Improving, Understanding and Predicting Cognitive Outcomes in Herpes Simplex Virus Encephalitis

Thesis submitted in accordance with the requirements of the University of Liverpool, for the degree of Doctor in Philosophy in Neurological Sciences

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Declaration

Except for the assistance outlined in the roles and responsibilities section, the work described is my own work and has not been submitted for a degree or other qualification to this or any other university. I confirm that the work submitted is my own, except where work which has formed part of jointly authored publications has been included. My contribution and the contribution of other authors to this work have been explicitly indicated below and appropriate credit has been given within the thesis where reference has been made to the work of others.

Abstract

Herpes simplex virus (HSV) encephalitis is a severe neurological infection and the most common cause of acute viral encephalitis worldwide. With the introduction of aciclovir in the 1980s, mortality rates decreased from around 80% to 20%. However, many patients experience significant cognitive difficulties, which impact their quality of life. Converging lines of evidence suggest that the host immune and inflammatory response mediates at least some neurological damage and, consequently, poor outcomes, and might be modifiable with the anti-inflammatory drug dexamethasone. Yet, key questions remain about the mechanisms underlying cognitive impairment and the potential for recovery.

My research aimed to (i) assess the impact of adjunctive dexamethasone on cognitive outcomes in HSV encephalitis, (ii) characterise the prevalence, nature, and potential for long-term recovery of cognitive deficits, and (iii) evaluate the ability of cognitive screening and neuroimaging to better identify poor cognitive outcomes.

A multicentre randomised controlled trial was conducted to compare aciclovir alone with aciclovir plus adjunctive dexamethasone, using verbal memory as the primary outcome. Although verbal memory did not differ between groups at 26 weeks, within the dexamethasone group, earlier administration was associated with improved scores.

This trial generated a unique dataset of longitudinal neuropsychological assessments in patients with HSV encephalitis. Using this dataset, I examined the full cohort to characterise the prevalence and pattern of cognitive impairments and explore the potential for recovery. The findings revealed substantial, widespread cognitive deficits that persisted over time and, in some cases, worsened.

In light of these persisting impairments, I examined the ability of the Addenbrooke's Cognitive Examination (ACE-III) to detect cognitive impairment cross-sectionally and to determine whether early cognitive screening could predict those who would continue to experience persistent deficits. The ACE-III lacked sufficient sensitivity and specificity, particularly for identifying milder impairments.

Since the ACE-III was only of limited value in predicting those with persistent deficits, I investigated early MRI markers as potential predictors of cognitive outcome, with the aim of identifying more reliable biomarkers. I found that early volumetric changes in the hippocampus and temporal lobe were associated with long-term cognitive outcomes, particularly verbal memory. The use of adjunctive dexamethasone appeared to mitigate these volume–cognition associations, suggesting that early immunomodulation may help reduce damage.

Collectively, these findings have important implications for clinical practice and future research. They highlight the potential benefit of early dexamethasone, the variety of patterns of cognitive impairment, the need for more disease-specific cognitive assessment tools, and the value of early neuroimaging biomarkers in predicting

cognitive outcomes. These findings can help inform clinical management and rehabilitation strategies, ultimately aiming to improve long-term cognitive outcomes and HSV encephalitis patients' quality of life.

Preface - A Research Odyssey

The hum of tyres on tarmac was my constant companion during my PhD studies. A soundtrack to a journey that stretched across 35 cities, countless cups of service station coffee, and more than 30,000 miles of UK motorways. As a researcher working on a nationwide clinical trial, my role was equal parts scientist and navigator. I travelled the UK by car, train, and plane, lugging assessment kits into patients' homes, care homes, and hospitals to collect the data for this thesis.

But fieldwork, as I learned, has a way of rewriting even the best-laid plans. Take the morning I flew to Dublin to assess a participant enrolled in a sister study in France. Minutes after landing, the Irish government announced a sudden COVID-19 lockdown. The empty streets felt surreal as I scrambled to complete the assessment before travelling home on one of the last flights out.

Then there was the 5 a.m. mishap—a bleary-eyed dash to catch a Manchester flight to Newquay. Half-asleep, I boarded the wrong train and only realised my mistake as the conductor announced, “Next stop…. Huddersfield”. This was the final day I could see this patient, and I was now travelling in the opposite direction. When studying a rare disease these follow-ups matter. I doubled back, traded my flight for an eight-hour drive, and arrived in Newquay just in time.

The resilience, flexibility and ingenuity I had to show in order to meet with and assess all the patients in my study reflects the broader resilience, flexibility and ingenuity I needed to address the scientific challenges of the PhD thesis. But this was a physical, mental and emotional journey that was definitely worthwhile.

The roles and responsibilities of the work

Chapter 3 - This chapter describes the findings of a clinical trial conceived and designed by researchers in the Liverpool Brain Infections Group.

My contributions include neuropsychological and neuroimaging data collection, data checking and cleaning, writing neuroimaging statistical analysis plan, analysing and interpreting data, visualisation of data, writing the initial manuscript draft, and responding to reviewers' comments following submission.

Additional contributions are as follows:

Tom Solomon Ph.D., Ava Easton Ph.D., Anna Rosala-Hallas MSc., Bethany Facer MSc, Perry Moore Ph.D., Simon Keller Ph.D., Tom Whitfield Ph.D., Cristina Fernandez MB ChB, Rachel Kneen BM BS., Michael Griffiths Ph.D, Kumar Das Ph.D, Shona Claire Moore Ph.D., Kelly Davies BSc, Dianne Wheatley BA, Jean Paul Stahl Ph.D, Ben Hardwick MRes, Sylvianne Defres Ph.D., Ben D. Michael Ph.D., Girvan Burnside Ph.D., Mark A. Ellul Ph.D.

TS, AE, RK, MG, SD and BMD devised the idea for the study. TS, AE, PM, SK, CF, RK, MG, KD, BH, BDM and GH Wrote the protocol and submitted the ethics and research and development applications. ARH, TW, CF, SCM, BH, SD and MAE collected data. TS, ARH, BF, PM, SK, KD, SCM, KD, DW, GB and MAE analysed and interpreted data. TS, SCM, GB and MAE wrote the initial draft of the manuscript

and had access to all the data in the study. All authors critically reviewed the manuscript drafts, approved the final draft, and revised versions for submission.

In addition, the Oxford Autoimmune Neurology Group conducted the anti-NMDAR antibody testing of cerebrospinal fluid and serum samples for the DexEnceph trial.

Chapters 4, 5 & 6 - Subsequent chapters include the data collected in chapter 2. I designed and conceived these studies with support from my supervisory team, Prof Tom Solomon, Prof Simon Keller, Dr Perry Moore, and Prof Benedict Michael. I conducted all formal analysis, visualisation and writing. I would also like to thank Dr Girvan Burnside for his advice on statistical analysis and Bethany Facer who assisted with the stereological analysis of magnetic resonance imaging scans in chapter 6.

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I was supported in this research by Encephalitis International, and I would like to thank the staff for their ongoing support. I would also like to thank all the patients for taking part in the study, and for the cups of tea!

It has been a privilege to have worked with my supervisory team, Professor Tom Solomon, Professor Simon Keller, Dr Perry Moore and Professor Benedict Michael. I am particularly grateful to Tom Solomon, my primary supervisor, for giving me the opportunity to work in this fascinating area and the support during my PhD. Thank you to the colleagues and friends in the Liverpool Brain Infections group and the BRAIN lab for their informal advice and support over the last six years.

Finally thank you to my wonderful parents, none of this would be possible without you. And to Emily, thank you for your patience, love and support, I owe you.

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List of abbreviations

ACE-III	Addenbrookes Cognitive Examination-III
ADC	Apparent Diffusion Coefficient
AI	Artificial Intelligence
AMI	Auditory Memory Index
AUC	Area Under the Curve
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CI	Confidence Intervals
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DMI	Delayed Memory Index
DNA	Deoxyribonucleic Acid
DWI	Diffusion Weighted Imaging
FLAIR	Fluid Attenuated Inversion Recovery
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Score Extended
HDU	High Dependency Unit
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
ICC	Intraclass Correlation Coefficient
ICU	Intensive Care Unit
ICV	Intracranial Volume
IDSMC	Independent Data Safety and Monitoring Committee
IL	Interleukin
IMI	Immediate Memory Index
IQ	Intelligence Quotient
IQR	Interquartile Range
ITU	Intensive Care Unit
IV	Intravenous
LOS	Liverpool Outcome Score
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NMDAR	N-Methyl-D-Aspartate receptor
NPV	Negative Predictive Value
OR	Odds Ratio

PCR	Polymerase Chain Reaction
PDQ	Perceived Deficits Questionnaire
PPV	Positive Predictive Value
PSI	Processing Speed Index
RF	Radiofrequency
ROC	Receiver Operator Curve
SAEs	Serious Adverse Events
SD	Standard Deviation
TDS	Three Times Daily
TE	Echo Times
TMT	Trail Making Test
TOPF	Test of Premorbid Functioning
TR	Short Repetition
VMI	Visual Memory Index
WAIS	Weschler Adult Intelligence Scale
WASI	Weschler Adult Scale of Intelligence
WBV	Whole. Brain Volume
WCST	Wisconsin Card Sorting Test
WMI	Working Memory Index
WMS	Weschler Memory Scale
WTAR	Weschler Tests of Adult Reading

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Chapter 1 Introduction

1.1 Encephalitis: A Global Neurological Challenge

Encephalitis, defined as inflammation of the brain parenchyma, is a life-threatening neurological condition with significant morbidity and mortality (Hansen et al., 2020; Singh et al., 2015a). The condition arises from a variety of aetiologies, including viral infections, autoimmune processes, and, less commonly, bacterial or parasitic infections (Granerod et al., 2010). Despite advances in diagnostic techniques and therapeutic interventions, encephalitis remains a major public health concern, with an estimated global incidence of 3.5–8.7 cases per 100,000 individuals annually (Granerod et al., 2013; Granerod & Crowcroft, 2007; Jmor et al., 2008). Mortality rates range from 5.6% to 39.3%, depending on the cause, timeliness of treatment, and access to healthcare resources (Jmor et al., 2008; Rezaei & Mateen, 2021; Vora et al., 2014). People post HSV encephalitis often face long-term neurological sequelae, including cognitive impairment, epilepsy, motor deficits and psychiatric impairment, which contribute to a substantial socioeconomic burden (Venkatesan, 2015; H. Wang et al., 2022).

1.2 Herpes Simplex Virus (HSV) Encephalitis

HSV encephalitis is the most common cause of sporadic viral encephalitis worldwide, accounting for around 50% of all encephalitis cases (Singh et al., 2015b).

With the introduction of aciclovir in the 1980s, mortality rates decreased from approximately 80% to 20% (McGrath et al., 1997). However, many people post HSV encephalitis experience significant cognitive and psychiatric impairments, which profoundly impact their quality of life and ability to reintegrate into society. The pathogenesis of HSV encephalitis involves direct viral cytotoxicity and immune-mediated damage, creating a complex interplay between viral replication and host immune responses. This dual pathology underscores the need for adjunctive therapies targeting viral replication and neuroinflammation to improve outcomes.

1.2.1 Epidemiology

HSV encephalitis occurs sporadically across all age groups, with a bimodal distribution peaking in individuals under 20 and more than 50 years of age (Abel et al., 2010; George et al., 2014). Immunocompromised individuals, such as those with human immunodeficiency virus/acquired immunodeficiency syndrome or undergoing immunosuppressive therapy, are at increased risk of HSV encephalitis, though most cases occur in immunocompetent hosts (Tang et al., 2024). Geographic and socioeconomic disparities influence outcomes, with higher mortality rates in low-resource settings due to delayed diagnosis and limited access to antiviral therapy (Granerod et al., 2023). In high-income countries, the incidence of HSV encephalitis is estimated at 2–4 cases per million individuals annually, with no significant seasonal variation (Defres et al., 2023; Granerod et al., 2013; R. J. Whitley, 2006).

1.3 Mechanisms, Clinical Manifestations and Management

1.3.1 Virology and pathogenesis

Herpes Simplex Virus types 1 and 2 (HSV-1 and HSV-2) are double-stranded DNA viruses of the Herpesviridae family, are transmitted via direct contact with infected secretions, infecting more than 50% of adults globally (Bradley et al., 2014). HSV initially gains access to host tissues through mucosal surfaces or microscopic breaks in the skin, where it replicates locally (R. Whitley et al., 2007). From there, the virus travels to peripheral sensory nerve endings and undergoes retrograde axonal transport, travelling along microtubules within neurons to reach the neuronal cell bodies in sensory ganglia (Zhu & Viejo-Borbolla, 2021).

After primary infection, HSV-1 establishes latency in the trigeminal ganglia, reactivating periodically to produce mucocutaneous lesions (e.g., cold sores) (Marcocci et al., 2020). In contrast, HSV-2 establishes latency in the sacral ganglia and primarily causes recurrent genital lesions (Cook et al., 2018; Holmes et al., 2008). The establishment of latency is a hallmark of HSV infection and occurs when viral DNA circularizes and persists as an episome within neurons, avoiding detection by the host immune system (Whitley & Roizman, 2001). During latency, the virus expresses only a subset of genes, such as the latency-associated transcripts, which play a role in maintaining the latent state and promoting reactivation (Perng & Jones, 2010) (see figure 1-1 for illustrative example of acute and latent infection). Reactivation can be triggered by various stimuli, including stress, fever and immunosuppression (Perng & Jones, 2010; R. J. Whitley & Roizman, 2001). Notably, HSV-1 is more commonly associated with HSV encephalitis, accounting for 90% of

cases (Raschilas et al., 2002). While HSV-2 can cause HSV encephalitis it is more frequently linked with aseptic meningitis (Jarratt & Hubler, 1974)

The route by which HSV gains access to the brain is incompletely understood. Retrograde axonal transport from peripheral sites has been proposed, where viral particles hijack the microtubule-based transport machinery within neurons to travel from the periphery to the Central Nervous System (CNS) (Bradshaw & Venkatesan, 2016). Hematogenous spread during viremia has also been proposed as a potential mechanism for CNS invasion; however, the localized nature of HSV-1 infection in the medial temporal lobes makes this route less likely. Factors such as viral load, host immune status, and genetic predisposition are thought to influence the likelihood of CNS invasion, although the precise interplay between these factors remains poorly understood (Bradshaw & Venkatesan, 2016).

1.3.2 Pathophysiology

Once HSV-1 enters the brain, it exhibits a marked tropism for both neurons and astrocytes in the medial temporal lobes (Ando et al., 2008). During lytic replication, viral tegument proteins and the virion host shutoff protein collaborate to degrade host messenger ribonucleic acid (mRNA), inhibiting normal cellular protein production and redirecting the cell's transcriptional and translational machinery toward viral gene expression (Zhu & Viejo-Borbolla, 2021). This disruption triggers endoplasmic reticulum stress and mitochondrial dysfunction, ultimately leading to neuronal necrosis (Rashidi et al., 2024), particularly in the hippocampus—a region integral to

memory (Ando et al., 2008; Michael et al., 2020). Histopathological hallmarks of HSV encephalitis include neuronal loss, intranuclear Cowdry A inclusions, and syncytia formation (Ak et al., 2025). Although these direct viral effects are critical contributors to the disease process, recent findings underscore the pivotal role of the host immune response in shaping the pathology of HSV encephalitis.

1.3.3 Host Immune Response

The innate immune response is paramount in controlling HSV infection within the CNS. However, immune dysregulation can drive significant pathology (Piret & Boivin, 2015). Pattern recognition receptors, such as Toll-like receptors, detect both pathogen-associated molecular patterns—including viral glycoproteins and double-stranded RNA generated during HSV-1 replication—and damage-associated molecular patterns released by injured or necrotic host cells (Michael et al., 2020; Paludan et al., 2011; Rock et al., 2004; Takeuchi & Akira, 2010). Microglia and astrocytes express multiple toll-like receptors that, upon encountering these signals, activate NF-KB and interferon-regulatory pathways (Spatola & Du Pasquier, 2014), leading to the production of pro-inflammatory cytokines (e.g., IL-6, tumour necrosis factor-α) and chemokines (CCL2–CCR2) (Kamei et al., 2009; Michael et al., 2020; Sergerie, Rivest, et al., 2007).

Although these mediators are crucial for restricting viral spread, they also promote leukocyte infiltration across a compromised blood-brain barrier, exacerbating neuroinflammation and oedema (Michael et al., 2020). There is a delicate balance of

toll-like receptor signalling in HSV encephalitis. For example, TLR2 deficiency in mice can mitigate immunopathology (Kurt-Jones et al., 2004). While TLR3 mutations in humans can lead to severe or recurrent HSV encephalitis (Sironi et al., 2017).

Recent work highlights how different innate cell populations variably affect disease severity. CCL2–CCR2 signalling drives the recruitment of inflammatory monocytes essential for clearing HSV-1; when this pathway is disrupted, viral load rises, and morbidity increases (Michael et al., 2020). In contrast, CXCL1–CXCR2-mediated neutrophil infiltration markedly compromises the blood-brain barrier and exacerbates immunopathology without significantly altering viral titres. Neutrophils formed dense perivascular swarms and correlated with increased blood-brain barrier permeability and oedema, whereas blocking CXCR2 reduced tissue damage and improved survival. Several clinical investigations reinforce the link between heightened pro-inflammatory responses and poor prognosis in HSV encephalitis. Elevated Cerebrospinal Fluid (CSF) interferon-γ, monocyte chemoattractant protein (MCP)-1 and IL-6 in the CSF of adult HSV encephalitis patients correlated strongly with worse outcomes (Kamei et al., 2009). Similarly, a higher CSF IL-1β/IL-1 receptor antagonist (IL-1RA) ratio correlates with poor outcomes and brain swelling (Michael et al., 2016).

There is increasing recognition of the development of autoimmune encephalitis post-HSV encephalitis. Antibodies primarily targeting N-methyl-D-aspartate receptors (NMDAR) can develop as a complication of HSV encephalitis. Following HSV-1 infection, molecular mimicry or bystander activation of the immune system can lead to the production of autoantibodies against NMDAR, particularly the GluN1 subunit

(Armangue et al., 2015).These autoantibodies disrupt NMDAR function, leading to symptoms such as psychosis, seizures, movement disorders, and cognitive impairment, which often manifest weeks to months after the initial HSV encephalitis episode (Armangue et al., 2015). The exact mechanisms triggering this autoimmune response remain unclear, but genetic predisposition, excessive inflammation during acute HSV encephalitis, and prolonged antigen exposure have previous been suggested as potential mechanisms (Cleaver et al., 2024). Importantly, patients with post-HSV encephalitis autoimmune encephalitis typically exhibit pro-inflammatory CNS cytokine profiles associated with neuronal cell death, which can vary depending on the clinical trajectory (Kothur et al., 2017).

HSV-1 pathogenesis involves a complex interplay between viral mechanisms and host immune responses. Understanding these processes not only sheds light on the pathophysiology of HSV encephalitis but also informs the development of improved diagnostic tools and therapeutic intervention.

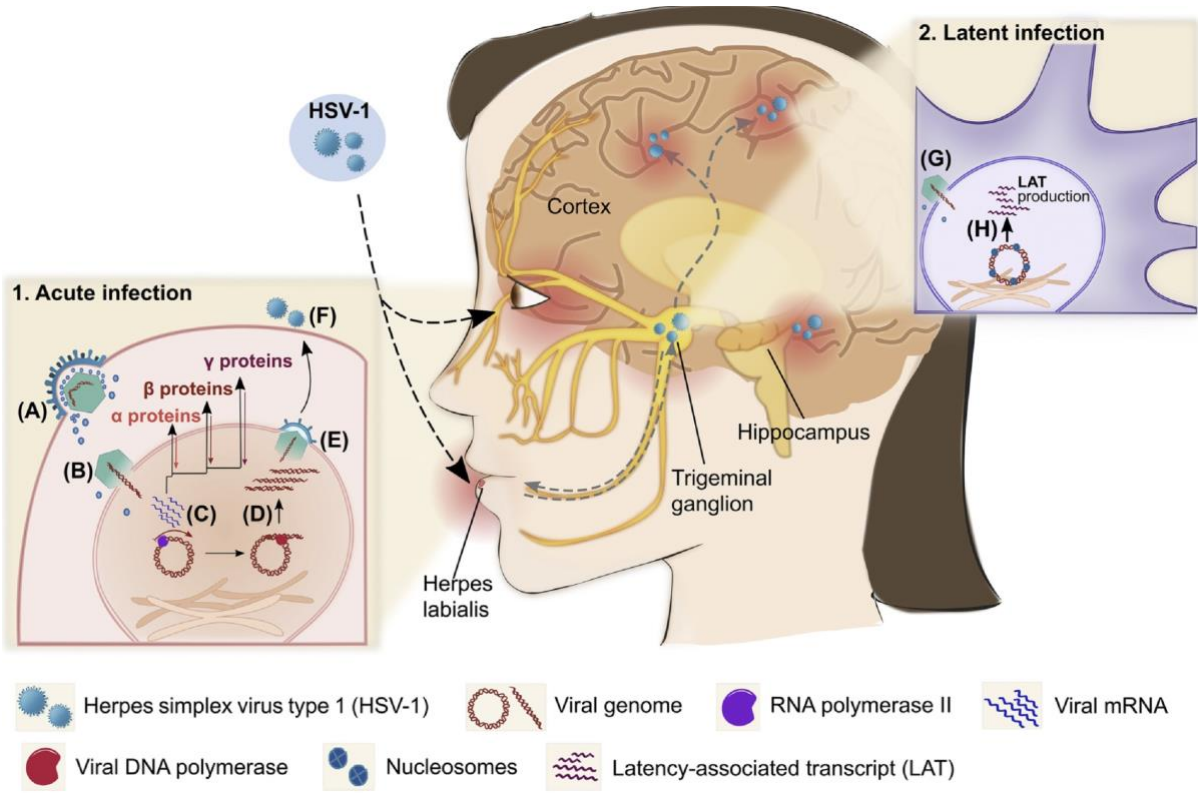

Figure 1-1: Schematic representation of acute and latent HSV-1 infection in humans.

