi.org/10.1146/annurev.neuro.24.1.167>

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: A latent variable analysis. *Cognitive Psychology*, 41(1), 49–100. <https://doi.org/10.1006/cogp.1999.0734>

Monsell, S. (2003). Task switching. *Trends in Cognitive Sciences*, 7(3), 134–140. [https://doi.org/10.1016/s1364-6613\(03\)00028-7](https://doi.org/10.1016/s1364-6613(03)00028-7)

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neuroscience*, 9(11), 856–869. <https://doi.org/10.1038/nrn2478>

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, 53(4), 695–699. <https://doi.org/10.1111/j.1532-5415.2005.53221.x>

Nys, G. M. S., Van Zandvoort, M. J. E., De Kort, P. L. M., Jansen, B. P. W., De Haan, E. H. F., & Kappelle, L. J. (2007). Cognitive Disorders in Acute Stroke: Prevalence and Clinical Determinants. *Cerebrovascular Diseases*, 23(5–6), 408–416. <https://doi.org/10.1159/000101464>

O'Donnell, M. J., Chin, S. L., Rangarajan, S., Xavier, D., Liu, L., Zhang, H., Rao-Melacini, P., Zhang, X., Pais, P., Agapay, S., Lopez-Jaramillo, P., Damasceno, A., Langhorne, P., McQueen, M. J., Rosengren, A., Dehghan, M., Hankey, G. J., Dans, A. L., Elsayed, A., ... Yusuf, S. (2016). Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE):

A case-control study. *The Lancet*, 388(10046), 761–775.  
[https://doi.org/10.1016/S0140-6736\(16\)30506-2](https://doi.org/10.1016/S0140-6736(16)30506-2)

Owen, G. S., Freyenhagen, F., Martin, W., & David, A. S. (2017). Clinical assessment of decision-making capacity in acquired brain injury with personality change. *Neuropsychological Rehabilitation*, 27(1), 133–148.  
<https://doi.org/10.1080/09602011.2015.1053948>

Owensworth, T. (2014). *Self-identity after brain injury*. Psychology Press.

Owensworth, T., & Clare, L. (2006). The association between awareness deficits and rehabilitation outcome following acquired brain injury. *Clinical Psychology Review*, 26(6), 783–795. <https://doi.org/10.1016/j.cpr.2006.05.003>

Pendlebury, S. T., & Rothwell, P. M. (2009). Risk of recurrent stroke, other vascular events and dementia after transient ischaemic attack and stroke. *Cerebrovascular Diseases*, 27 Suppl 3, 1–11. <https://doi.org/10.1159/000209260>

Pucciarelli, G., Lee, C. S., Lyons, K. S., Simeone, S., Alvaro, R., & Vellone, E. (2019). Quality of Life Trajectories Among Stroke Survivors and the Related Changes in Caregiver Outcomes: A Growth Mixture Study. *Archives of Physical Medicine and Rehabilitation*, 100(3), 433–440.e1. <https://doi.org/10.1016/j.apmr.2018.07.428>

Pustina, D., Avants, B., Faseyitan, O. K., Medaglia, J. D., & Coslett, H. B. (2018a). Improved accuracy of lesion to symptom mapping with multivariate sparse canonical correlations. *Neuropsychologia*, 115, 154–166.  
<https://doi.org/10.1016/j.neuropsychologia.2017.08.027>

Pustina, D., Avants, B., Faseyitan, O. K., Medaglia, J. D., & Coslett, H. B. (2018b). Improved accuracy of lesion to symptom mapping with multivariate sparse canonical correlations. *Neuropsychologia*, 115, 154–166.  
<https://doi.org/10.1016/j.neuropsychologia.2017.08.027>

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, 98(2), 676–682.  
<https://doi.org/10.1073/pnas.98.2.676>

Ramier, A. M., & Hécaen, H. (1970). [Respective rôles of frontal lesions and lesion lateralization in “verbal fluency” deficiencies]. *Revue Neurologique*, 123(1), 17–22.

Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Perceptual and Motor Skills*, 8(3), 271–276.  
<https://doi.org/10.2466/pms.1958.8.3.271>

Ribeiro, M., Yordanova, Y. N., Noblet, V., Herbet, G., & Ricard, D. (2024). White matter tracts and executive functions: A review of causal and correlation evidence. *Brain: A Journal of Neurology*, 147(2), 352–371. <https://doi.org/10.1093/brain/awad308>

Rogers, R. D., & Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General*, 124(2), 207–231. <https://doi.org/10.1037/0096-3445.124.2.207>