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1.3.4 Clinical Features and Disease Course

Early symptoms are typically non-specific, including fever, headache, and malaise, which can rapidly progress to significant neurological impairment (Hansen et al., 2020). Altered mental status is a hallmark feature, with confusion, disorientation, and decreased consciousness observed in most cases. Psychiatric and behavioural

manifestations, such as agitation, and personality changes, are common, reflecting limbic system involvement (Granerod et al., 2010).

Seizures are a frequent early manifestation, occurring in up to 75% of patients at presentation, and may progress to status epilepticus in severe cases (Misra & Kalita, 2009). Focal neurological deficits, particularly speech difficulties and memory impairment, correspond to viral damage within the medial temporal lobes, while hemiparesis, one sided muscle weakness, and cranial nerve dysfunction may indicate more extensive cortical involvement (Chow et al., 2015; Venkatesan et al., 2019). Patients with HSV encephalitis more often present with fever, lower serum sodium levels, and typically lack a rash compared to alternative encephalitis diagnoses (Defres et al., 2023).

Without antiviral therapy, HSV encephalitis progresses rapidly, leading to coma and high mortality (R. J. Whitley et al., 1977). Even with early administration of aciclovir, long-term neurological sequelae, particularly persistent memory impairment, remain common (Harris et al., 2020; McGrath et al., 1997; R. J. Whitley et al., 1986). While viral relapse following HSV encephalitis is rare, a subset of patients develop post-infectious autoimmune encephalitis, frequently mediated by anti-NMDA receptor antibodies. This immune-mediated complication typically manifests weeks after the initial infection, characterized by distinct neuropsychiatric features (e.g., psychosis, movement disorders), recurrent seizures, and progressive cognitive impairment (Armangue et al., 2015, 2018).

Given the fulminant nature and the potential for irreversible neurological injury, early recognition of HSV encephalitis based on the characteristic clinical features is imperative to enable timely diagnosis and intervention.

1.3.5 Diagnosis

The diagnosis of HSV encephalitis relies on a combination of identifying clinical features, described in the previous section, CSF analysis, and neuroimaging.

CSF analysis typically reveals lymphocytic pleocytosis, elevated protein levels, and the presence of HSV DNA detected by polymerase chain reaction (PCR) (Ak et al., 2025; Saraya et al., 2016). PCR is highly sensitive and specific, with accuracy exceeding 95% (Ak et al., 2025).

Magnetic resonance imaging (MRI) is the most sensitive and specific imaging method for diagnosing HSV encephalitis (Bradshaw & Venkatesan, 2016). Characteristic findings include T2/Fluid Attenuated Inversion Recovery (FLAIR) hyperintensities in the medial temporal lobes, insulae, and cingulate gyri. Diffusion-weighted imaging (DWI) often shows restricted diffusion in acute necrotizing lesions (Demaerel et al., 1992; Granerod et al., 2016). Computed tomography may be used but is less sensitive, particularly in the early stages, as abnormalities can be subtle or absent before the fifth day of illness (Zimmerman et al., 1980).

1.3.6 Treatment

Aciclovir

The primary treatment for HSV encephalitis is intravenous acyclovir, which has significantly improved prognosis (Solomon et al., 2012; R. J. Whitley et al., 1986). Acyclovir is a nucleoside analogue that inhibits viral DNA replication by selectively targeting the HSV thymidine kinase enzyme, which phosphorylates acyclovir into its active form. This active metabolite disrupts viral DNA polymerase activity, halting viral replication (Aboelezz & Mahmoud, 2024). Administered at a dose of 10 mg/kg every 8 hours for 14–21 days, acyclovir reduces mortality from approximately 70% to 20% (McGrath et al., 1997; R. J. Whitley et al., 1986).

Early initiation of treatment is critical as delays beyond 48 hours after symptom onset can worsen outcomes (Raschilas et al., 2002). Ideally, lumbar puncture should be performed immediately in patients with suspected brain infection, and empirical acyclovir treatment initiated without delay. If lumbar puncture is delayed for more than 6 hours, empirical acyclovir should still be started promptly to avoid worsening outcomes (Solomon et al., 2012).

Patients with HSV encephalitis often remain PCR-positive in the CSF for several days after starting treatment. Therefore, a follow-up lumbar puncture is recommended after 2 weeks of therapy to confirm clearance of the virus. If the PCR

remains HSV positive, acyclovir should be continued, with repeat lumbar punctures performed weekly until the PCR becomes negative (Solomon et al., 2012).

Corticosteroids

Corticosteroids, such as dexamethasone, are synthetic anti-inflammatory agents widely used in clinical practice. Corticosteroids modulate both acute and chronic inflammation by suppressing pro-inflammatory signalling pathways and reducing the expression of inflammatory mediators (Cruz-Topete & Cidlowski, 2018). Their efficacy in various infectious and non-infectious neurological diseases has been demonstrated (de Gans & van de Beek, 2002; Ryken et al., 2010; Thwaites et al., 2004). Given their ability to reduce cerebral oedema and reduce neuroinflammation, some have suggested that they may be beneficial in HSV encephalitis (Openshaw & Cantin, 2005).

The use of corticosteroids in HSV encephalitis dates back to the pre-acyclovir era when clinicians sought ways to alleviate cerebral oedema and reduce intracranial pressure in patients with severe encephalitis (Upton et al., 1971). Even after the advent of acyclovir, corticosteroids have occasionally been used as adjunctive therapy to address complications arising from excessive neuroinflammation (Venkatesan et al., 2019).

Although some retrospective studies have shown potential benefits of corticosteroids in HSV encephalitis, their effectiveness remains unproven (Kamei et al., 2005). A

recent randomised control trial addressing steroids in HSV encephalitis failed to reach the primary endpoint, highlighting the challenges of conducting studies in critically ill patients with CNS infections (U. Meyding-Lamadé et al., 2019). Furthermore, there are theoretical concerns regarding the potential risk of exacerbating uncontrolled viral replication.

The host immune response significantly contributes to neuronal damage in HSV encephalitis. Adjunctive treatments that can modulate excessive inflammation without compromising viral control are needed. However, until further evidence becomes available, corticosteroids are not currently recommended as part of standard treatment (Solomon et al., 2012). An adequately powered randomised controlled trial is urgently needed to clarify the safety and efficacy of corticosteroids at reducing poor outcomes in HSV encephalitis.

1.4 Neuropsychology of HSV Encephalitis

1.4.1 Determinants of Cognitive Outcomes in Herpes Simplex Encephalitis

Neuropsychology explores how distinct cognitive domains—such as memory, attention, language, and executive function—influence daily life (Andrewes, 2015). In herpes simplex encephalitis (HSV encephalitis), damage to these domains can impair everyday activities (Harris et al., 2020; Raschilas et al., 2002).

The biopsychosocial model posits that outcomes arise from the interplay of biological factors (e.g. lesion extent and location), premorbid characteristics (such as age, education, and cognitive reserve), and psychosocial influences (including psychological health, social support, and access to rehabilitation) (Mamman et al., 2024; Yeates et al., 2008). Given the limited HSV encephalitis-specific data, insights from wider acquired brain injury and other forms of limbic encephalitis can help elucidate these determinants.

Comparative evidence from limbic-predominant autoimmune encephalitis supports the inference that injury to medial temporal networks leads to enduring morbidity beyond the acute phase. In a multicentre cohort study of LGI1-antibody encephalitis, despite favourable functional recovery on standard disability scales, return to premorbid employment was uncommon. Residual deficits across cognition, mood, and fatigue were frequent. Fatigue was the most prevalent long-term symptom and correlated with poorer cognitive performance (Binks et al., 2021). In a different cohort, prospectively evaluated patients during the post-acute year and showed that unrecognised yet treatable drivers of morbidity; REM sleep behaviour disorder, fragmented sleep, and nocturnal focal seizures, were common soon after initial immunotherapy and improved with additional immunotherapy. Nevertheless, by about 12 months most patients still had measurable cognitive deficits (13/20; 65%). Absence of early rituximab, REM sleep without atonia, and persistent serum LGI1 antibodies at study entry were associated with poorer cognitive outcomes, supporting structured, longitudinal, multi-domain follow-up (Muñoz-Lopetegi et al., 2024). Across autoimmune encephalitis more broadly, fatigue is highly prevalent (61–65%), often missed by conventional disability scales (with >80% scoring mRS

0–2) and not fully explained by depression or sleep quality, supporting routine screening and inclusion as an outcome measure (Diaz-Arias et al., 2021).

1.4.2 Illness severity

Acute illness severity is a key predictor of cognitive outcome in HSV encephalitis. Lower Glasgow Coma Scale (GCS) scores at admission are associated with more functional outcomes. (Raschilas et al., 2002; Wei et al., 2023). Longer delays in initiating antiviral treatment correlate with poorer intelligence, memory, and executive function (Harris et al., 2020). Moreover, bilateral temporal lobe damage, particularly involving the hippocampi, is strongly linked to severe memory impairment, while unilateral damage may result in milder deficits (Kapur et al., 1994). In addition, the presence of seizures, which are common during the acute phase, signals a greater extent of oedema and is associated with poorer functional outcomes (Alam et al., 2022; Misra & Kalita, 2009). Seizures not only reflect severe underlying pathology but can also exacerbate injury through excitotoxicity, further disrupting cognitive networks.

1.4.3 Premorbid Characteristics

Premorbid factors significantly influence recovery. Older age has been linked to deficits in naming and executive functions (Harris et al., 2020). However, it is unclear whether this is due to more severe acute illness or reduced neuroplasticity in

recovery (de la Plata et al., 2008). Equally important is cognitive reserve. Evidence from the wider acquired brain injury demonstrates that individuals with higher reserve appear better able to compensate for neural damage literature (Rosenich et al., 2020; Steward et al., 2018). Pre-existing psychological difficulties, such as a history of depression or anxiety, can lead to persistent cognitive complaints (Beier et al., 2015; van Rijsbergen et al., 2019). Research in HSV encephalitis has demonstrated correlations between depressive symptoms and poorer performance in working memory, selective attention, and verbal fluency (Pewter et al., 2007). Additionally, shifts in self-identity following HSV encephalitis can affect motivation and engagement in rehabilitation, further influencing cognitive recovery (Dewar & Gracey, 2007)

1.4.4 Social Support and Rehabilitation

Psychosocial outcomes are poor in encephalitis (Ramanuj et al., 2014). Although research specific to encephalitis is limited, studies in acquired brain injury indicate that strong support networks facilitate better recovery. Support from family and peers helps reduce stress and encourages adherence to cognitive strategies, which in turn can enhance rehabilitation efforts (Fisher et al., 2020; Hibbard et al., 2002).

Although HSV encephalitis-specific research is limited, insights from broader acquired brain injury studies help illustrate how multiple factors—illness severity, premorbid characteristics, and psychosocial supports—interact to shape long-term cognitive functioning. In HSV encephalitis, low GCS, delayed treatment, bilateral

temporal lobe damage, and seizures set the biological basis for impairment, while age, education, cognitive reserve, and psychological well-being may modulate recovery. Understanding what the spectrum of cognitive outcomes are in HSV encephalitis could help patients and families adjust their expectations and plan for recovery and engage more effectively with rehabilitation, while also equipping clinicians with the evidence needed to plan interventions and tailor long term rehabilitation. Therefore, in the next section I conducted a systematic review on the neuropsychological outcomes in HSV encephalitis.

1.4.5 Neuropsychological Outcomes in HSV Encephalitis: A Systematic Review

Overview

Verbal memory deficits have long been emphasised as a defining cognitive outcome in HSV encephalitis (Kapur et al., 1994; Utley et al., 1997). However, this characterisation stems largely from early case reports highlighting dramatic deficits (Hokkanen & Launes, 2000). Recent cohort studies challenge this narrow focus, revealing a broader spectrum of cognitive dysfunction (Harris et al., 2020), though methodological inconsistencies in assessment tools and designs limit robust conclusions. A key limitation across the literature is the reliance on single time-point assessments, which obscures long-term cognitive trajectories.

The lack of standardised testing protocols and the scarcity of longitudinal data make prognosis and rehabilitation planning challenging. I conducted a review of neuropsychology studies with three primary objectives: (1) to define the spectrum and prevalence of domain-specific cognitive deficits in people post HSV encephalitis; (2) to evaluate differences in assessment tools; and (3) to compare cognitive deficits in the acute phases to chronic phase to infer recovery trajectories.

Methods

The full methods and summary tables can be found in appendix D pp 287-293.

Search Strategy

A comprehensive literature search was performed of the Medline, Embase, PsycINFO, and CINAHL databases to identify articles published between 1985 and 2020 related to cognitive outcomes in herpes simplex encephalitis (HSV encephalitis). The search strategy combined medical subject headings (MeSH), and free-text terms related to “herpes simplex encephalitis,” “HSV encephalitis”, “neuropsychol*,” “cogniti*. The full search string is detailed in appendix D p 287.

Eligibility

Studies were included if they reported on adult (> 16 years) patients with a definitive HSV encephalitis diagnosis (confirmed by polymerase chain reaction) and provided a formal neuropsychological assessment using validated measures in more than five patients. I included articles describing the outcomes of these assessments in sufficient detail to infer whether performance was impaired or spared. Studies with only brief cognitive screening (for example, Mini Mental State Examination) and no additional tests were excluded unless the text unambiguously indicated specific cognitive deficits. Patients with a history of other significant neurological diseases, premorbid intellectual disability, or alcohol/substance dependence were excluded. Studies in which HSV encephalitis was suspected or had undefined antigens were also excluded. Finally, Articles were excluded if the approximate time point of the neuropsychological assessment could not be established (appendix D, p 288)

Study Selection

All references identified by the search were imported into EndNote (version 20). Duplicates were initially removed automatically and then manually. I screened titles and abstracts against the inclusion and exclusion criteria. Articles deemed potentially eligible were retrieved for a second round of full-text screening.

Data Extraction

For group-design (e.g., cohort, case-control) studies, the following information was extracted: Study Identifiers: Author(s), publication year, country of origin; Patient Details: Sample size, age, sex; Time of Assessment: Months post-infection when cognitive testing was performed; Neuropsychological Protocol: Tests administered, threshold for defining deficits; Main Outcomes: Domain-specific impairments (memory, executive function, language, attention, visuospatial function), psychological/psychiatric status, and any relevant functional outcomes; Data Presentation: Whether outcomes were reported at the group or individual level.

Data Synthesis

A descriptive synthesis was performed to summarise overall patterns of cognitive impairment in people post HSV encephalitis. Where feasible, comparisons of deficits across these time frames were made to infer possible recovery patterns or persistent deficits. Given the heterogeneity of outcome measures and timing of assessments, a formal meta-analysis was deemed inappropriate.

1.4.6 Results

Verbal Memory

Verbal memory was one of the most consistently impaired domains, with most studies administering story recall, word-list learning, or recognition tasks. In one study, 76% of participants (13/17) performed at least two standard deviations below controls on verbal memory measures (Hokkanen et al., 1996). On the WMS-R Verbal Memory Quotients reported by Kapur et al. (1994), 7 out of 10 patients (70%) scored below 70, indicating marked verbal memory impairment. Of these, four patients had quotients below 50, suggesting particularly severe deficits. Utley et al. (1997) reported that 3 of 22 participants showed mild verbal memory impairment and a further 8 of 22 demonstrated moderate or severe impairment. Harris et al. (2020) observed verbal recall and recognition deficits at both four months (short-term) and twelve months (long-term) post-illness compared with matched controls, suggesting limited recovery in this domain. Pewter (2007) also noted difficulties in learning new verbal material in all four HSV encephalitis patients defined as falling below 5th percentile.

Visual Memory

Visual memory impairments were equally prominent, with a variety of measures used across studies. Hokkanen et al. (1996) used the Benton Visual Retention Test and the WMS Visual Reproduction subtest, finding that 59% of participants (10/17) scored at least two standard deviations below control means. Kapur et al. (1994),

reported 4 out of 10 patients (40%) scored below 70, indicating moderate to severe impairment in visual memory, representing a lower prevalence compared to the 70% observed for verbal memory deficits in the same cohort. Harris et al. (2020) reported poorer visual recall and recognition in both short-term (<12 months) and long-term cohorts (>12 months) relative to controls, while Utley et al. (1997) documented mild visual memory impairment in 10 of 22 participants, with another 4 showing moderate or severe deficits.

General intellectual functioning

General intellectual functioning was evaluated in several studies using composite measures derived from instruments such as the WAIS, WAIS-R, or WASI-II. For instance, Harris et al. (2020) employed the WASI-II and WTAR, while Hokkanen et al. (1996) and Utley et al. (1997) reported verbal and performance IQ scores obtained from WAIS subtests. Similarly, Kapur et al. (1994) incorporated WAIS subtests into their cognitive battery, defining deficits as scores falling more than one standard deviation below the normative mean. However, these composite scores combine several cognitive processes—including working memory, processing speed, and reasoning—and therefore make it difficult to isolate deficits in specific areas.

Harris et al. (2020) reported significant differences in composite IQ measures between HSV encephalitis patients and matched controls, although details regarding performance on individual subdomains were not provided.

Hokkanen et al. (1996), reported that HSV encephalitis patients performed significantly worse than both controls and patients with other encephalitis aetiologies on measures of verbal and performance IQ; specifically, 41% of patients were impaired in verbal logical thinking and 53% in visual logical thinking. Utley et al. (1997) observed reduced overall cognitive performance, with 13 of 22 participants showing mild impairment on composite measures. In contrast, Kapur et al. (1994) did not report overall impairments in composite IQ scores. Instead, their findings revealed that on the verbal IQ subtests, the information subtest was most frequently impaired, with 40% of patients scoring between 5 and 6 (i.e. more than one standard deviation below the normative mean).

In the performance domain, only one patient obtained an impaired score on the digit symbol subtest, suggesting relatively preserved processing speed. Few studies examined processing speed as a primary outcome, but some provided relevant data. Harris et al. (2020) included the Trail Making Test Part A, demonstrating that participants with herpes simplex encephalitis (HSV encephalitis) performed significantly worse than matched controls. Utley et al. (1997) did not separate processing speed from other domains but noted that overall cognitive slowing was common in their sample.

Language

Language impairments, particularly in naming and fluency, were frequently reported across studies. Harris et al. (2020) found pronounced naming deficits on the Graded Naming Test in their short-term cohort of HSV encephalitis patients, with

performance significantly worse than that of both matched controls and patients with other encephalitis aetiologies; however, in the long-term cohort no significant differences between groups were observed. Kapur et al. (1994) reported naming impairment in 4 out of 10 patients, with impairment defined as a score lower than expected based on reading ability and educational background. Pewter (2007) reported that four out of four patients assessed on naming exhibited category-specific deficits, with scores falling more than two standard deviations below the normative mean. By contrast, Utley et al. (1997) employed a brief version of the Minnesota Test for Differential Diagnosis of Aphasia and observed that while classical aphasia was uncommon, subtle language impairments did persist in some individuals.

Visuospatial Function

Visuospatial abilities were assessed using tasks involving figure copying, shape discrimination, or object recognition. Hokkanen et al. (1996) reported that 82% of participants met criteria for visuo-perceptual impairment on tasks such as the Benton Visual Retention Test. Similarly, Utley et al. (1997) employed the Rey Complex Figure to assess visuospatial and constructional abilities, finding that up to 59% of patients exhibited mild to severe deficits. Pewter (2007) found that 2 out of 4 patients demonstrated visual perceptual problems on Visual Object and Space Perception battery, with one patient also showing generally impaired visuospatial problem-solving on the WASI Block Design subtest. By contrast, Harris et al. (2020) included measures such as the Visual Object and Space Perception battery and the Benton Facial Recognition Test in their assessment; however, all patient groups scored

within the non-impaired range, with no significant differences observed in statistical analyses.

Executive Function

Executive dysfunction was frequently noted across studies, with assessments often including the Wisconsin Card Sorting Test (WCST), Trail Making Test Part B, or verbal fluency tasks (e.g., FAS). Harris et al. (2020) documented significant group-level impairments in planning, rule detection, and cognitive flexibility, although specific percentages were not provided. Utley et al. (1997) reported that 8 of 22 participants (36%) showed mild executive deficits, while 3 of 22 (14%) exhibited severe executive impairment in the context of broader cognitive dysfunction. Kapur et al. (1994) evaluated executive function using card sorting tasks and found that, among 10 patients, 2 exhibited mild impairment and another 2 showed pronounced impairment (with 6 patients performing normally), although the cut-off used for impairment was not clearly defined.

Psychological Functioning

Depressive and anxiety symptoms are elevated after HSV encephalitis. In a multicentre case–control study, HSV patients had higher mean scores than matched controls at around 4 months (Beck Depression Inventory 16.76 [SD 12.41] vs 6.31 [5.89]; Beck Anxiety Inventory 12.12 [12.51] vs 4.83 [5.00]; overall group p=0.001 and p=0.03) and at ≥12 months (BDI 13.81 [8.13] vs 5.48 [5.37]; BAI 10.04 [9.51] vs

4.36 [4.64]; p<0.001 and p=0.004), indicating sustained psychiatric burden into the chronic phase. Further, a long-term volunteer cohort (including a HSV subgroup) showed group-level elevations on the SCL-90-R across all indices except paranoid ideation, with interpersonal sensitivity, depression and phobic anxiety >2 SD above norms and obsessive–compulsive symptoms approaching 3 SD above norms; individual-level prevalences were not reported. Depressive symptom scores correlated with poorer working memory (r=−0.55), selective attention (r=−0.62), and verbal fluency (r=−0.53), highlighting the coupling between mood alterations and cognitive outcomes after HSV encephalitis.

Longitudinal Trajectories

Longer-term follow-up was reported by Harris et al. (2020) at 4–12 months after the initial assessment. However, these analyses combined encephalitis aetiologies, so change in scores for the HSV encephalitis group could not be determined. Overall, there appeared to be limited change; in non-HSV groups there were both improvements and declines in performance. Harris et al. (2020) also assessed a separate cohort more than 12 months post-illness and found less widespread impairment, largely confined to anterograde verbal and visual memory.

1.4.7 Discussion

This systematic review synthesised evidence from observational and cohort studies to describe the neuropsychological outcomes in people post HSV encephalitis. Consistent with historical case reports, the findings demonstrate that deficits in verbal memory are prevalent among people post HSV encephalitis. However, the evidence also indicates a broader spectrum of impairments, including deficits in visual memory, executive functioning, language, attention, and visuospatial abilities. No studies longitudinally assessed the same cohort of patients over time.

Inconsistent use of neuropsychological assessments and variable criteria for deficits limited direct comparisons of cognitive outcomes across studies. Most investigations relied on single time-point assessments no studies tracked long-term recovery in prospective cohorts. Small sample sizes and infrequent evaluation of psychological comorbidities further reduced generalisability and limits our understanding of relationships between mood and cognition.

These limitations highlight several areas for improvement in future research, some of which were addressed in this thesis. First, the adoption of standardised neuropsychological assessment batteries is essential to allow for uniformity in testing and more reliable cross-study comparisons. Second, longitudinal studies that include assessments in both the acute (≤12 months) and chronic (>12 months) phases are needed to elucidate recovery patterns and to identify potential windows for rehabilitation. Third, future investigations should incorporate larger, multi-centre

samples and include control groups to improve statistical power and control for confounding variables such as premorbid cognitive status and comorbid psychiatric conditions.

In summary, while the current literature demonstrates the persistence of multifaceted cognitive impairments following HSV encephalitis, methodological variability and the scarcity of longitudinal data limit our understanding of recovery processes. Addressing these challenges through standardised, comprehensive, and longitudinal research will be essential for developing effective interventions and improving outcomes for patients.

1.5 Neuroimaging in HSV Encephalitis

1.5.1 Fundamentals of Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is a non-invasive imaging modality that exploits the magnetic properties of hydrogen nuclei (protons) in water and fat to generate detailed anatomical and functional images (Berger, 2002). MRI relies on three key principles: (1) alignment of nuclear spins (usually protons in water molecules) by a strong static magnetic field, (2) radiofrequency (RF) excitation that tips those spins away from alignment, and (3) relaxation processes (and associated signal detection) that occur as the spins return to equilibrium (Grover et al., 2015).

When a patient is placed within the strong static magnetic field of an MRI scanner (B_0), protons in their tissues align either parallel or antiparallel to the magnetic field, creating a net magnetization vector (Grover et al., 2015). Protons spin or 'precess' around the magnetic field axis at a specific frequency, called the Larmor frequency, which depends on the strength of the magnetic field (Sharma, 2009). To generate a signal, a brief radiofrequency (RF) pulse is applied at the Larmor frequency, which tips the protons into a transverse plane, disrupting their equilibrium. After the RF pulse ceases, protons gradually return to their original alignment, a process termed relaxation. During relaxation, they emit detectable RF signals, which are spatially encoded using magnetic gradients to construct an image (Pipe, 1999).

Image contrast in MRI arises from differences in how protons relax. T1 relaxation (longitudinal recovery) reflects the time required for protons to recover 63% of their original alignment with the magnetic field (Grover et al., 2015). Tissues with high lipid or macromolecule content, such as grey matter, recover quickly and appear bright on T1-weighted images (Bitar et al., 2006). Conversely, T2 relaxation (transverse decay) measures how rapidly protons lose coherence in the transverse plane; free water molecules, as seen in oedema or CSF, retain coherence longer, producing bright signals on T2-weighted images (Bitar et al., 2006).

1.5.2 Clinical MRI Sequences & Pathological Correlates

Pathological changes in HSV encephalitis have clear correlates on MRI. T1-weighted imaging, achieved using short repetition (TR) and echo times (TE), provides high anatomical detail, distinguishing grey and white matter (Roberts & Mikulis, 2007). T1-weighted scans can be enhanced with gadolinium-based contrast agents. These highlight areas where the blood-brain barrier is disrupted, such as inflamed tissues in HSV encephalitis (Bulakbasi & Kocaoglu, 2008).

T2-weighted imaging, using longer TR and TE, is highly sensitive to fluid accumulation, making it important for detecting acute inflammation or oedema (Ho et al., 2012). A variant called Fluid-Attenuated Inversion Recovery (FLAIR) suppresses the bright CSF signal on T2-weighted images, improving visualisation of lesions near ventricles (Misra et al., 2010).

DWI exploits the random motion of water molecules. By applying strong magnetic gradients, DWI detects restricted water diffusion—a hallmark of cytotoxic oedema in acute HSV encephalitis (Ho et al., 2012). Apparent Diffusion Coefficient (ADC) maps, derived from DWI, quantify diffusion magnitude, with low ADC values confirming true restriction, distinguishing acute injury from artefactual T2 shine-through (Dmytriw et al., 2017). Diffusion Tensor Imaging extends this concept, measuring the directional preference of water diffusion to infer white matter tract integrity.

In clinical practice, these sequences are frequently combined. Acute HSV encephalitis is marked by T2/FLAIR hyperintensities and restricted diffusion on DWI, while the combination of these with post-gadolinium T1-weighted imaging can aid in identifying blood-brain barrier breakdown. However, the relationship between these neuroimaging biomarkers and long-term outcomes remains poorly understood

These sequence–pathology relations are reinforced by a multicentre, blinded MRI study comparing LGI1/CASPR2-antibody autoimmune encephalitis with viral encephalitis (largely HSV-1) and Creutzfeldt–Jakob disease (Kelly et al., 2024). Autoimmune encephalitis showed mesial temporal T2/FLAIR change typically without diffusion restriction or contrast enhancement; viral encephalitis more often had restricted diffusion, enhancement, and extratemporal spread. A composite of mesial temporal signal without restriction, enhancement, or extratemporal involvement identified autoimmune encephalitis with AUC 0·97, 90% sensitivity, and 95% specificity, supporting early differential diagnosis.

1.5.3 Neuroimaging research in HSV encephalitis

HSV encephalitis selectively targets limbic structures, and neuroimaging, particularly MRI, has emerged as a critical tool for understanding long-term cognitive and functional outcomes. However, the relationship between MRI findings and cognitive outcomes has not been well characterised.

1.5.4 Cross-Sectional Evidence Linking Structural Damage to Cognitive Deficits

Yoneda et al. (1994) compared volumetric MRI findings in five HSV encephalitis patients (assessed 12–52 months post-infection) with age-matched controls, revealing significant atrophy in the hippocampal formation and parahippocampal gyrus. Hippocampal volume loss correlated strongly with persistent anterograde amnesia, while parahippocampal atrophy predicted retrograde memory deficits. Kapur et al. (1994) expanded on this, demonstrating that bilateral medial temporal lobe damage (encompassing the hippocampus, parahippocampal gyrus, and amygdala) in 10 HSV encephalitis patients was closely linked to severe, persistent amnesia. Additionally, A voxel-based morphometry analysis of 13 HSV encephalitis patients showed that grey matter loss in the left hippocampus correlated with verbal memory decline, whereas atrophy in the lateral temporal lobe, thalamus, and left insula was linked to naming problems. This study highlights substantial inter-individual variability in lesion patterns but confirms that these patterns predict

specific cognitive impairments (Frisch et al., 2015). Although these studies have small samples, they demonstrate the value of quantitative MRI for understanding how structural brain changes relate to cognitive outcomes in HSV encephalitis.

1.5.5 Prognostic Value neuroimaging

The utility of early MRI for predicting outcomes remains unclear. Kim et al. (2016) prospectively evaluated 29 HSV encephalitis patients, finding no association between initial MRI lesion volume/extent (scanned at a median of three days post-onset) and six-month outcomes. Methodological heterogeneity—variable scan timing (days 0–7) and inconsistent imaging protocols—likely contributed to these null findings. In contrast, Sener (2001) identified diffusion MRI patterns as potential prognostic markers: cytotoxic oedema during acute stages predicted poorer recovery, whereas vasogenic oedema correlated with better outcomes.

The largest study to date by Sarton et al. (2021), a multicentre retrospective analysis of 138 HSV encephalitis patients, showed that early MRI features-more than three lobes affected, involvement, left thalamic lesions, bilateral diffusion abnormalities-strongly predicted 90-day disability/mortality. However, the study's retrospective design, reliance on heterogeneous MRI protocols, and lack of long-term outcomes limit its clinical applicability.

1.6 Scope and aims of thesis

People post HSV encephalitis often face enduring cognitive deficits despite timely antiviral treatment. The immune response, while essential for viral clearance, can lead to acute neuronal injury and chronic neuroinflammation. These processes may contribute to unpredictable recovery patterns—initial improvements may be undermined by later relapses, resulting in variable and non-linear recovery trajectories. Although validated rapid screening tools would be ideal for repeated assessments, their applicability in HSV encephalitis remains uncertain. In the absence of a reliable cognitive screening tool, early MRI biomarkers, such as hippocampal integrity and oedema subtypes, may offer valuable prognostic insights, supporting more flexible and responsive care planning. This thesis therefore focuses on addressing these clinical challenges and underlying mechanistic gaps in improving, understanding and predicting long-term cognitive outcomes in HSV encephalitis. Specifically, I set out to answer the following questions:

1) Does early adjunctive dexamethasone therapy improve outcomes as demonstrated in a multicentre randomised controlled trial?

2) What is the prevalence, nature, and long-term recovery trajectories of cognitive impairments in people post HSV encephalitis, as determined by a comprehensive, longitudinal neuropsychological battery?

3) How effective are existing cognitive screening tools in identifying patients at risk for persistent deficits?

4) To what extent are MRI biomarkers associated with domain-specific cognitive performance in HSV encephalitis?

Chapter 2 General Methods

2.1 Overview

In this chapter, I describe in detail some of the research methods presented throughout the chapters of this thesis. The cohort studied comprised participants in the DexEnceph clinical trial, which focused on the primary outcome of verbal memory. The trial also included a comprehensive battery of neuropsychological tests, along with clinical, functional, health-related quality of life, neuroimaging, and biomarker assessments. Here, I describe the trial design, the patient cohort, and the outcomes utilised throughout the thesis. Each subsequent chapter provides a description of the specific methods unique to that chapter.

2.2 DexEnceph Trial

2.2.1 Aim and design

DexEnceph was a pragmatic, multicentre, randomised, controlled, observer-blind trial to determine whether intravenous dexamethasone, in addition to standard care, improves verbal memory score in adults with HSV encephalitis at 26 weeks after treatment compared with standard care alone. Additionally, other neuropsychological assessments, neuroimaging and biomarkers were assessed along with detection of

HSV in the CSF at 2 weeks after randomisation to monitor for difference in viral replication between the two groups. Ethical approval came from the UK National Research Ethics Committee (reference number: 15/NW/0545). The full protocol (https://fundingawards.nihr.ac.uk/award/12/205/28) and the published protocol are available online (Whitfield et al., 2021).

2.2.2 Patients

94 Patients were recruited across 53 National Health Service hospitals across the UK between Sept 9, 2016, and Feb 21, 2022.

2.2.3 Inclusion/Exclusion criteria

Eligible patients were included if they had presented with suspected encephalitis—defined by the presence of a new-onset seizure, new focal neurological signs, or an alteration in consciousness, cognition, personality, or behaviour (including manifestations such as agitation, psychosis, somnolence, insomnia, catatonia, mood lability, or altered sleep patterns)—and had a positive HSV DNA PCR result from CSF reported within 7 days prior to randomization. In addition, patients had been receiving intravenous aciclovir at a dose of 10 mg/kg three times daily (or a clinically appropriate reduced dose), were at least 16 years old, and had provided written informed consent either personally or via a legally authorized representative.

Patients were excluded if they had received oral or injectable corticosteroids within the 30 days prior to study entry (except for topical or inhaled formulations; corticosteroids administered after hospital admission did not result in exclusion if consent was provided), or if they had a history of hypersensitivity to corticosteroids. Further exclusions applied to those with immunosuppression resulting from a documented HIV infection with a CD4 count below 200/mm³, current use of biological therapy or other immunosuppressive agents (such as azathioprine, methotrexate, or ciclosporin), a previous solid organ transplant with ongoing immunosuppressive therapy, a prior bone marrow transplant, active chemotherapy or radiotherapy, a known primary immunodeficiency syndrome, or a current haematological malignancy. Additionally, the presence of pre-existing indwelling ventricular devices, a history of peptic ulcer disease within the 6 months prior (as evidenced by an endoscopically confirmed ulcer or an upper gastrointestinal bleed causing a haemoglobin drop of 2 or more units), or the use of an antiretroviral regimen containing rilpivirine (due to its significant interaction with dexamethasone, unless an alternative regimen had been implemented) precluded participation.

2.2.4 Randomisation

Patients were randomised (1:1) to receive dexamethasone alongside aciclovir treatment or aciclovir alone with minimisation for variables known to be associated with outcome in HSV encephalitis (age, steroid use since hospital admission, Glasgow Coma Score, delay in aciclovir administration). Randomisation was performed by a 24-hour secure web-based system. Throughout the thesis, patients

randomised to receive dexamethasone are referred to as the dexamethasone group, and patients randomised to receive aciclovir are referred to as the control group.

As the assistant psychologist collecting the primary outcome and neuropsychological data, I was blinded to randomisation during the trial. Radiologists, statisticians, and lead investigators were also blinded. To minimise the risk of unblinding, I explicitly informed participants of the importance of not discussing their treatment or experiences that may indicate group assignment.

2.2.5 Procedure

2.2.6 Treatment

The care for both groups was provided according to UK national guidelines for managing viral encephalitis (Solomon et al., 2012). Every patient received intravenous aciclovir (10 mg/kg three times daily—or a dose adjusted for renal function) from NHS hospital supplies for at least 14 days. Randomisation to the two treatment arms occurred within seven days of the initial lumbar puncture. In the intervention arm, patients were given intravenous dexamethasone 10 mg four times a day for four days, beginning within 24 hours of randomisation, and drawn from the standard ward supply. Clinicians could alter or discontinue dexamethasone, or introduce alternative therapies, if this was deemed best for the patient.

A second lumbar puncture was carried out in both groups after 14 days (± three days) of aciclovir treatment, unless there was a clinical reason not to. Where HSV DNA remained detectable in the CSF after this period, indicated by PCR, aciclovir therapy was continued, with weekly lumbar punctures until the CSF became PCR-negative. To evaluate the impact of dexamethasone on HSV in the CSF, PCR analyses of centrally processed CSF samples at baseline and at week two were performed. IgG antibodies to NMDAR were assessed by slightly adapting a live cell-based assay (Makuch et al., 2018).

2.2.7 Outcome measures

The primary outcome for the DexEnceph clinical trial was verbal memory, assessed with the Auditory Memory Index (AMI) of the Weschler Memory Scale – Fourth Edition. Data were collected at baseline, at day 14, and again at discharge or day 30 (whichever came first), with follow-up at 26 and 78 weeks. Figure 2-1 shows an illustrative schematic of data collection and timing.

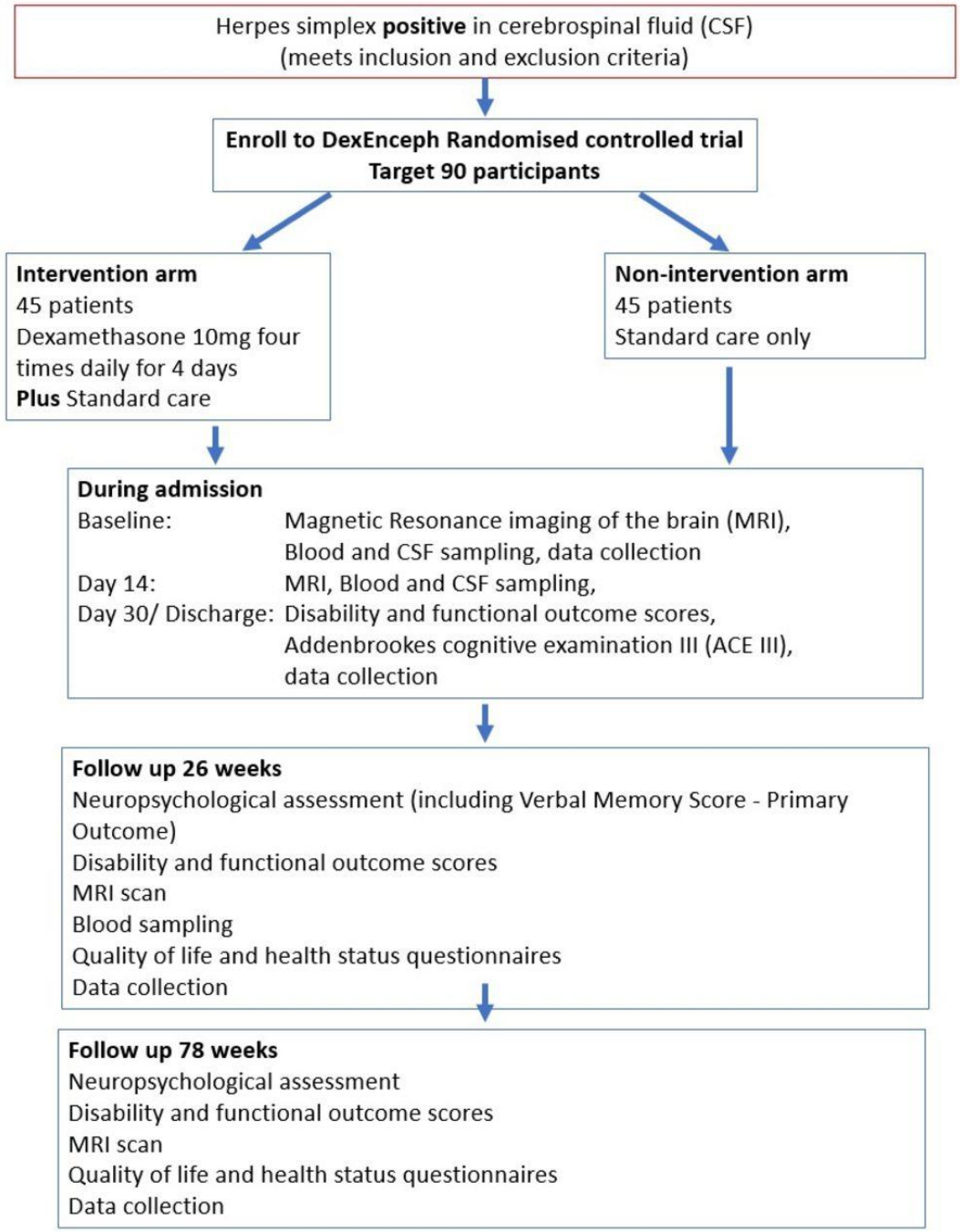

Figure 2-1: Schematic design of DexEnceph randomised control trial

2.3 Neuropsychological battery

Wechsler Memory Scale–Fourth Edition (WMS-IV)

The WMS-IV, a comprehensive neuropsychological battery (Drozdick et al., 2018), was used to assess memory; Auditory Memory Index (AMI), Visual Memory Index (VMI), Immediate Memory Index (IMI), and Delayed Memory Index (DMI) composite scores were calculated for each patient. These indices were derived from subtests evaluating story recall, word pairs, geometric designs, and visual patterns. For Auditory memory, patients recalled stories(logical memory subtest) or word pairs (verbal paired associates subtest). For visual memory, patients recalled and drew geometric patterns (visual reproduction subtest) or recalled visual patterns (designs subtest. Delayed recall was tested after a 20–30 minute interval.