Rohde, D., Gaynor, E., Large, M., Mellon, L., Bennett, K., Williams, D. J., Brewer, L., Hall, P., Callaly, E., Dolan, E., & Hickey, A. (2019). Cognitive impairment and medication adherence post-stroke: A five-year follow-up of the ASPIRE-S cohort. *PloS One*, 14(10), e0223997. <https://doi.org/10.1371/journal.pone.0223997>

Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Connors, J. J. B., Culebras, A., Elkind, M. S. V., George, M. G., Hamdan, A. D., Higashida, R. T., Hoh, B. L., Janis, L. S., Kase, C. S., Kleindorfer, D. O., Lee, J.-M., Moseley, M. E., Peterson, E. D., Turan, T. N., Valderrama, A. L., ... Council on Nutrition, Physical Activity and Metabolism. (2013). An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, 44(7), 2064–2089. <https://doi.org/10.1161/STR.0b013e318296aeca>

Sánchez-Cubillo, I., Periañez, J. A., Adrover-Roig, D., Rodríguez-Sánchez, J. M., Ríos-Lago, M., Tirapu, J., & Barceló, F. (2009). Construct validity of the Trail Making Test: Role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *Journal of the International Neuropsychological Society*, 15(3), 438–450. <https://doi.org/10.1017/S1355617709090626>

Schaefer, A., Kong, R., Gordon, E. M., Laumann, T. O., Zuo, X.-N., Holmes, A. J., Eickhoff, S. B., & Yeo, B. T. T. (2018). Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cerebral Cortex*, 28(9), 3095–3114. <https://doi.org/10.1093/cercor/bhx179>

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 27(9), 2349–2356. <https://doi.org/10.1523/JNEUROSCI.5587-06.2007>

- Shallice, T., & Burgess, P. W. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain: A Journal of Neurology*, 114 ( Pt 2), 727–741. <https://doi.org/10.1093/brain/114.2.727>
- Shin, M., Sohn, M. K., Lee, J., Kim, D. Y., Lee, S.-G., Shin, Y.-I., Oh, G.-J., Lee, Y.-S., Joo, M. C., Han, E. Y., Han, J., Ahn, J., Chang, W. H., Shin, M. A., Choi, J. Y., Kang, S. H., Kim, Y., & Kim, Y.-H. (2020). Effect of Cognitive Reserve on Risk of Cognitive Impairment and Recovery After Stroke: The KOSCO Study. *Stroke*, 51(1), 99–107. <https://doi.org/10.1161/STROKEAHA.119.026829>
- Siciliano, M., Chiorri, C., Battini, V., Sant’Elia, V., Altieri, M., Trojano, L., & Santangelo, G. (2019). Regression-based normative data and equivalent scores for Trail Making Test (TMT): An updated Italian normative study. *Neurological Sciences*, 40(3), 469–477. <https://doi.org/10.1007/s10072-018-3673-y>
- Siddiqi, S. H., Kording, K. P., Parvizi, J., & Fox, M. D. (2022). Causal mapping of human brain function. *Nature Reviews. Neuroscience*, 23(6), 361–375. <https://doi.org/10.1038/s41583-022-00583-8>
- Siddiqi, S. H., Taylor, S. F., Cooke, D., Pascual-Leone, A., George, M. S., & Fox, M. D. (2020). Distinct Symptom-Specific Treatment Targets for Circuit-Based Neuromodulation. *The American Journal of Psychiatry*, 177(5), 435–446. <https://doi.org/10.1176/appi.ajp.2019.19090915>
- Siegel, J. S., Seitzman, B. A., Ramsey, L. E., Ortega, M., Gordon, E. M., Dosenbach, N. U. F., Petersen, S. E., Shulman, G. L., & Corbetta, M. (2018). Re-emergence of modular brain networks in stroke recovery. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, 101, 44–59. <https://doi.org/10.1016/j.cortex.2017.12.019>
- Sörös, P., Harnadek, M., Blake, T., Hachinski, V., & Chan, R. (2015). Executive dysfunction in patients with transient ischemic attack and minor stroke. *Journal of the Neurological Sciences*, 354(1–2), 17–20. <https://doi.org/10.1016/j.jns.2015.04.022>
- Sporns, O. (2011). The human connectome: A complex network. *Annals of the New York Academy of Sciences*, 1224, 109–125. <https://doi.org/10.1111/j.1749-6632.2010.05888.x>
- Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society: JINS*, 8(3), 448–460.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, 47(10), 2015–2028. <https://doi.org/10.1016/j.neuropsychologia.2009.03.004>

Stern, Y., Arenaza-Urquijo, E. M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W. S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksima, E., & the Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup. (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 16(9), 1305–1311. <https://doi.org/10.1016/j.jalz.2018.07.219>

Stinear, C. M., Barber, P. A., Smale, P. R., Coxon, J. P., Fleming, M. K., & Byblow, W. D. (2007). Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain: A Journal of Neurology*, 130(Pt 1), 170–180. <https://doi.org/10.1093/brain/awl333>