The WMS-IV provides age-adjusted norms (16–90 years) with scaled scores (mean = 10, SD = 3) and index scores (mean = 100, SD = 15) based on a representative sample. It has high reliability: Internal consistency (α = 0.95 for indices), test-retest stability in healthy adults (r = 0.80–0.90) and strong reliability in clinical populations (e.g., ICCs = 0.82–0.85 in dementia (S.-C. Lee et al., 2023). Additionally, it has strong validity: Content validity (auditory/visual modalities, immediate/delayed recall), construct validity (factor-analytic separation of memory domains), and criterion validity (correlations with hippocampal/temporal lobe function) (Drozdick et al., 2018).

Across cohorts of HSV encephalitis, auditory/verbal episodic memory is the most consistently and prominently impaired domain, and patients frequently describe learning and retaining verbal information as their most pervasive day-to-day difficulty (See chapter 1; Kapur et al., 1994; Harris et al., 2020). On this empirical and clinical basis, the Auditory Memory Index (AMI) was pre-specified as the primary outcome. From a neuroanatomical standpoint, verbally mediated episodic memory relies predominantly on language-dominant (typically left) medial temporal networks, including the hippocampus and parahippocampal regions, whereas non-verbal and visuospatial episodic memory is more dependent on right medial temporal structures; bilateral involvement produces the most severe and generalised amnesia (Yoneda et al., 1994; Frisch et al., 2015). Because lesion laterality in HSV encephalitis is variable, with right-sided, left-sided, and bilateral patterns all observed, the Visual Memory Index (VMI) was designated as a secondary outcome to capture deficits expected with right temporal or bilateral involvement and to complement AMI in profiling selective versus widespread impairment. This selection provides a clear, anatomically and clinically informed justification for focusing on verbal memory while ensuring that right-hemisphere and bilateral medial temporal dysfunction are adequately characterised.

Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV)

The WAIS-IV (Wechsler, 2008) was used to assess working memory, and processing speed via two primary indices: the Working Memory Index (WMI) and the Processing Speed Index (PSI). The WMI is derived from subtests Digit Span and Arithmetic, which measure the capacity to hold and manipulate information

temporarily. The PSI is derived from Coding and Symbol Search subtests that evaluate visual scanning and visuomotor processing speed and accuracy. The WAIS-IV provides age-adjusted norms (16–90 years) with scaled scores (mean = 10, SD = 3) and composite scores (mean = 100, SD = 15) based on a representative sample. It demonstrates high internal consistency (e.g. $\alpha = 0.94$) and strong test-retest reliability ($r > 0.80$), with well-established construct and criterion validity (Wechsler, 2008). Notably, the WMS-IV was co-normed with the WAIS-IV (Wechsler Adult Intelligence Scale) to ensure compatible normative data, enhancing interpretive accuracy (Drozdick et al., 2018).

The WAIS-IV allowed quick and reliable assessment of these domains within a single testing session.

Trail Making Test (TMT), Parts A & B

The TMT was administered to index distinct but related cognitive constructs. Part A primarily measures visual scanning/visual search and speed of information processing (psychomotor/graphomotor speed) with a visuomotor tracking component; executive demands are minimal. Patients connect sequentially numbered circles (1–25) as quickly as possible, providing a completion time that reflects how efficiently they scan, locate, and motorically link targets under time pressure. By contrast, Part B imposes a substantially greater executive load, measuring set-shifting (mental flexibility) and divided attention, with contributions from working memory (maintaining two sequences and the alternation rule) and sequencing. Patients alternate between numbers and letters (1–A–2–B…), so

performance depends on switching between stimulus classes while sustaining speeded visual search. Completion times were recorded and compared with age- and education-adjusted norms. In line with standard neuropsychological interpretation, Part A is treated as an index of visual scanning and processing speed, whereas Part B indexes executive control (set-shifting/divided attention) over and above basic speed/visual search (Sherman et al., 2023). The TMT has moderate-to-high test-retest reliability (r = 0.44–0.89) and strong construct validity for detecting executive dysfunction (Golden et al., 1981).

Test of Premorbid Functioning (TOPF)

The TOPF (Wechsler, 2009) is a reading-based measure designed to estimate premorbid intellectual functioning by assessing the pronunciation of irregularly spelt words. Performance on the TOPF is relatively resistant to cognitive decline whilst also highly correlated with general intelligence (IQ) measures. The TOPF score is converted into an estimated IQ based on age and education using co-normed data from the WAIS-IV. The test has high internal consistency (α = 0.96–0.99) and strong test-retest reliability (r = 0.90). In HSV encephalitis, determining premorbid cognitive ability is critical for gauging the extent of decline post-encephalitis and ensuring treatment groups' premorbid functioning is comparable. It has a brief administration time (approximately 5–10 minutes).

Addenbrooke's Cognitive Examination-III (ACE)

The ACE-III is a brief cognitive screening tool that evaluates multiple domains—attention, memory, fluency, language, and visuospatial abilities—to detect early cognitive impairment (Hsieh et al., 2013; Mioshi et al., 2006). It was initially designed as a screening tool to aid in diagnosing dementia; however, it is now widely used as a cognitive screening tool in clinical practice. It is scored out of 100 points, with subdomain scores indicating specific deficits. Administration takes approximately 15–20 minutes. When used for its intended purpose, screening for dementia, the ACE has strong psychometric properties, with high sensitivity and specificity and good test-retest reliability (r = 0.85). In the context of HSV encephalitis, where multifaceted cognitive deficits are common, the ACE provides a rapid global assessment of cognitive function, and it is unique for a brief screening tool to provide scores across a range of cognitive domains.

Perceived Deficits Questionnaire (PDQ)

The PDQ is a 20-item self-report measure that assesses patients' perceived cognitive difficulties across domains, including attention, retrospective memory, prospective memory, and planning. Each item is rated on a 5-point scale (0 = 'Never' to 4 = 'Almost always'), with higher total scores indicating more significant perceived impairment. Initially developed for multiple sclerosis research (Sullivan et al., 1990), the PDQ has been validated in various neurological populations (Strober et al., 2016). It exhibits high internal consistency (α = 0.88–0.94). In HSV encephalitis, patients may report significant subjective cognitive difficulties even when objective deficits are modest. Thus, the PDQ provides insight into the subjective perception of cognitive impairments, complementing the objective tests and informing clinical

management. Its brief administration (approximately 5 minutes) ensures minimal patient burden.

Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI)

The BDI-II (Jackson-Koku, 2016) and the BAI (Beck et al., 2012) are self-report measures used to assess the severity of depressive and anxiety symptoms, respectively. The BDI-II comprises 21 items rated on a 0–3 scale to yield an overall depression severity score, while the BAI consists of 21 items assessing common anxiety symptoms. Both instruments have robust psychometric properties, with high internal consistency (α = 0.90–0.94) and good test-retest reliability (Y.-P. Wang & Gorenstein, 2013). Normative data are available to categorise symptom severity. In HSV encephalitis, mood disturbances can exacerbate cognitive deficits and impact quality of life (Harris et al., 2020). The BDI-II and BAI provided quantifiable information about the patient's psychiatric functioning.

Table 2-1: Summary of cognitive assessment battery.

Test	Cogntive domain/Index	Subtest
Weschler Memory Scale-IV (WMS-IV)[a]	Auditory Memory Index (AMI)	Logical Memory I & II
		Verbal Paired Associates I & II
	Visual Memory Index (VMI)	Visual reproduction I & II Designs[d] I & II
	Immediate Memory Index (IMI)	Logical Memory I Verbal Paired Associates I Visual Reproduction I Designs I*
	Delayed Memory Index (DMI	Logical Memory II
		Verbal Paired Associates II
		Visual Reproduction II
		Designs II*
Weschler Adult Intelligence Scale (WAIS-IV)[b]	Working Memory Index	Digit Span Arithmetic
	Processing Speed Index (PSI)	Symbol Search Coding
Trail Making Test[c]	Attention	Trail Making Test A
	Executive Function	Trail Making Test B

[a] Weschler (2009); [b] Weschler (2008); Reitan (1956); [d]Designs only administered in adult version (18-69) of WMS-IV. *Designs subtest is omitted from older adult version of battery (aged >65 years)

2.4 Covid-19 Impact

Between March 20, 2020 to June 15, 2020, recruitment was delayed due to the impact of COVID-19. However, I was able to continue assessing eight patients who had previously been recruited through remote assessments, following British Psychological Society, Division of Neuropsychology Professional Standards Unit Guidelines to colleagues on the use of Tele-neuropsychology. Previous studies have shown that there is concordance between remote and in person neuropsychology assessments, particularly for verbal tasks, which was the primary outcome in this research (Brown et al., 2024).

2.5 Functional Outcome Measures

Liverpool Outcome Score (LOS)

The LOS is a clinician-rated measure to assess overall recovery following acquired brain injury. It evaluates physical, cognitive, and psychosocial functioning, with higher scores reflecting better outcomes. The LOS has demonstrated good inter-rater reliability and sensitivity to change over time (Lewthwaite et al., 2010). HSV encephalitis offers a comprehensive summary of global recovery, which is essential for understanding the real-world impact of the illness.

Barthel Index

The Barthel Index (Mahoney & Barthel, 1965) measures functional independence in activities of daily living. Scored from 0 to 100, it covers domains such as mobility, self-care, and continence. It has high inter-rater reliability (>0.90) and robust validity in stroke and brain injury populations, the Barthel index quantifies the degree of disability in HSV encephalitis patients, enabling a clear interpretation of their independence in daily life.

Glasgow Outcome Score (GOSE)

The GOSE is a global outcome scale that categorises patients into seven levels, ranging from death to upper good recovery (Wilson, Boase, et al., 2021). It is simple

to administer and widely used in neurological research. It has established inter-rater reliability and construct validity. The GOSE offers a quick overview of overall recovery and functional outcomes for HSV encephalitis patients.

Modified Rankin Scale (mRS)

The mRS (van Swieten et al., 1988) is a 7-point scale (0–6) that measures global disability following neurological events. 0 represents no symptoms, and 6 indicates death. The scale is commonly used in stroke research and has been validated in various neurological populations. Its simplicity and sensitivity to functional change make it valuable for summarising long-term outcomes in HSV encephalitis.

2.6 Neuroimaging

Stereology

I conducted volumetric analysis using the Cavalieri principle, a design-based stereological method that utilises point-counting protocols. This method ensures statistically unbiased and reliable volume estimations from Magnetic Resonance Imaging data (MRI), validated for precision in prior neuroimaging studies (Dohertya et al., 2000; García-Fiñana et al., 2009). Analyses were conducted using Easy Measure, a platform employed in multiple prior neuroanatomical investigations (Keller et al., 2012).. The technique involves overlaying grid-based test probes onto MRI images and tallying grid intersections within defined regions of interest. Two

reviewers evaluated each image for overall quality and potential artefacts, deciding whether the temporal lobe boundaries were clearly visible. If these boundaries were not readily discernible, the scan was excluded from the analysis.

2.6.2 Temporal lobe volumetry

Temporal lobe volumetry was conducted on coronal imaging sequences following established anatomical criteria (Defres et al., 2017; Mackay et al., 1998, 2000). The anterior boundary was defined as the final coronal slice before the temporal pole merged with orbital structures (Figure 2-2A), while the posterior limit corresponded to the section where the lateral ventricle bifurcated into frontal and temporal horns (aligned with the visualizable crus of the fornix; Figure 2-2D). Transect areas were calculated by multiplying counted grid points by the calibrated area-per-point value (Figure 2-2B). Total temporal lobe volume was derived by summing transect areas across sequential slices and multiplying by the interslice distance. Approximately 24 systematically randomised slices were analysed per temporal lobe, yielding at least 300 grid-point counts, previously shown to be a reliable number of grid points for volumetric analysis of neuroanatomical structures (Defres et al., 2017; Keller & Roberts, 2010).

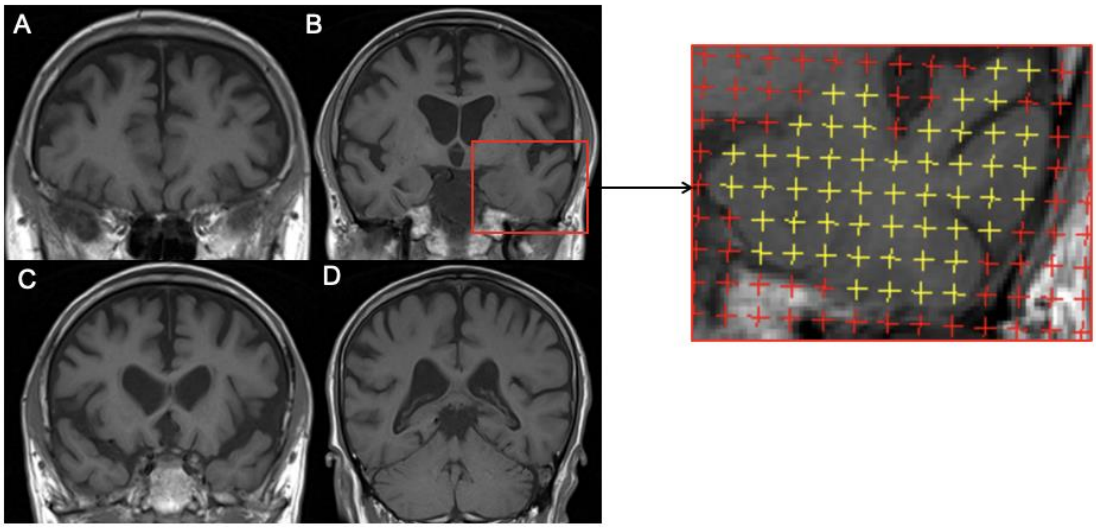

Figure 2-2: Coronal T1-weighted scan in one patient

(A) final coronal slice before the temporal pole merged with orbital structures. (B) transect coronal slice of the temporal lobe and example of stereological point counting grid overlayed.(D) section where the lateral ventricle is bifurcated into frontal and temporal horns.

2.6.3 Lesion Volumetry

Total oedema volume

Hyperintense regions on T2-weighted-Fluid-Attenuated Inversion Recovery (FLAIR) scans were quantified using the same stereological methods as temporal lobe estimation. Unlike conventional T2-weighted sequences, FLAIR suppresses the bright CSF signal, allowing oedema-related hyperintensity to emerge at tissue-CSF interfaces (e.g., periventricular regions). Oedema manifests as T2 prolongation due to increased free water in extracellular spaces, showing vasogenic and cytotoxic processes. Therefore, hyperintense regions quantified on T2 flair scans were

considered total oedema, reflecting the measurement of vasogenic and cytotoxic oedema together (Figure 2-3).

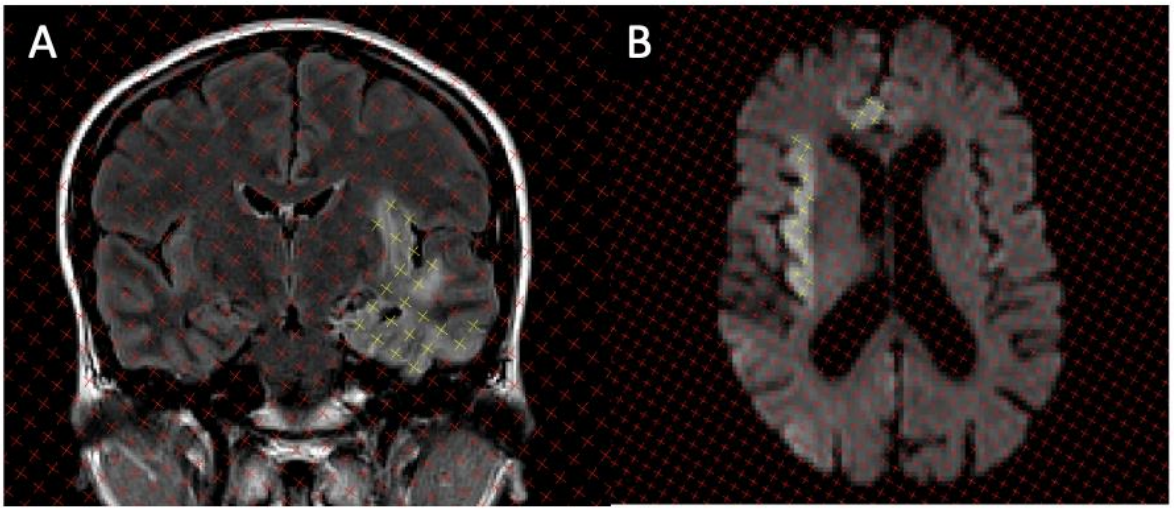

Figure 2-3: Example of stereological quantification of oedema on coronal (A) and axial MRI slices (B)

2.6.4 Cytotoxic and Vasogenic Oedema

T2-FLAIR cannot differentiate vasogenic from cytotoxic oedema, as both subtypes elevate free water content. Therefore, I used complimentary DWI and ADC to isolate cytotoxic oedema. Cytotoxic oedema was quantified by analysing hyperintense regions on DWI, with corresponding ADC maps used to confirm true diffusion restriction. ADC hypointensity (low values) served to exclude confounding T2 shine-through effects—bright DWI signals caused by inherent T2 prolongation rather than restricted water mobility (Table 2-2). Vasogenic oedema was calculated by subtracting the volume of cytotoxic oedema from the volume of total oedema.

Table 2-2: Example of imaging characteristics in different types of oedema

	T2-FLAIR	DWI	ADC	Interpretation
Cytotoxic Oedema	Normal	Bright	Dark	True diffusion restriction
Vasogenic Oedema	Marked ↑	Bright	Normal/Bright	T2 Shine through

Imaging characteristics adapted and tabulated from Ho et al., 2012.

I used the same T2-FLAIR sequence to quantify whole-brain volume, expressing total, cytotoxic, and vasogenic oedema as a percentage of whole-brain volume. To assess reproducibility, I repeated measurements for intra-rater analysis on a random sample of 10 scans. Inter-rater reliability was assessed by a second investigator, who independently quantified bilateral temporal lobe volumes and oedema extent on the same 10 scans; inter-rater reliability statistics were then calculated.

2.6.5 Hippocampal Volumetry

For each patient, the best available clinical MRI scan was selected (using a 3D acquisition when available). Without any additional pre-processing, the raw clinical scans were directly entered into SynthSeg version 2.0 using its default parameter settings. SynthSeg is a convolutional neural network designed to robustly segment brain structures from heterogeneous clinical MRI data (Billot, Greve, et al., 2023). It

employs a joint super-resolution and segmentation pipeline, via integrated SynthSR, which synthesises a high-resolution (1 mm isotropic) MP-RAGE– image from the input scan irrespective of its original resolution, orientation, or contrast (Iglesias et al., 2021). The network was trained on synthetically generated data from 3D segmentations, which enables it to generalise across different acquisition protocols and clinical conditions. The segmentation output of SynthSeg provides volumetric labels for various brain structures, including the hippocampi and the intracranial volume (ICV) and is robust to atrophies and lesioned brains (Billot, Magdamo, et al., 2023). For subsequent analysis, the absolute volumes of the left and right hippocampi, as well as the total ICV, were extracted directly from the segmentation maps. No additional normalisation was applied.

I used SynthSeg's built-in automated quality control module to further assess segmentation quality. This module uses a regression network to predict Dice scores—quantitative estimates of segmentation accuracy—for 10 key brain regions (white matter, cortex, lateral ventricle, cerebellum, thalamus, hippocampus, amygdala, pallidum, putamen, and brainstem) based solely on the segmentation outputs (Billot, Magdamo, et al., 2023). Regions with predicted dice scores below 0.65 were flagged as potential failures. I combined these automated quality control results with visual inspection of the segmentations; any scans flagged by the module or judged visually to have poor segmentation were excluded from further analyses.

To assess the reliability of the segmentations, I selected five patients who had both high-quality 3D scans and 2D scans available. I compared the segmentation results from the two scan types using intraclass correlation coefficient. This confirmed that

the segmentation of brain structures (including the hippocampi) was consistent between different scan modalities.

Furthermore, to verify that ICV was estimated accurately, I processed the higher-quality 3D scans through FreeSurfer, a widely used brain segmentation tool (Fischl, 2012), and compared the ICV estimates from FreeSurfer with those produced by SynthSeg when applied to the corresponding 2D scans. The comparison of ICV values, using the intraclass correlation coefficient, provided insight into the reliability of the segmentation approach across different automated analysis techniques. Data from multiple sites were processed in this standardised manner, ensuring that the segmentation results were comparable across the diverse clinical MRI datasets.

2.7 Antibody testing

We conducted NMDAR-antibody testing in CSF and serum at 2 weeks, and in serum at 26 weeks, where samples were available. Stored serum and CSF samples were screened for IgG NMDAR antibodies using a live cell–based immunofluorescence assay adapted from established protocols (Irani et al., 2010; Makuch et al., 2018). Briefly, HEK293T cells were transiently transfected to express the GluN1 (NR1) subunit of the NMDAR and incubated with patient serum or CSF. After washing and fixation, bound human IgG was detected with an unconjugated goat anti-human IgG antibody specific to the Fcγ region (Invitrogen 31125), followed by a fluorescent donkey anti-goat secondary reagent (Invitrogen A11057). Samples showing specific surface staining were then serially diluted to determine end-point titres.

2.8 Additional outcomes

Our protocol included the SF-36 to capture health-related quality of life; this data was collected but the scoring was not completed in time to be included in this thesis and will be reported separately. Dedicated measures of fatigue, sleep, and carer burden were not administered, reflecting limits on session length and the priority given to completing the core cognitive battery during post-acute recovery. As a result, the present study quantifies domain-specific cognitive outcomes but may underestimate the lived impact of HSV encephalitis on energy, sleep, participation, and family life. As summarised in Chapter 1, fatigue and sleep disturbance are common after encephalitis and can amplify cognitive complaints even when formal test scores improve, while demands on family members and carers may remain substantial. Future studies in HSV encephalitis should incorporate validated instruments for these domains alongside cognitive testing to capture the full burden and identify modifiable targets for rehabilitation.

2.9 Power Calculation

The power calculation was based on the DexEnceph trial, Chapter 3, and was designed to detect differences in verbal memory between treatment groups. Based on published data (Utley et al., 1997), a mean verbal memory score of 88.9 (SD 18.9) was expected, with a 10% mortality rate assumed before the 26-week primary outcome. After adjusting for this mortality, the mean was revised to 84.8 (SD 23.1). In cases where patients had died or were too unwell for neuropsychological

assessment, an independent committee, blinded to treatment allocation, determined whether the cause was encephalitis related. If unrelated, the patient's data were excluded; if related, a score of 40 was assigned. Committee decisions were reached by consensus, with disagreements resolved by vote. A 15.5-point difference in verbal memory was considered clinically meaningful, as it exceeded one standard deviation on the Weschler Memory Scales–IV (15) and aligned with cut-offs for impairment in previous neuropsychology studies (Heine et al., 2021). Accordingly, a sample of 36 participants per group would detect this difference with 80% power at a two-sided 5% significance level. Allowing for 20% dropout gave a final target of 45 participants per group, for a total of 90.

Analyses in subsequent chapter (chapters 4, 5,6) represents a secondary exploration of data originally gathered for the clinical trial, and as such, no a priori power calculations were conducted. All available clinical data were included in these analyses, precluding the need for a conventional power calculation. Where appropriate, I report effect sizes along with 95% confidence intervals to provide an indication of the precision and reliability of estimates. Some analyses may be underpowered to detect small effect sizes, and therefore, the results should be interpreted as exploratory. Each results chapter contains its own dedicated statistical methods section.

Chapter 3 Adjunct Dexamethasone in Adults with Herpes Simplex Encephalitis: a Phase III multicentre, observer-blind, randomised controlled trial.

The contents of this chapter have been submitted to The Lancet (see appendix A; pp 231-232)

3.1 Summary

Background

HSV encephalitis is characterised by inflammation and swelling of the brain, resulting in death or severe neurocognitive sequelae. It is treated with the antiviral aciclovir. The effect of adjunct corticosteroids is unclear.

Methods

In this multicentre, randomised, observer-blind trial, adults with HSV encephalitis were randomly assigned to receive dexamethasone (10 mg IV, four times daily for 4 days) plus intravenous acyclovir (10mg/kg three times daily for at least 14 days), or intravenous aciclovir alone (control group). The primary outcome was verbal memory score at 26 weeks, measured by the Wechsler Memory Scale WMS-IV auditory

memory index. The trial was registered as ISRCTN11774734, and EUDRACT 2015-001609-16.

Findings

Between Sept 22, 2016, and Feb 2, 2022, 94 patients with HSV encephalitis were recruited, 47 (20 [43%] female) to the treatment group (dexamethasone plus aciclovir), and 47 (24 [51%] female) to the control group (aciclovir alone). Dexamethasone was initiated a median (range) 7 (3-21) days after hospital admission. Seven patients withdrew consent, and six were lost to follow-up. Thus, 81 were included in the intention-to-treat population (39 dexamethasone, 42 control). The primary outcome, verbal memory score at 26 weeks, did not differ significantly between the groups (1·8, 95% Confident Interval(CI): -9·6 - 13·1, P = 0·76). Other neuropsychology, imaging and functional outcomes did not differ between the groups. In a post-hoc analysis of patients receiving dexamethasone, earlier treatment was associated with a significantly better verbal memory score, even allowing for known prognostic factors (estimate -4·89, 95% CI: -7·08, -2.70, p<·001). There were similar numbers of notable adverse events in the two groups.

Interpretation

In adults with HSV encephalitis, dexamethasone (started up to 21 days after hospital admission) plus aciclovir had a satisfactory safety profile but did not improve verbal memory score compared with aciclovir alone. However, earlier treatment with dexamethasone was associated with a better verbal memory score than delayed

treatment. Dexamethasone treatment in HSV encephalitis is not harmful and may be beneficial if given early.

Funding

NIHR funded: Efficacy and Mechanism Evaluation Award ID 12/205/28

3.2 Research in Context

Evidence before this study

Converging lines of evidence from in vitro studies and animal models suggest that immune system mediated pathology contributes to adverse outcome in HSV encephalitis. Corticosteroids, including dexamethasone, are used in some neurological infections, including bacterial meningitis and tuberculous meningitis, and in autoimmune encephalitis. Although corticosteroids are sometimes used as an adjunct to aciclovir for HSV encephalitis, there is no strong evidence to support their use, and there is a theoretical concern that they may lead to unrestricted viral replication. We searched PubMed from database inception to July 8th, 2024, using the following search terms: “HSV encephalitis”, “clinical trials”. A retrospective, non-randomised study including 45 patients with HSV encephalitis found that lack of corticosteroid administration was associated with poor outcome, alongside older age and lower Glasgow Coma Scale score. A previous clinical trial which randomised 41 patients to dexamethasone or placebo, in addition to aciclovir, was stopped

prematurely owing to slow recruitment and was therefore inconclusive. Analysis of patients recruited showed no difference in the primary endpoint (a binary functional outcome based on the modified Rankin scale).

Added value of this study

This is the first completed randomised controlled trial of corticosteroids in HSV encephalitis, with 94 participants from UK hospitals. Dexamethasone, at a dose of 10mg/kg four times daily, did not improve the primary outcome of verbal memory at 26 weeks compared with standard treatment with aciclovir alone. There was no difference in secondary outcomes including other neuropsychological, functional or imaging outcomes. However, dexamethasone was safe and well tolerated, and did not lead to an increased detection of HSV in the CSF at 14 days. Dexamethasone was initiated up to 21 days after hospital admission. A post-hoc analysis showed that in the dexamethasone group earlier treatment was strongly associated with better outcome.

Implications of all the available evidence

We have demonstrated that corticosteroids are safe in HSV encephalitis and may be beneficial if given early enough. Currently, in patients with suspected encephalitis where the aetiology may be HSV or autoimmune, corticosteroids are not usually given until HSV has been excluded. Our data suggest that corticosteroids can be safely given to all such patients as soon as encephalitis is suspected, without waiting for the aetiology to be confirmed.

3.3 Introduction

HSV encephalitis is the most common sporadic cause of viral encephalitis with an incidence of between 1 in 250 000 and 1 in 500 000 per year (Defres et al., 2023; Granerod et al., 2013; R. J. Whitley, 2006b). HSV encephalitis causes a broad range of neurocognitive impairments, but impaired memory, especially verbal memory, is the most common and relates to the viral predilection for the temporal lobe of the brain (Frisch et al., 2015; Utley et al., 1997). Verbal memory relates to the use of linguistic information, and when impaired leads to difficulties remembering names, words and details, joining conversations and following instructions. Since the introduction of the antiviral drug aciclovir in the 1970s, mortality has reduced from around 70% to 5·5%–12% (McGrath et al., 1997). However, the disease has a disproportionately large impact due to its devastating long term neuropsychological sequelae: less than 20% of patients are able to return to work and 48% are classed as moderately to severely disabled (Harris et al., 2020; Raschilas et al., 2002)

Evidence from *in vitro* studies and animal models suggests that, in addition to direct viral infection and destruction of neurons, the host immune response causes additional neuronal injury in viral encephalitis (Aurelius et al., 1994; Michael et al., 2016, 2020). In the CSF, higher levels of proinflammatory chemokines, especially monocyte chemotactic protein-1, interferon γ, interleukin(IL)-1 and IL-6 are associated with a worse prognosis (Rösler et al., 1998). Poor clinical outcome is also associated with the extent of inflammation seen on neuroimaging, and the degree of temporal lobe swelling is correlated with the severity of verbal memory impairment (Kapur et al., 1994; Taira et al., 2009). Relapse occurs in 27% of patients with HSV

encephalitis and is thought to be predominantly immune-mediated, sometimes associated with the development of anti-N-Methyl-D-aspartate receptor (NMDAR) antibodies (Armangue et al., 2018).

Corticosteroids modulate both acute and chronic inflammation by suppressing pro-inflammatory signalling pathways and reducing the expression of inflammatory mediators (Cruz-Topete & Cidlowski, 2018). Before the availability of aciclovir, corticosteroids were sometimes used as a treatment in humans with HSV encephalitis and continue to be used at clinician's discretion (Lizarraga et al., 2013; Musallam et al., 2007; Upton et al., 1971). However, because of their broad immunosuppressive effects, there is concern that their use could be associated with uncontrolled viral replication, and worse outcomes. Patients with HSV encephalitis can present in a similar way to those with autoimmune encephalitis, which is treated with corticosteroids. However, in current practice corticosteroids are not initiated for encephalitis patients until HSV has been excluded by PCR of the CSF. In other brain infections, including bacterial meningitis and tuberculous meningitis the benefit and safety of corticosteroids has been demonstrated in large clinical trials (Brouwer et al., 2015; Thwaites et al., 2004).

Retrospective studies and case series have investigated corticosteroids as an adjunct to aciclovir therapy for HSV encephalitis, including a retrospective analysis showing that lack of corticosteroid administration was a predictor of poor outcome (Kamei et al., 2005; Maraş Genç et al., 2016; Nakano et al., 2003). One previous randomised controlled trial, the German trial of Aciclovir and Corticosteroids in HSV encephalitis (the GACHE trial) was stopped early because of poor recruitment rates,

with 41 patients randomised to either dexamethasone or placebo, in addition to aciclovir (U. Meyding-Lamadé et al., 2019). Although underpowered, there was no difference between treatment groups in the primary outcome (a binary functional outcome based on the modified Rankin scale).

We therefore designed the DexEnceph trial to investigate the safety and efficacy of dexamethasone as an adjunct to intravenous aciclovir in adults with HSV encephalitis. Beyond the primary outcome of verbal memory score, we were also interested in the impact of corticosteroids on brain swelling, relapse and persistence of HSV in the CSF.

3.4 Methods

Study design

DexEnceph was a pragmatic, multicentre, randomised, controlled, observer-blind trial in 53 National Health Service hospitals in the UK (appendix A pp 241-242). We compared dexamethasone plus aciclovir with aciclovir alone in adult patients with HSV encephalitis. Ethics approval was obtained from the UK National Research Ethics Committee (reference number: 15/NW/0545). The trial protocol is available online and has been published previously (Whitfield et al., 2021). During the COVID-19 pandemic, recruitment was delayed from March 20, 2020 to June 15, 2020, though we were able to continue following up patients already in the study, following British Psychological Society guidelines for remote assessments.

Patients

We screened patients aged at least 16 years, with a suspected diagnosis of encephalitis, defined as: new-onset seizure or new focal neurological signs or alteration in consciousness, cognition, personality or behaviour. Personality/ behavioural change included agitation, psychosis, somnolence, insomnia, catatonia, mood lability, and altered sleep pattern. We included patients meeting these criteria for suspected encephalitis who had positive polymerase chain reaction (PCR) for HSV DNA in CSF, reported no longer than seven days prior to randomisation and receiving intravenous aciclovir dosed at 10mg/kg three times daily, or reduced dose if clinically indicated.

Patients were excluded if they received oral or injectable corticosteroid therapy within the 30 days prior to entering the study, except for the use of topical or inhaled corticosteroids. Other exclusion criteria were: a history of hypersensitivity to corticosteroids; immunosuppression, which included known HIV infection with a CD4 white cell count below 200/mm^3, current use of biological therapy or other immunosuppressive agents, a history of solid organ transplant with ongoing immunosuppression, a previous bone marrow transplant, current chemotherapy or radiotherapy, a known primary immunodeficiency syndrome, or a current haematological malignancy; the presence of pre-existing indwelling ventricular devices; a history of peptic ulcer disease within the last six months, defined as a peptic ulcer observed during endoscopy or an upper gastrointestinal bleed; or current treatment with an antiretroviral regimen containing rilpivirine, although a switch to a suitable alternative would allow trial entry.

Randomisation and masking

We randomised patients (1:1) to receive dexamethasone alongside aciclovir treatment (dexamethasone group), or aciclovir alone (control group), with minimisation for variables known to be associated with outcome in HSV encephalitis (age, steroid use since hospital admission, Glasgow Coma Score, delay in aciclovir administration). Randomisation was performed by a 24-hour secure web-based system.

The neuropsychologist collecting the primary outcome data, and other outcome assessors including radiologists, statisticians and lead investigators were blinded to randomisation during the trial. Trial participants and local site study teams, as well as the trial data manager at the clinical trials unit were aware of randomisation. To minimise the risk of unblinding, the neuropsychologist explicitly reminded patients prior to the visit the importance of to refrain from discussing their treatment or experiences that might indicate group assignment. The Independent Data Safety and Monitoring Committee (IDSMC) had access to unblinded data grouped by intervention throughout the trial and made recommendations to the trial's steering committee who could be unblinded if a serious adverse event occurred.

3.4.2 Procedures

Standard care for patients in both groups was given according to UK national clinical guidelines for the management of viral encephalitis(Solomon et al., 2012). All

patients received intravenous aciclovir (10 mg/kg three times daily, or appropriate reduced dose according to renal function) from NHS hospital stock for a minimum of 14 days. Patients were randomised to treatment groups within seven days of the initial lumbar puncture, and patients in the intervention group received intravenous dexamethasone 10 mg four times daily for four days, starting within 24 hours of randomisation, from the ordinary ward stock. Clinicians were free to modify or discontinue the dexamethasone regimen or to give alternative treatments at any stage, if this was judged to be in the best interest of the patient. After 14 days (+/- three days) of aciclovir treatment we repeated the lumbar puncture in both groups, unless clinically contraindicated. If HSV DNA was detected after 14 days of aciclovir treatment by PCR in the CSF, aciclovir was continued with weekly lumbar punctures until the CSF was HSV PCR negative. To monitor the effect of dexamethasone treatment on HSV in the CSF, we analysed CSF samples centrally, by PCR at baseline and week two. IgG antibodies to NMDAR were measured through minor modifications of an established live cell-based assay (Makuch et al., 2018). Data were collected at baseline, 14 days and at discharge or 30 days (whichever was sooner); we followed patients up at 26 and 78 weeks (details of data collected at each timepoint are available in the appendix A pp 237-238). Additional samples were collected for biomarker detection, to explore disease mechanisms in HSV encephalitis, which will be reported separately.

3.4.3 Outcomes

The primary outcome measure was verbal memory score, assessed using the Auditory Memory Index of the Wechsler Memory Scale fourth edition (WMS-IV), derived from a comprehensive neuropsychological battery that was administered at 26 weeks (+/- two weeks) by a single study neuropsychologist based out of the Walton Centre NHS Foundation Trust. The median WMS-IV for the population is normalised to 100, with scores ranging from 40 to 160. Where a patient had died or was too poorly to be assessed by the neuropsychologist an independent committee, blind to treatment group, determined whether the reason for this was related to the encephalitis; if they were felt not to be related to encephalitis the data from such patients were not used, and if they were felt to be related, the patient was attributed a score of 40. The committee decision was by consensus, and disagreements were resolved through a vote. These assessments were conducted at the patient's residence or recruiting hospital depending on convenience. We designed the neuropsychological battery to cover a broad range of cognitive domains, including visual memory, immediate memory, and delayed memory (WMS-IV); working memory and processing speed (Weschler Adult Intelligence Scale-IV); attention and executive functioning (Trail Making Test A & B respectively); cognitive screening (Addenbrookes Cognitive Examination-III); premorbid memory ability (Test of Premorbid Functioning); depression, anxiety, and subjective cognitive deficits (Beck Depression Inventory, Beck Anxiety Inventory & Perceived Deficits Questionnaire respectively; appendix A p 244).

Secondary clinical outcomes were requirement of high-dependency unit or intensive care unit admission up to 30 days after randomisation; time taken to be free of ventilatory support for 14 days (if on ventilatory support at time of randomisation);

time to reach maximum recorded Glasgow Coma Scale (GCS); time to hospital discharge; incidence of epilepsy; survival. Disability and functional outcome assessed at discharge or 30 days, 26 weeks, and 78 weeks consisted of modified Rankin scale: Barthel Index and Liverpool outcome score. The Glasgow outcome scale extended (GOS-E) was administered at 26 weeks and 78 weeks.

We collected a baseline Magnetic Resonance Imaging (MRI) scan, performed as part of the patient's standard medical care, between the time of hospital admission and seven days post-randomisation. We obtained research MRI scans at two weeks after randomisation (+/- seven days), at 26 weeks (+/- four weeks) and 78 weeks (+/- six weeks). Volumes of oedema and temporal lobe volumes were assessed using the Cavalieri method alongside stereological point counting, using the EASY MEASURE platform (Puddephat, 1999). This is an established approach for quantifying brain changes in patients with HSV Encephalitis (Defres et al., 2017). First, we quantified hyperintense regions on T2-weighted-Fluid-Attenuated Inversion Recovery (FLAIR) scans, considered total oedema. Second, we quantified cytotoxic and vasogenic oedema separately to explore the treatment effect on each type. Cytotoxic oedema was quantified by measuring hyperintense regions on DWI, and corresponding Apparent Diffusion Coefficient (ADC) scans were used to identify hypointense regions, eliminating T2 shine through (high signal on DWI that is not due to restricted diffusion)(J. Lee et al., 2024). Vasogenic oedema was calculated by subtracting the volume of cytotoxic oedema from the volume of total oedema. Third, we used the same T2 FLAIR scan to quantify the whole-brain volume, adjusting the total, cytotoxic and vasogenic oedema as a percentage of whole-brain volume. Temporal lobe volume was quantified on the coronal images of the best available

scan, using the same anatomical boundaries as defined previously (Defres et al., 2017). We used SynthSeg, a deep learning tool for segmentation validated for its robustness to poor contrast, resolution and diseased brains (Billot, Magdamo, et al., 2023), to quantify intracranial volume (ICV). Temporal lobe volume was calculated as a percentage of ICV. We conducted Anti-NMDAR antibody testing at 26 weeks, and at 2 weeks where CSF and serum were available. Safety was assessed via adverse events and reactions, defined according to the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions. In addition, the proportion of patients with detectable HSV in CSF by PCR at 2 weeks was monitored.