Stolwyk, R. J., Mihaljcic, T., Wong, D. K., Chapman, J. E., & Rogers, J. M. (2021a). Poststroke Cognitive Impairment Negatively Impacts Activity and Participation Outcomes: A Systematic Review and Meta-Analysis. *Stroke*, 52(2), 748–760. <https://doi.org/10.1161/STROKEAHA.120.032215>

Stolwyk, R. J., Mihaljcic, T., Wong, D. K., Chapman, J. E., & Rogers, J. M. (2021b). Poststroke Cognitive Impairment Negatively Impacts Activity and Participation Outcomes: A Systematic Review and Meta-Analysis. *Stroke*, 52(2), 748–760. <https://doi.org/10.1161/STROKEAHA.120.032215>

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, 18(6), 643–662. <https://doi.org/10.1037/h0054651>

Stuss, D. T., & Alexander, M. P. (2007). Is there a dysexecutive syndrome? *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 362(1481), 901–915. <https://doi.org/10.1098/rstb.2007.2096>

Sun, J.-H., Tan, L., & Yu, J.-T. (2014). Post-stroke cognitive impairment: Epidemiology, mechanisms and management. *Annals of Translational Medicine*, 2(8), 80. <https://doi.org/10.3978/j.issn.2305-5839.2014.08.05>

Tay, M. R. J. (2021). Hospital readmission in stroke survivors one year versus three years after discharge from inpatient rehabilitation: Prevalence and associations in an Asian cohort. *Journal of Rehabilitation Medicine*, 53(6), jrm00208. <https://doi.org/10.2340/16501977-2849>

- Tian, Y., Margulies, D. S., Breakspear, M., & Zalesky, A. (2020). Topographic organization of the human subcortex unveiled with functional connectivity gradients. *Nature Neuroscience*, 23(11), 1421–1432. <https://doi.org/10.1038/s41593-020-00711-6>
- Umarova, R. M., Sperber, C., Kaller, C. P., Schmidt, C. S. M., Urbach, H., Klöppel, S., Weiller, C., & Karnath, H.-O. (2019). Cognitive reserve impacts on disability and cognitive deficits in acute stroke. *Journal of Neurology*, 266(10), 2495–2504. <https://doi.org/10.1007/s00415-019-09442-6>
- van Swieten, J. C., Koudstaal, P. J., Visser, M. C., Schouten, H. J., & van Gijn, J. (1988). Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, 19(5), 604–607. <https://doi.org/10.1161/01.str.19.5.604>
- Varoquaux, G. (2018). Cross-validation failure: Small sample sizes lead to large error bars. *NeuroImage*, 180(Pt A), 68–77. <https://doi.org/10.1016/j.neuroimage.2017.06.061>
- Wagner, T., Rushmore, J., Eden, U., & Valero-Cabre, A. (2009). Biophysical foundations underlying TMS: Setting the stage for an effective use of neurostimulation in the cognitive neurosciences. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, 45(9), 1025–1034. <https://doi.org/10.1016/j.cortex.2008.10.002>
- Ward, N. S., Brown, M. M., Thompson, A. J., & Frackowiak, R. S. J. (2003). Neural correlates of motor recovery after stroke: A longitudinal fMRI study. *Brain: A Journal of Neurology*, 126(Pt 11), 2476–2496. <https://doi.org/10.1093/brain/awg245>
- Yang, J., Gao, Y., Yang, L., Jiang, Y., Wan, B., Bayrak, Ş., Liang, X., Valk, S. L., Corbetta, M., & Gong, G. (2026). *Structural brain networks shape individual-level progression of brain atrophy after stroke*. *Neuroscience*. <https://doi.org/10.64898/2026.05.08.723677>
- Yeh, F.-C. (2022). Population-based tract-to-region connectome of the human brain and its hierarchical topology. *Nature Communications*, 13(1), 4933. <https://doi.org/10.1038/s41467-022-32595-4>
- Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., & Gerig, G. (2006). User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *NeuroImage*, 31(3), 1116–1128. <https://doi.org/10.1016/j.neuroimage.2006.01.015>

Zinn, S., Bosworth, H. B., Hoenig, H. M., & Swartzwelder, H. S. (2007a). Executive function deficits in acute stroke. *Archives of Physical Medicine and Rehabilitation*, 88(2), 173–180. <https://doi.org/10.1016/j.apmr.2006.11.015>

Zinn, S., Bosworth, H. B., Hoenig, H. M., & Swartzwelder, H. S. (2007b). Executive function deficits in acute stroke. *Archives of Physical Medicine and Rehabilitation*, 88(2), 173–180. <https://doi.org/10.1016/j.apmr.2006.11.015>