Oversight of the trial was provided by the trial steering committee, which met at least annually to review trial progress, safety, and serious adverse events (SAEs). The committee was also informed of any protocol changes by Liverpool Clinical Trials Centre.

3.4.4 Statistical analysis

The sample size was estimated with the following considerations. Firstly, we anticipated a 10% mortality rate before the primary outcome could be assessed (24 weeks). Secondly, verbal memory scores were expected to average 88·9 (SD 18·9), based on a published series of adult who survived HSV encephalitis (Utley et al., 1997), which was adjusted to a population mean of 84·8, (SD 23·1), adjusting for the expected 10% mortality rate. Thirdly, a 15.5 point difference on the verbal memory

score reflects a clinically meaningful difference, which would be above than one standard deviation aligning with the Weschler Memory Scales – IV standardised standard deviation of 15, and a conventional cut-off in neuropsychology studies. A final sample size of 36 participants per group would allow us to detect a clinically meaningful difference of 15·5 on the verbal memory score with 80% power, at a two-sided significance level of 0·05. Allowing for up to 20% dropout gave a target sample size of 45 participants per group, for a total of 90.

For both primary and secondary outcomes, participants were included in the analysis based on the intention-to-treat principle. Verbal memory scores were compared between groups using linear regression. The model was adjusted for the prespecified minimisation factors: age (<65 vs 65+ years), steroid use since hospital admission, hospital admission Glasgow Coma Scale Score (≤8 vs 9+), and delay in aciclovir treatment (≤2 vs 3+ days). Secondary cognitive and psychiatric outcome variables were analysed as per the primary outcome. Time to event outcomes were analysed using Kaplan-Meier curves, log rank tests and Cox proportional hazards models. Binary secondary outcomes were analysed using logistic regression. Pre-specified sensitivity analyses were carried out on the primary outcome, i) adjusting for premorbid memory ability, ii) excluding participants who received dexamethasone prior to randomisation, iii) excluding control group participants who received dexamethasone during the study, and iv) using multiple imputation to assess the impact of missing data. Post-hoc analysis used regression analysis to explore associations of timing of dexamethasone with the primary outcome.

Cognitive scores were age scaled based on normative data according to test manuals (WMS-IV, WAIS-IV, TOPF) to derive cognitive domain index scores which have a mean of 100 and an SD of 15. For the Trail Making Test, raw scores (in seconds) were compared between groups, as were measures from questionnaires assessing neuropsychiatric status (BDI & BAI) and subjective cognitive deficits (PDQ).

The Independent Data and Safety Monitoring Committee (IDSMC) monitored the trial throughout. Trial registration numbers were ISRCTN11774734, EUDRACT 2015-001609-16. The trial was funded by the NIHR Efficacy and Mechanism Evaluation Programme for the Department of Health (12/205/28).

3.4.5 Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this report.

3.5 Results

Between Sept 9, 2016, and Feb 21, 2022, 94 patients were recruited. 47 (50%) were randomly allocated dexamethasone (plus aciclovir) and 47 (50%) to the control (aciclovir only) group (Figure 3-1). Six patients could not be contacted for the 26 week follow up; two of whom (one in each group) were discovered later to be

completely dependent on others for care, and so were deemed unlikely to have been able to complete the primary outcome assessment due to severity of illness. Seven patients withdrew consent. Thus, the intention-to-treat population included 81 patients, 39 in the dexamethasone group and 42 in the control group.

The deaths of eight patients (four in each group) were attributed directly to encephalitis; additionally, seven patients (two in the dexamethasone group), with severe neuropsychological sequelae were unable to complete the primary outcome assessment. All 15 were attributed the lowest verbal memory score.

Baseline characteristics between the two groups were similar (Table 3-1), except for a difference in the HSV strains detected in the CSF: while most patients had HSV type 1 detected, six patients, all in the dexamethasone group, had HSV type 2. None of the patients with HSV2 encephalitis had clinical relapse, none of them required ITU and none died. Upon hospital admission, both groups presented with similar signs and symptoms characteristic of HSV encephalitis, including fever (86%), headache (68%) and seizures (49%). The groups were also comparable in age, Glasgow Coma Scale score, and delay between hospital admission and aciclovir treatment, characteristics previously shown to be related to outcome. Premorbid memory abilities were approximately 95 in both groups, indicating memory abilities prior to HSV encephalitis were within the average range.

One participant randomised to the dexamethasone group did not receive any dexamethasone. All others received at least 12 doses, with 35 (74%) receiving at least 16 doses, as specified in the protocol.

There was no difference in the primary outcome, verbal memory score at 26 weeks, between the treatment groups (Table 3-2). The mean score at 26 weeks was 71 (SD = 26) in the dexamethasone group, and 69 (SD = 25) in the control group (adjusted difference, 1·77; 95% CI, -9·57, 13·12; P=0·76). No beneficial effect of dexamethasone on the primary outcome was observed in any of the prespecified subgroup analyses, or in the sensitivity analysis to adjust for missing data (appendix A, pp 263-265). There was no significant difference in verbal memory score at 78 weeks for the 41 patients assessed at this time point (adjusted difference, -2·31; 95% CI, -19.04, 14·42; P=0·78). Likewise, there was no difference between the treatment groups in the other cognitive assessments administered at 26 weeks (Table 3-2) or 78 weeks (appendix A; pp 268-269). In the control group, eight (17%) patients received dexamethasone before randomisation (as empirical treatment for bacterial meningitis during the diagnostic workup) and four (9%) after randomisation at the discretion of the treating clinician (for details of dosage, see appendix A; pp 254-255); sensitivity analyses excluding these patients did not alter the result (appendix A; p 265).

Patients in the treatment group received dexamethasone a median of seven (Range 3 - 21) days after hospital admission. In a post-hoc analysis, we looked for an association between time to dexamethasone and outcome. This showed that verbal memory score fell an adjusted estimate 4.89 (95% CI, 2.70, 7.08) points, for every

day of delay in starting dexamethasone (p<·001) (Figure 3-3). In a further analysis, using time to randomisation instead of time to dexamethasone, and thus including the control group, the association was evident for the treatment group, but not the control group, although differences between groups were not statistically significant. (appendix A; p 266)

There was an improvement in functional outcomes over the observed period, with most improvement occurring between the initial 30-day/discharge assessment and the subsequent assessment at 26 weeks (Table 3-3; Figure 3-2). However, there was no significant difference between the treatment groups in the comparative analysis (appendix A; p 270)

Quantitative longitudinal analysis of MRI scans between baseline and week two showed a decrease in temporal lobe volume of the most affected side by 0·1% (SD 1·1) in the control group and an increase in the dexamethasone group by 0·2% (SD 0·5), however, there were no significant differences between the two groups (adjusted estimate, -0·21; 95% CI, -1·11, 0·69; P=0·57). At 26 weeks, temporal lobe volume in the control group decreased by 0·6% (SD 1·2) compared to baseline, and by 0·6% (SD 1.0) in the dexamethasone (adjusted estimate, 0·42; 95% CI, -0·65, 1·49; P=0·38). Between baseline and week two total oedema decreased by 1·1% (SD 2.0) in the control group and by 0·8% (SD 2·5) in the dexamethasone group (adjusted estimate, -0·31; 95% CI, -2·17, 1.55; P=0·73). Cytotoxic oedema reduced on average by 0·7% in the control group and by 0·4% in the dexamethasone group (adjusted estimate, 0.14; 95% CI, -0.12, 0.41; P=0·27). There was a reduction of vasogenic oedema by 0·1% (SD 2.0) in the control group, and of 0·8% (SD 1·8) in

the dexamethasone group (adjusted estimate, -1.83; 95% CI, -4.27, 0.62; P=0·13; Figure 3-4).

There was no significant difference in the proportion of patients who had HSV detected in their CSF at two weeks: four (11%) of 36 patients in the dexamethasone group versus nine (21%) of 43 in the control group (adjusted OR 0·47; 95% CI 0.1, 1.7; P=0·25). Likewise, there were no differences in peripheral white blood cell count between the two groups at 26 weeks (adjusted estimate, 0·93; 95% CI, -0·57, 2·42; P=0·22). Five patients (all dexamethasone) had clinical relapses, as determined by judgement of the treating clinicians and lead investigators, two of whom were positive for NMDAR antibodies in serum and CSF. Relapses occurred at a median of 24 weeks after randomisation (range 12-52 weeks). None of the patients were PCR positive for HSV at two weeks, or at time of relapse. Three of the patient with relapse were treated with immune therapy for autoimmune encephalitis, while the other two were treated with further courses of aciclovir. Four further patients were positive for NMDAR antibodies in CSF, serum or both; one in the dexamethasone group and three in the control group.

The incidence of secondary clinical endpoints was similar. There were 12 deaths across the follow-up period, 6 (13%) in each group. There was a similar likelihood of seizures up to 26 weeks in both groups (adjusted OR 0·71; 95% CI, 0·22, 2·22; P=0·55) and a similar time to hospital discharge (adjusted HR 0·93; 95% CI, 0·58, 1·48; P=0·75).

Dexamethasone was well tolerated, with no differences in notable adverse events between the groups. Eighteen (38%) of 47 patients in the control group had one or more notable events, four (9%) with one or more serious adverse events. In the dexamethasone group, 18 (40%) patients had one or more notable events, and seven (15%) had one or more serious adverse events. No suspected unexpected serious adverse events (SUSARs) were recorded.

3.6 Discussion

In this multicentre, randomised, observer-blind trial, adding dexamethasone to the standard treatment of aciclovir did not alter the primary outcome of verbal memory score at 26 weeks for adults with HSV encephalitis. Nor were there differences at 78 weeks for verbal memory score, or for other neuropsychological, functional or imaging outcomes. Administration of dexamethasone was safe. There was no increased detection of HSV in the CSF patients treated with dexamethasone, which was one of the concerns of this broad immunosuppressive therapy, and adverse events were similar between the treatment and control groups.

For some patients in the treatment group there was a long delay to receive dexamethasone (up to 21 days after hospital admission), and a post-hoc analysis showed earlier dexamethasone treatment was associated with a better outcome in this group. Allowing this broad time window for patient entry into the study was one of several measures we introduced to try and improve recruitment for this rare disease, and overcome the limitations of the previous German trial on Aciclovir and

Corticosteroids in Herpes-Simplex-Virus-Encephalitis (GACHE),(U. Meyding-Lamadé et al., 2019) which terminated early due to poor enrolment. That study allowed just five days between hospital entry and recruitment into the study and specified patients must have focal neurological signs. We allowed a longer time window, and any clinical features of HSV encephalitis. Our open label observer-blind study design using ward stocks of dexamethasone made our study logistically easier than the placebo-controlled double-blind GACHE study. Our choice of verbal memory score as the primary outcome, which is more specific to the nature of sequelae from HSV encephalitis, rather than the modified Rankin Scale, which was designed for stroke, allowed for a much smaller sample size (90 patients versus 372). We also used innovative methods to ensure staff at recruitment sites remained aware of the study over its long duration, working closely with the non-profit, Encephalitis International, and the patient community to promote it (Whitfield et al., 2021). A high proportion of eligible patients were recruited, with a low attrition rate. Having all the neuropsychological testing conducted by a single psychologist who visited patients at study sites or at home minimised variability in data collection.

Our approaches thus ensured successful recruitment and retention into the study, achieving our sample size five and a half years after we started. However, by allowing patients to be entered into the study so late after hospital admission we may have inadvertently masked the effect of dexamethasone treatment; corticosteroids three weeks into HSV encephalitis are unlikely to have the same impact on brain inflammation as in the first few days. Confounding factors influencing time to study recruitment and dexamethasone administration cannot be completely excluded, although controlling for time to aciclovir administration, age, and GCS at admission

did not abolish the effect of time to dexamethasone on outcome. The apparent beneficial effect of early corticosteroid treatment we found is consistent with findings from case reports and case series (Kamei et al., 2005; Maraş Genç et al., 2016; Musallam et al., 2007; Nakano et al., 2003; Ramos-Estebanez et al., 2014). One retrospective analysis found a better outcome for 22 of 45 HSV encephalitis patients who received corticosteroids in addition to aciclovir; the corticosteroids were given a median 5 (range 1-13) days, after hospital admission (Kamei et al., 2005).

Five patients had a clinical relapse, all allocated to dexamethasone. CSF HSV PCR was negative at 2 weeks and at relapse in each case, making virological reactivation unlikely. NMDAR-IgG was detected in equal numbers in dexamethasone and standard-care groups; differential rates of post-HSV autoimmunity are therefore an unlikely explanation. Relapse intervals were generally longer than those described for post-HSV autoimmune encephalitis, making a steroid rebound or withdrawal effect unlikely. Our sampling schedule (CSF at 2 weeks; serum thereafter) might have missed CSF-restricted or later-emerging responses. Baseline imbalances could also have contributed, including a greater number of HSV-2 cases in the dexamethasone group. Given the small number of events, chance clustering remains possible.

We chose a corticosteroid dose similar to that which has proven beneficial in mouse models of HSV encephalitis (Sergerie, Boivin, et al., 2007) and in phase III clinical trials of other brain infections (bacterial meningitis (de Gans & van de Beek, 2002), and tuberculous meningitis (Thwaites et al., 2004), rather than the higher doses used in inflammatory conditions such as anti-NMDAR encephalitis (Nosadini et al., 2021).

Autoimmune encephalitis has been recognised increasingly over the last 15 years (Granerod et al., 2010), and may have a broadly similar presentation to HSV encephalitis with encephalopathy, seizures, and evidence of brain inflammation from imaging and/or CSF analysis. First line treatment is corticosteroids, but because of possible deleterious effects in HSV encephalitis, they are usually withheld until a negative CSF PCR for the virus. Our findings that corticosteroids do no harm in HSV encephalitis open the potential for their earlier use in all patients with encephalitis whether HSV or autoimmune aetiology is suspected.

Our trial has several limitations, beyond the wide time window for recruitment. Firstly, by designing a pragmatic study which focused on recruiting patients and achieving the primary outcome, some of the secondary outcomes were underpowered, especially for the imaging analyses. Secondly we were impacted by social distancing restrictions during the Covid-19 pandemic; although recruitment had to be paused, we managed to complete all neuropsychological evaluations for patients already in the study, by switching from in-person to on-line assessments and following British Psychological Society guidelines for remote testing (Brown et al., 2024). Thirdly, despite achieving our sample size, we were not adequately powered to explore subgroup analyses among patients from diverse backgrounds, which is now recognised as having an important impact on the incidence and outcomes of encephalitis (Wu et al., 2024). Whether the post hoc improvement observed at 26 weeks was sustained at 78 weeks is unknown. Fourthly, owing to the pragmatic nature of the trial, some patients in the control group received dexamethasone at the discretion of the treating clinician, while some patients randomised to the dexamethasone group did not receive a full dexamethasone course. Sensitivity

analyses adjusting for these deviations did not alter the result. Finally, beyond the predefined anti-NMDAR testing (CSF/serum at 2 weeks and serum at 26 weeks), we did not screen for other neuronal autoantibodies (for example LGI1, and CASPR2). Alternative or concomitant autoimmune encephalitis therefore could not be excluded, and unrecognised autoimmunity may have contributed to outcome heterogeneity.

Corticosteroids have broad anti-inflammatory and immunosuppressive effects. Using samples from this study, including peripheral blood mononuclear cells, we plan to examine the host response in HSV encephalitis and investigate how it is impacted by dexamethasone. Ultimately more targeted therapy aimed at modulating specific deleterious immune pathways may reduce brain injury in HSV encephalitis more effectively than the non-specific effects of corticosteroids. Until then our study has shown that dexamethasone treatment for HSV encephalitis is safe, and whilst we could not show any benefit for patients overall, our results suggest dexamethasone is beneficial if given soon after hospital admission.

3.7 Conclusions

Further study of the overall nature and long-term trajectories of cognitive outcomes in HSV encephalitis is needed. Because obtaining detailed longitudinal neuropsychological data in these patients is exceptionally challenging, the data from the clinical trial offer a rare opportunity to assess the long term cognitive outcomes in

HSV encephalitis. In the next chapter, I analyse the entire cohort to determine the prevalence of various cognitive and psychiatric impairments and to describe the pattern of cognitive recovery among these patients.

Table 3-1: Baseline Characteristics of randomised patients

	Dexamethasone (n=47)	Control (n=47)
Mean age (years)	64 (13)	67 (15)
Gender (female)	20 (43%)	24 (51%)
Ethnicity[1]		
Asian or Asian British	2 (4%)	1 (2%)
Black/African/Caribbean/Black British	0 (0%)	1 (2%)
Mixed/multiple ethnic groups	1 (2%)	0 (0%)
Other ethnic group	0 (0%)	2 (4%)
White	43 (93%)	43 (91%)
Stratification factors		
Age categorical (65+ years)	25 (53%)	28 (60%)
GCS ≤8	8 (17%)	9 (19%)
Steroid use prior to randomisation	7 (15%)	8 (17%)
delay in receiving aciclovir (≥3 days)	8 (17%)	7 (15%)
Clinical factors		
Days from hospital to randomisation	7 (5, 10)	8 (6, 11)
In ITU/HDU on day of randomisation	11 (23%)	12 (26%)
Receiving ventilator support on day of randomisation	7 (15%)	9 (19%)
CSF PCR Results		
HSV1 Positive	41 (87%)	47 (100%)
HSV2 Positive[2]	6 (13%)	0 (0%)
Symptoms		
Fever (>37·5)	38 (81%)	43 (91%)
Headache[3]	26 (68%)	28 (67%)
Seizures[4]	20 (47%)	23 (51%)
Photophobia	8 (31%)	8 (32%)
Neck stiffness/signs of meningism	8 (25%)	3 (14%)
Dysphasia	17 (55%)	21 (62%)

Data are mean (standard deviation), median (IQR), or n (%). GCS = Glasgow Coma Score. ITU = Intensive Care Unit. HDU = High Dependency Unit. 1 Unobtainable for 2 in Dexamethasone group, 1 in Control group 2 Unobtainable for 1 in Dexamethasone group, 3 in Control group.
3 Not recorded for 9 in Dexamethasone group, 5 in Control group.4 Not recorded for 4 in Dexamethasone group, 2 in Control group.5 Not recorded for 22 in Dexamethasone group, 19 in Control group.

Table 3-2: Primary and secondary outcomes at week 26 endpoint

	Dexamethasone		Control		difference, hazard ratio or odds ratio (95% CI)*	p value
	N		N			
Primary outcome						
Verbal memory (WMS-IV) at 26 weeks	39	71 (26)	42	69 (25)	Adjusted difference in means 1.77 (-9.57, 13.12)	0.76
Secondary neuropsychology outcomes at 26 weeks						
Visual memory (WMS-IV)	33	69 (25)	31	71 (26)	Adjusted difference in means -1.09 (-13.40, 11.22)	0.86
Immediate memory (WMS-IV)	33	71 (25)	31	67 (24)	Adjusted difference in means -1.19 (-14.14, 11.75)	0.85
Delayed memory (WMS-IV)	33	68 (24)	31	65 (24)	Adjusted difference in means -0·02 (-13.26, 13.21)	1.0
Working memory (WAIS-IV)	36	85 (25)	36	82 (27)	Adjusted difference in means 4.55 (-7.81, 16.91)	0.47
Processing speed (WAIS-IV)	33	80 (23)	32	77 (26)	Adjusted difference in means 4.00 (-7.87, 15.87)	0.50
Trail Making Test A (seconds)	34	96 (99)	35	134 (119)	Adjusted difference in means -38.29 (-89.16, 12.57)	0.14
Trail Making Test B (seconds)	33	165 (96)	34	202 (106)	Adjusted difference in means -33.72 (-80.25, 12.81)	0.15
ACE-III	32	69 (28)	28	63 (29)	Adjusted difference in means 4·85 (-9·32, 19.02)	0.50
Perceived deficits questionnaire	29	30 (17)	25	28 (14)	Adjusted difference in means 2·52 (-6·42, 11·46)	0.57

Beck Anxiety Inventory	27	14 (11)	26	11 (11)	Adjusted difference in means 3·33 (-2.99, 9·64)	0.29
Beck Depression Inventory	27	17 (12)	26	14 (11)	Adjusted difference in means 2·72 (-3·84, 9·29)	0.41
Clinical outcomes						
All-cause mortality	..	6/47 (13%)	..	6/47 (13%)	..	..
Frequency of seizures at 26 weeks	..	7/36 (19%)	..	10/38 (26%)	Adjusted OR 0.71 (0.22, 2.22)	0.55
Time to hospital discharge	..	..	..	..	Adjusted HR 0.93 (0.58, 1.48)	0.75
Hospital admission to ITU/HDU following randomisation[†]	..	0/34 (0%)	..	1/35 (3%)	..	..
Time to reach 14 days without ventilatory support[‡§]	..	4/7 (57%)	..	8/9 (90%)	..	..
Quality of Life outcomes at 26 weeks						
SF-36						
Physical functioning	31	61 (35)	24	70 (32)	Adjusted difference in means -6.79 (-24.73, 11.15)	0.45
Physical role limitations	31	54 (38)	24	54 (38)	Adjusted difference in means 3.16 (-17.35, 23.66)	0.76
Bodily pain	31	68 (30)	24	78 (26)	Adjusted difference in means -9.44 (-25.57, 6.68)	0.24
General health perceptions	31	51 (27)	24	60 (25)	Adjusted difference in means -7.70 (-22.15, 6.75)	0.29
Energy/vitality	31	40 (27)	24	52 (26)	Adjusted difference in means -10.26 (-24.70, 4.18)	0.16
Social functioning	31	52 (34)	24	67 (26)	Adjusted difference in means -12.91 (-29.46, 3.64)	0.12
Emotional role limitations	31	56 (37)	24	63 (36)	Adjusted difference in means -4.35 (-24.86, 16.16)	0.67
Mental health	31	62 (24)	24	68 (20)	Adjusted difference in means -4.32 (-16.68, 8.04)	0.49
EQ-5D-5L	30	64 (25)	23	75 (18)	Adjusted difference in means -9.55 (-21.38, 2.28)	0.11

Data are mean (standard deviation), or n/N (%). OR = odd ratio. HR = hazard ratio. WMS-IV = Weschler Memory Scale fourth edition. WAIS-IV = Weschler Adult Intelligence Scale fourth edition. ACE-III = Addenbrookes Cognitive Examination-III. ITU = Intensive Care Unit. HDU = High Dependency Unit. SF-36 = Short-Form Health Survey. * Adjusted for age, steroid use since hospital admission, Glasgow Coma Score and delay in aciclovir administration. † Includes only those patients not in ITU/HDU at the time of randomisation. ‡ Includes only those patients that were on ventilatory support at the time of randomisation. § model not fitted as Kaplan-Meier curves cross several times (appendix A; pp 271-274).

Table 3-3: Descriptive statistics of functional outcome measures at all follow up timepoints

	30 Days/Discharge		26 Weeks		78 Weeks	
	Control	Dexamethasone	Control	Dexamethasone	Control	Dexamethasone
Modified Rankin Scale (MRS)						
N	41	43	33	35	22	22
Mean (SD)	2·85 (1·49)	2·51 (1·7)	1·85 (1·56)	1·86 (1·33)	1·64 (1·53)	1·59 (1·18)
Barthel Index						
N	41	43	33	35	22	22
Mean (SD)	13·63 (7·53)	13·47 (8·17)	17·06 (5·34)	17·17 (5·16)	16·77 (5·74)	18·91 (1·63)
Liverpool Outcome Score (LOS)						
N	41	39	30	35	22	21
Mean (SD)	2·68 (0·72)	2·74 (0·79)	3·43 (1·04)	3·2 (0·96)	3·36 (1·14)	3·57 (0·98)

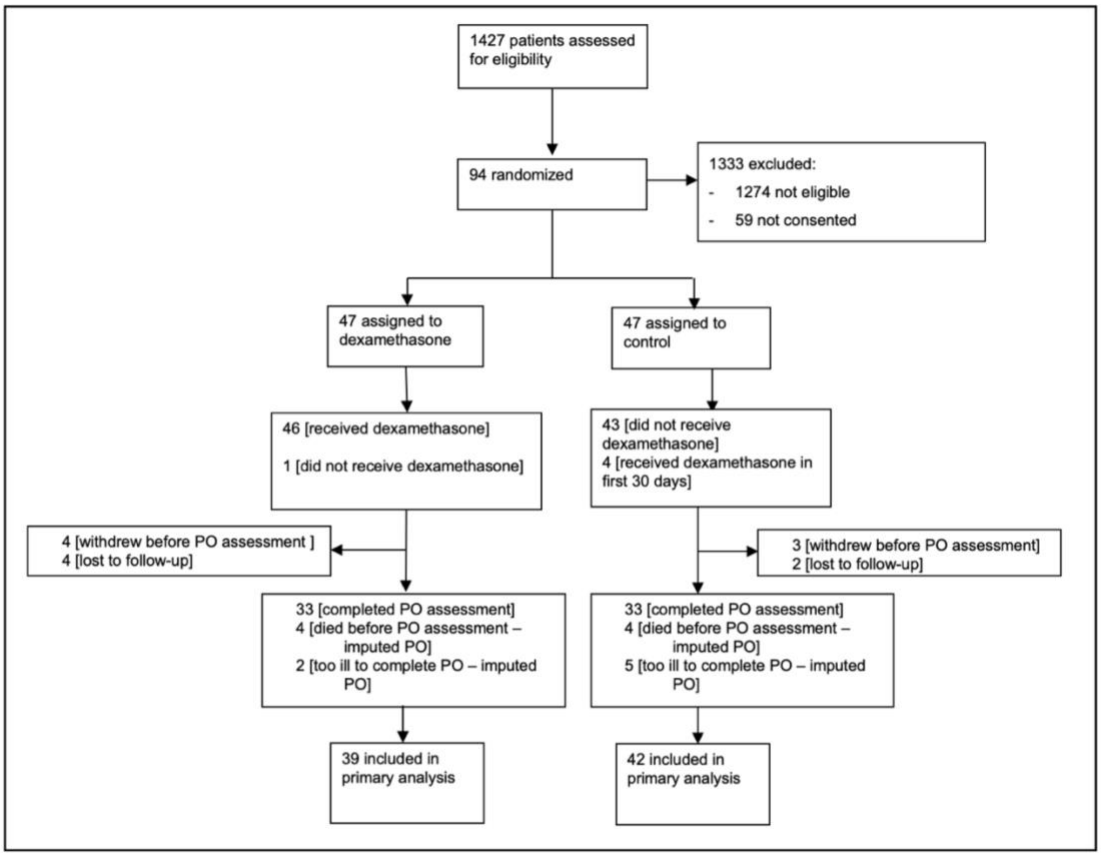

Figure 3-1: Patient flow diagram

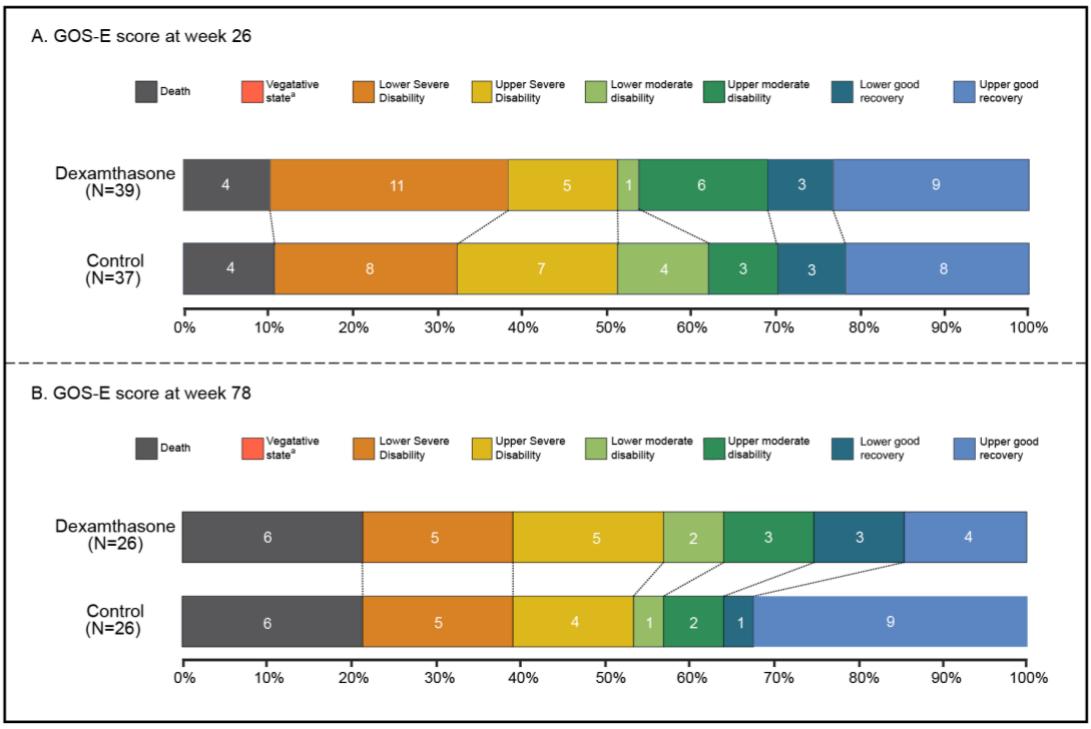

Figure 3-2: Distribution of Glasgow Outcome Score Extended (GOS-E) at week 26 (A) and week 78 (B)

Stacked bar chart showing the percentage of patients at each Glasgow Outcome Scale extended (GOS-E) score in the dexamethasone and control groups at week 26 (A) and week 78 (B). The categories are death; vegetative state (unresponsive/speechless); lower severe disability (dependent on others for daily care); upper severe disability (ability to attend to basic needs, but may require assistance with more complex tasks); lower moderate disability (independent but may have some cognitive and/or physical disability that interfere with some aspects of daily activities); upper moderate disability (independent in daily life but may have some cognitive and/or physical disability but with less disruption than lower moderate); lower good recovery (can resume most normal activities but with some mild problems); upper good recovery (no problems). No patients were recorded as vegetative state on the GOS-E at week 26 or week 78.

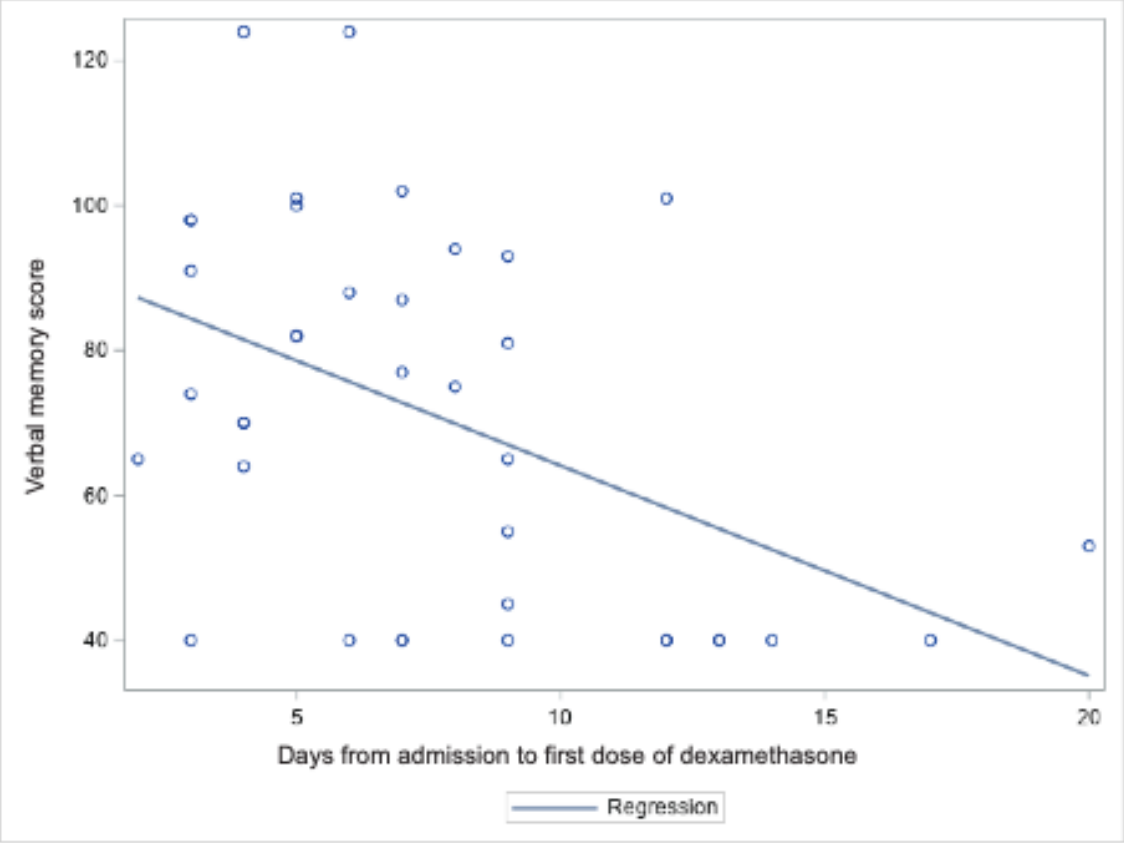

Figure 3-3: Scatterplot of Verbal Memory score at 26 weeks versus days from hospital admission to first dose of dexamethasone, for the dexamethasone group

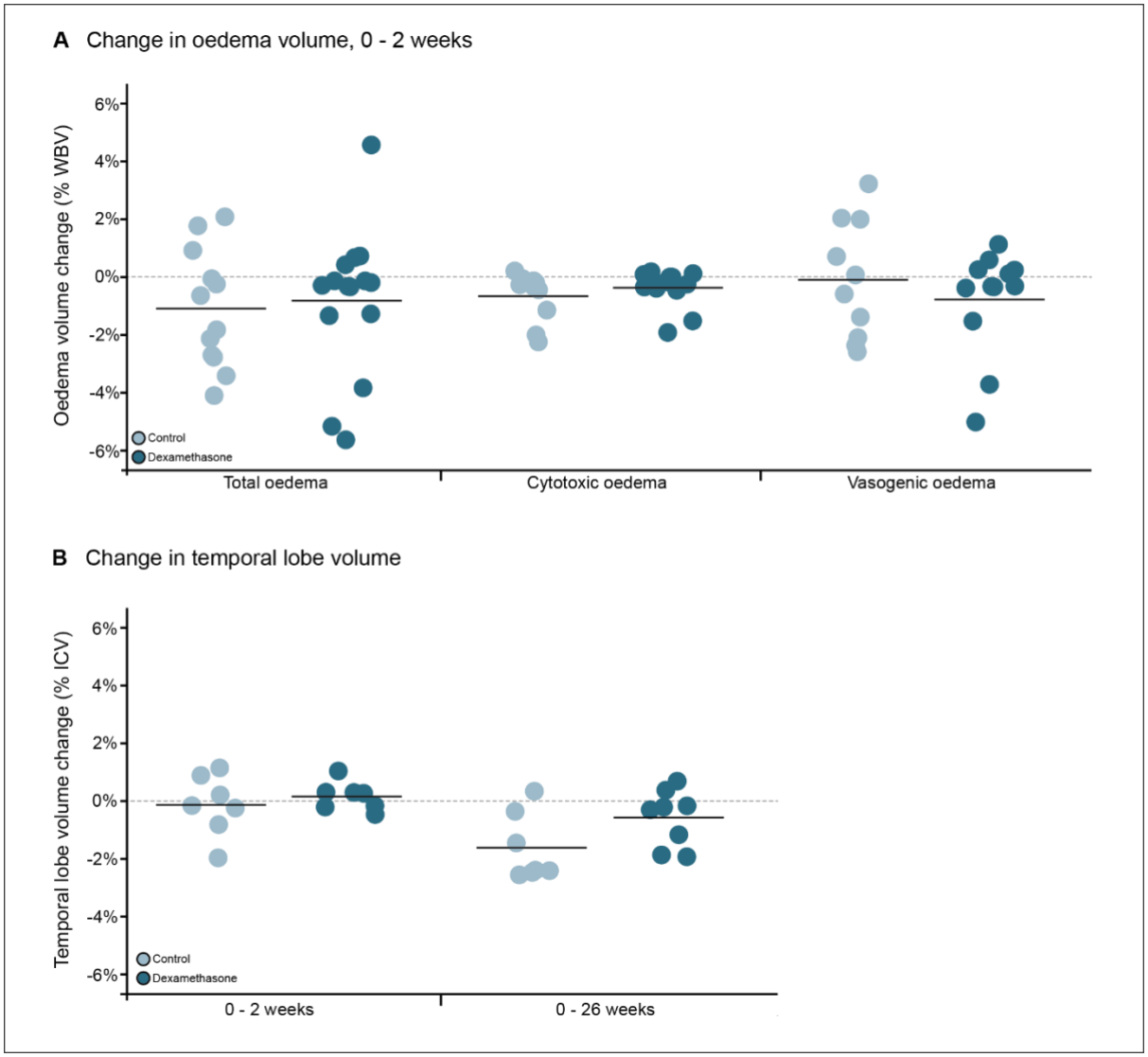

Figure 3-4: Secondary MRI outcomes

The mean and individual patient values are shown for volume change in total oedema, cytotoxic oedema and vasogenic oedema (left to right) between baseline and week two magnetic resonance imaging (MRI) scans (A); change in volume of the most affected temporal lobe between baseline and two weeks and baseline and 26 weeks. The mean is indicated by a solid bar, and individual patient values are light blue for control group and dark blue for dexamethasone group. Percentages are presented as percentage points. WBV = whole brain volume. ICV = intracranial volume.

Chapter 4 Cognitive and Psychiatric Outcomes in Herpes Simplex Encephalitis.

4.1 Summary

Background

Cognitive impairment is a debilitating consequence of HSV encephalitis, yet its long-term trajectories and predictors of that trajectory remain poorly characterised.

Methods

In this secondary analysis of the DexEnceph trial cohort, adults with PCR-confirmed HSV encephalitis completed neuropsychological assessments at 26 weeks and 78 weeks. A standardised battery evaluated verbal/visual memory, attention, executive function, processing speed, working memory, psychiatric symptoms, and subjective cognitive complaints. I converted cognitive scores to age adjusted z-scores. Cut-off for mild/moderate impairment group was a score <-1 (2^{nd} - 16^{th} percentile) and severe impairment was z score <-2 (<2^{nd} percentile). Longitudinal trajectories were analysed with paired t tests and reliable change indices. Correlation analyses were used to explore the relationship between objective and subjective cognitive functioning and psychiatric outcome.

Results

Among 66 participants (median age 66; 57% male), cognitive impairment was pervasive at 26 weeks: 60% exhibited deficits in verbal memory, 66% in delayed memory, 56% in executive function, and 51% in attention. Severe impairment was most frequent in verbal memory (39%) and attention (31%). Psychiatric symptoms were prevalent (59% anxiety, 47% depression), and correlated with subjective complaints ($r = 0.46–0.65$, $p<0.001$) but weakly with objective deficits. At 78 weeks ($n=32$), group-level deficits persisted ($p >0.05$), but individual trajectories diverged: 23% improved in immediate/visual memory, while 9–18% declined. Improvement rarely restored normal function ($z >−1$).

Interpretation

Cognitive deficits after HSV encephalitis are severe and persistent. Recovery trajectories vary significantly, highlighting the need for personalised rehabilitation and long-term monitoring.

4.2 Introduction

In Chapter 1, I conducted a systematic review that demonstrated people post HSV encephalitis experience multifaceted cognitive impairments. However, methodological variability and the scarcity of long-term data limit our understanding of how these deficits evolve. In the previous chapter, I demonstrated that early dexamethasone treatment may improve verbal memory outcomes, yet the overall long-term cognitive profile and recovery trajectories are poorly understood. The clinical trial dataset offers a unique opportunity to address these gaps. In this chapter, I analyse the prospectively collected neuropsychological assessments from the entire cohort to determine the prevalence and severity of cognitive and psychiatric impairments and to describe the pattern of long-term recovery among people post HSV encephalitis.

Verbal memory - the ability to store, encode and retrieve verbally presented information- is widely recognised as a core cognitive deficit in HSV encephalitis. Early case studies and small group studies have highlighted this; however, these often included selected patients with unique profiles of neuropsychological impairment, potentially introducing selection bias (Cermak, 1976; Rose & Symonds, 1960). More extensive group studies with representative samples confirm the prevalence of verbal memory impairment but also reveal a broader spectrum of cognitive impairments affecting executive functioning, attention, visuospatial, language, and working memory abilities (Harris et al., 2020; Pewter et al., 2007; Utley et al., 1997). Nevertheless, variations in sample sizes, assessment methods,

and timing of follow-ups make comparisons of cognitive outcomes across studies difficult.

While cognitive impairments following HSV encephalitis have been documented in case studies and small case series, investigations of long-term cognitive recovery trajectories remain limited (Hokkanen et al., 1996; Hokkanen & Launes, 2000). A recent multi-centre case-control study compared HSV encephalitis with other types of encephalitis and controls in a short-medium term cohort (four to twelve months), reporting impairments in the HSV encephalitis group in full-scale IQ, verbal and visual anterograde memory, retrograde memory, and language. In a separate long-term cohort (at least one year after admission), impairment levels were lower, although they continued to find impairments in verbal and visual anterograde and retrograde memory (Harris et al., 2020). The limited data available from different post-illness timepoints and the absence of prospective studies hinder a comprehensive characterisation of recovery trajectories.

Moreover, relapse following HSV encephalitis is an important concern. It is estimated around 27% of patients will clinically relapse, often thought to be immune-mediated (Armangue et al., 2015). Considering that immune-mediated encephalitis, such as anti-NMDAR encephalitis, is associated with significant cognitive impairment (Heine et al., 2021), it is important to develop an understanding of how relapse interacts with cognitive recovery trajectories in HSV encephalitis. Interestingly, some studies have explored the relationship between NMDAR autoimmunity and cognitive recovery in patients with HSV encephalitis. Greater improvement in cognitive scores were observed in antibody negative patients compared with antibody positive patients

(Westman et al., 2016). However, there were no significant differences between NMDAR antibody-positive and -negative patients at any follow-up time point, and the improvement was primarily driven by recovery from worse baseline performance in the antibody-negative group. It is therefore important to consider that cognitive recovery in HSV encephalitis may not follow a linear trajectory.

The prevalence of psychiatric outcomes in HSV encephalitis has received less attention despite increasing awareness of the challenges patients face returning home from the hospital (Cooper et al., 2017). In HSV encephalitis, the prevalence of depressive symptoms has been reported as high as 39%, and patients often report being more impaired with affective than physical symptoms (Fazekas et al., 2006). The broader acquired brain injury literature suggests a complex relationship between neurological injury, cognitive impairment, and psychosocial factors (Mamman et al., 2024; Yeates et al., 2008). Importantly, depression is a potentially modifiable risk factor and could be a target to reduce poor outcomes and health-related quality of life (Stalder-Lüthy et al., 2013). Understanding the interplay between cognitive and psychiatric factors in HSV encephalitis could inform rehabilitation approaches.

Ultimately, we must better understand the natural history of cognitive and emotional difficulties to provide accurate prognoses, develop rehabilitation pathways, and provide insight into the acute and post-acute disease mechanisms contributing to poor functioning. Therefore, in this chapter I aim to (1) characterise the cognitive phenotype of HSV encephalitis in a large prospectively followed cohort; (2) examine long-term recovery trajectories of cognitive function; (3) explore the relationship

between cognitive impairments and psychiatric outcomes; (4) describe the impact of clinical relapse and immune-mediated processes on cognitive recovery.

4.3 Methods

4.3.1 Study Population and Setting

The neuropsychological and psychiatric data was obtained from the DexEnceph cohort. DexEnceph was a multicentre randomised control clinical trial investigating the use of dexamethasone in adults with HSV encephalitis. The published protocol provides a detailed summary of the trial methodology (Whitfield et al., 2021). To analyse the cognitive outcomes of HSV encephalitis in this study, I included only those participants who continued in the trial up to the 26-week neuropsychological assessment and completed at least part of the neuropsychology battery.

Briefly, patients over the age of 16 years with symptoms of suspected encephalitis and confirmed HSV encephalitis through positive Polymerase Chain Reaction (PCR) were enrolled. All participants were treated with intravenous acyclovir, dosed at 10mg/kg or a modified dose if clinically warranted, with half of the participants randomised to receive adjunctive dexamethasone therapy. Written consent was provided either personally or through a legal representative. The exclusion criteria were centred on omitting participants where corticosteroid treatment may be contraindicated due to the potential for adverse responses.

4.3.2 Neuropsychological Assessment

As part of this study, detailed neuropsychological assessment was conducted at two time points, 26 weeks (+/- 4 weeks) and 78 weeks (+/- 6 weeks) following randomisation into the trial (up to 21 days following hospital admission). A trained psychologist from the Walton Centre NHS Foundation Trust conducted the neuropsychological assessment at participants' homes or the recruiting site. The assessment included evaluation of verbal, visual, immediate, and delayed memory (Weschler Memory Scale fourth edition); working memory and processing speed (Weschler Adult Intelligence Scale fourth edition); attention and executive function (Trail Making Test A & B respectively); estimate of premorbid functioning (Test of Premorbid Functioning); subjective cognitive deficits (Perceived Deficits Questionnaire); psychological functioning (Beck Anxiety Inventory & Beck Depression Inventory). The neuropsychological test battery was selected due to its rigorous standards and alignment with tests commonly utilised in clinical neuropsychology practice within the United Kingdom (see Methods pp 59-64 for detailed description of subtests administered as part of the neuropsychological battery).

4.3.3 Statistical Analyses

Cross-sectional analyses

I investigated the cognitive profile of patients with HSV encephalitis at 26 weeks. According to test manuals, I converted raw scores on cognitive subtests to age-adjusted scores based on normative data. These scores were transformed into z-scores to enable direct comparison across cognitive test outcomes. I categorised each participant's impairment level by comparing their Z-scores with commonly reported thresholds in the existing literature. A Z-score greater than or equal to –1 was classified as no impairment (≥16th percentile), a Z-score less than –1 but greater than –2 was considered mild or borderline impairment (<16th percentile), and a Z-score less than or equal to –2 indicated severe impairment (<2nd percentile). By presenting these ranges, I aimed to provide a more complete picture of the spectrum of cognitive impairments. Raw scores on anxiety and depression questionnaires were compared to cut-offs provided in the test publishers manuals to determine the severity and prevalence of psychiatric symptoms. Where appropriate Benjamini-Hochberg correction for multiple testing was performed.

I performed sensitivity analyses to examine whether baseline characteristics differed between participants with complete and incomplete cognitive outcome data.

Longitudinal analyses

I investigated the change in the cognitive performance in patients with neuropsychological test results at week 26 and week 78. Shapiro-Wilk was used to determine the distribution of the data. If data were normally distributed, the difference in means was assessed using a paired sample t-test, and the Wilcoxon Signed rank test was used for repeated measures that were not normally distributed.

To explore recovery trajectories at the individual level, I calculated the modified Reliable Change Index. The Iverson method for reliable change is a statistical procedure used to determine whether an individual's change in test scores over time exceeds what would be expected from normal measurement error or chance fluctuations. I incorporated the test's reliability and standard error of measurement, obtained from test publishers manuals, to establish a threshold, so that observed changes greater than this threshold can be interpreted as clinically meaningful rather than simply random variation a detailed description of the formula used can be found at (Iverson, 2018).

Correlational analyses

Correlations between cognitive tests, self-report symptoms, psychiatric symptoms, age, and years of education were calculated using Spearman's rho.

4.4 Results

4.4.1 Study population

The baseline characteristics for patients at week 26 follow-up are shown in Table 4-1. The mean (SD) age was 63 (14) years, and 26 (43%) were female. The patients were typical of HSV encephalitis regarding demographic characteristics, acute symptoms, and disease course. Not all patients who underwent a neuropsychology

assessment completed all aspects of the battery, most often due to fatigue or unwillingness to continue. Patients who completed all tests in the cognitive battery (n=39) were more likely to be younger (p = 0.026) and more likely to be discharged before 30 days (p = 0.006) compared with those with incomplete cognitive outcomes (appendix B; p 281).

4.4.2 Post-acute cognitive impairment profile at 26 weeks

Impairments were observed in all of the cognitive domains assessed, and performance was significantly lower than expected compared to standard norms (Table 4-2)

The prevalence and severity of cognitive impairment at 26 weeks varied across cognitive domains (Figure 4-1). 40 (60%) of 66 patients were impaired (<16th percentile) in verbal memory, and 32 (55%) of 49 were impaired in visual memory. Severe impairment (<2nd percentile) was more common in verbal memory (39%) than in visual memory (31%). 29 (59%) of 49 were impaired in immediate memory, and 32 (66%) of 49 were impaired in delayed memory. 25 (51%) of 49 had impaired attention, with 31% severely impaired. 27 (56%) of 48 had impaired executive function, with 23% severely impaired. Patients were less impaired in tests of general intellectual functioning: 14 (25%) of 58 had impaired working memory, 9% were classified as severe, and 19 (38%) of 51 had impaired processing speed, 12% severe.

In an analysis of complete cases (n=39), there were no consistent patterns of cognitive impairment (Figure 4-2). 5 (90%) of 39 patients were impaired in at least one cognitive domain, Thus, only four (10%) patients showed no impairment in any of the cognitive domains assessed. Isolated auditory memory impairment was the most frequently observed pattern of impairment in Five (13%) patients. Isolated impairment in other domains was uncommon. Patterns of widespread impairment, often impacting more than three domains, were observed, although the domains impaired varied substantially.

4.4.3 Depression and anxiety screening

I found high levels of affective symptoms at the 26 week follow-up. Around one-third of patients experienced clinically relevant symptoms of depression: 7 (13%) mild, 9 (17%) moderate, and 9 (17%) severe. Overall, anxiety symptoms were more prevalent; 59% of patients reported clinically relevant symptoms of anxiety. However, these were milder than depressive symptoms: 16 (30%) mild, 11 (20%) moderate, and 5 (9%) severe.

4.4.4 Relationship between cognition, psychopathology, and cognitive reserve

Figure 4-5 shows significant correlations between outcome measures at 26 weeks. I found that perceived deficits were not associated with cognitive performance in most

domains, except for moderate associations in auditory memory (r = -0.45, p < 0.001) and visual memory (r = -0.38, p = 0.01). At the same time, perceived deficits showed strong/moderate associations with symptoms of depression (r = 0.65, P < 0.001) and anxiety (r = 0.46, p < 0.001). Depression symptoms were associated with poorer performance in verbal (r = -0.41, p = 0.003) and visual (r = -0.31, p = 0.047) Memory, whilst anxiety scores were associated with poorer performance in visual memory (r = -0.43, p = 0.004).

Years of education, a measure of cognitive reserve, was associated with better performance in verbal memory (r = 0.34, p = 0.009), visual memory (r = 0.36, p = 0.013), working memory (r = 0.47, p = < 0.001), and processing speed (r = 0.49, p = < 0.001). There were no associations between age and cognitive performance, except for a weak association with simple attention (all correlation results can be found in appendix B; pp 282-283)

4.4.5 Long-term cognitive recovery trajectories

I followed 32 patients up at 78 weeks. Cognitive functioning at 26 weeks, demographic and admission characteristics were similar between the patients who completed both the week 26 and week 78 and patients who completed only the week 26 assessment, except for processing speed, which was significantly lower in the week 26 only group (p=0.044; appendix B; pp 279-280)

At the Group level, cognitive impairment was persistent, with limited improvement in deficits between the initial assessment and follow-up. there were no significant differences between the week 26 and week 78 follow-up in any of the cognitive domains (Table 4-3; Figure 4-3).

However, analysis of individual patient data with the reliable change index showed that recovery trajectories varied between participants (Figure 4-4). The highest percentage of patients showed reliable improvement in Immediate Memory (23%), Visual Memory (23%), and Executive Function (18%). However, a comparable proportion of patients also had reliably lower scores in these domains; 9% experienced a reliable decline in Immediate Memory, 18% in Visual Memory, and 18% in Executive Function. Cognitive recovery (z score > -1, >16th percentile) was rare, even among patients who were cognitively impaired at the initial assessment and later showed improvement at week 78, as these improvements reflected a shift to milder impairment.

4.4.6 Relapse

Five patients experienced a clinical relapse, two of whom tested positive for NMDAR antibodies in serum, CSF, or both. Repeat neuropsychological and screening data was available for one patient. Serum and CSF showed presence of NMDAR autoantibody in CSF at 14 and 35 days after admission and in serum at 202 days after admission. The patient's cognitive trajectory revealed a marked decline over time. For example, the ACE-III score decreased from 88 at discharge to 78 at week

26, and further to 58 at week 78, indicating a substantial deterioration in global cognitive function. Working memory, processing speed, and executive function were classified as mild to moderate impairment at week 26, by week 78 three domains fell into the severely impaired range.

4.5 Discussion

This prospective, national, multicentre study demonstrates that patients with HSV encephalitis experienced significant long-term cognitive and psychiatric burden. Around 90% of patients experienced some degree of cognitive impairment, and around one-third of patients experienced moderate to severe symptoms of depression or anxiety. Perceived cognitive impairments were more closely related to affective symptoms than actual cognitive performance. This finding highlights the importance of prioritising mental health support in herpes encephalitis care, as treating depression and anxiety—potentially treatable contributors to subjective concerns—could reduce distress and help patients adapt more effectively to their cognitive difficulties, even if deficits remain. Additionally, whilst the impact of cognitive reserve was limited, increasing years of education was associated with better cognitive performance in some domains. By the 78-week follow-up, cognitive deficits persisted in all domains, contrasting with previous long-term studies that highlight the potential for recovery (Harris et al., 2020; Hokkanen & Launes, 1997a).

Verbal memory (Auditory Memory Index) was chosen as the primary endpoint because it is the domain most consistently impaired in herpes simplex encephalitis

and the difficulty most commonly reported by patients, not because of any presumed left-hemisphere predilection. I recognise that this choice could influence results: auditory tasks place higher demands on language, attention and arousal, and are typically administered earlier in the session, so more unwell participants may discontinue before visual subtests, concentrating poorer performance in the verbal domain. The WMS-IV visual indices are useful indicators of right medial temporal involvement but are not right-specific, as performance also depends on organisational strategy, visuoconstruction, attention and working memory, which can dilute lateralised effects. Future studies aiming for greater right-hemisphere sensitivity could include brief, right-leaning measures such as delayed recall of the Rey–Osterrieth Complex Figure, Warrington Recognition Memory Test (Faces), Doors (from Doors and People), the Four Mountains Test, or CANTAB Paired Associates Learning.

The pattern of impairment observed corresponds with the known neuropathology of HSV encephalitis, which predominantly affects structures in the temporal and frontal lobes (Kapur et al., 1994) - regions critical for memory and executive functioning (Alvarez & Emory, 2006; Duff et al., 2020). Yet, the exact mechanisms underlying cognitive impairment remain unclear. Early pathological processes involve not only direct cytolytic replication but also an immune-mediated inflammatory response (Rybak-Wolf et al., 2023). In particular, the breakdown of the blood-brain barrier and perivascular lymphocyte infiltration may play an important role (Michael et al., 2020).

The persistence, and in some cases worsening, of cognitive deficits over time highlights the chronic nature of cognitive impairment in HSV encephalitis. Between

5-27% of patients experience clinical relapse with immune-mediated encephalitis, often with the development of autoantibodies of the N-Methyl-D-Aspartate (NMDA) receptors (Cleaver et al., 2024). One study found an association between the development of NMDA receptor autoantibodies and impaired neurocognitive recovery (Westman et al., 2016), potentially through the prolongation of central nervous system inflammation (Westman et al., 2021). NMDA receptors regulate synaptic transmission and plasticity, which could impact the long-term recovery of cognitive functioning in HSV encephalitis. In this study, one patient who experienced worsening of cognitive performance and repeated NMDAR autoantibody positivity (2 weeks, 5 weeks, 30 weeks after admission) and clinically relapsed. While this cannot definitively attribute the cognitive decline to autoantibody production, the co-occurrence and along with previous research suggest a possible link and warrants further investigation.

The variability in cognitive profiles I observed among this cohort indicates a heterogeneous impact of HSV encephalitis on the brain. While I found strong correlations between certain cognitive outcomes, indicating a broad and interrelated effect of the disease, I unexpectedly observed a weaker correlation between auditory memory and executive functioning. The Individual analyses revealed significant variations in the domains impaired across patients, with no consistent pattern of deficits emerging. From a practice perspective, this highlights the importance of comprehensive neuropsychological assessments that cover multiple cognitive domains to identify and address the specific deficits in each individual. I considered a data-driven approach, using cluster or latent profile analyses, to explore potential cognitive phenotypes within this cohort; however, the limited patient data—

particularly the small number of patients who completed the full neuropsychological battery—made such analyses unfeasible.

Cognitive and psychiatric impairments were mostly unrelated to one another. Subjective cognitive complaints were associated with both objective functioning in verbal and visual memory but were more strongly associated with symptoms of depression and anxiety. This finding is consistent with the broader acquired brain injury literature showing patients are generally poor reporters of their cognitive abilities (Christodoulou et al., 2005; Coll-Martinez et al., 2023; Middleton et al., 2006; Nijsse et al., 2017). Clinicians should, therefore, interpret self-reported cognitive difficulties cautiously. Validation of a brief cognitive screening tool for HSV encephalitis could help clinicians decide which patients would benefit from a comprehensive neuropsychological evaluation.

These findings are clinically significant, highlighting the substantial long-term impact of HSV encephalitis on patients' cognitive and emotional sequelae. Persistent cognitive deficits can profoundly affect daily functioning, employment and quality of life (Karcz et al., 2022; Mitchell et al., 2010; Wilson, Horton, et al., 2021). The relationship between subjective deficits and affective symptoms highlights the need for integrated care approaches addressing the neurological and psychological aspects of recovery. Additionally, more accurate prognoses on the potential for prolonged cognitive and psychological difficulties could help manage expectations around recovery and improve engagement with rehabilitation.

Clinical profiles at 78 weeks ranged from normal to mild or moderate impairment, and standard performance tests may under-detect subtle disability. Health-related quality of life was captured with the SF-36 but scoring and verification were not completed before the thesis cut-off and will be reported separately. Future research in HSV encephalitis should incorporate brief patient- and carer-reported measures of fatigue (MFIS, Fisk et al., 1994; FSS, Krupp et al., 1989), sleep (PSQI, Buysse et al., 1989, or actigraphy, Ancoli-Israel et al., 2003), and carer burden (Zarit Burden Interview, Zarit et al., 1980), together with participation metrics such as return to work or education and WHODAS 2.0 (Üstün et al., 2010). This broader set of outcomes would provide a more sensitive index of residual disability. Future work could use exploratory factor analysis of the present dataset to identify the key latent domains and derive a minimal, clinic-ready battery. The resulting brief tool would then be validated in an independent sample using confirmatory factor analysis, with reliability, sensitivity to change, and predictive validity for participation outcomes, for example, return to work).

My study has several limitations. First, analyses were underpowered to tease apart the factors influencing differences in recovery patterns; larger samples of patients with clinical relapse and autoimmune positivity are crucial to understanding the impact on cognitive recovery. Second, I didn’t collect data from a control group, so I couldn’t adjust recovery trajectories based on practice effects. While some tests have normative test-retest data, this is limited to three-month intervals; considering the significant deficits observed at the first visit, I felt this would lead to a substantial overestimation of practice effects. Third, executive function was indexed mainly with Trail Making Test Part B because it is brief for multi-site assessment. However, TMT-

B conflates set-shifting with processing speed and visual search and is prone to ceiling and floor effects (Lezak et al., 2012; Sherman et al., 2023). For future studies, the Delis–Kaplan Executive Function System (D-KEFS) measure would be preferable (Delis et al., 2012). The D-KEFS Trail Making Test separates visual scanning, sequencing, and set-shifting and provides contrast scores that control for speed and motor components (Delis et al., 2012). If assessment burden permits, this could be expanded with other D-KEFS measures; the Color-Word Interference Test (inhibition and switching), Verbal and Design Fluency (generativity), and the Tower or Sorting tests (planning and concept formation), and summarised as a pre-specified executive composite (Delis et al., 2012; Sherman et al., 2023). Future research is needed to elucidate the mechanisms underlying poor cognitive recovery to inform targeted intervention trials.

4.6 Conclusions

In this chapter I demonstrate the substantial and enduring impact of HSV encephalitis on cognitive functioning and psychological health, highlighting the need for integrated care pathways that address the chronic neurological, and psychological aspects of recovery. Early recognition of cognitive impairment in herpes encephalitis patients enables timely personalised rehabilitation and supportive care to optimise quality of life and daily functioning; given this clinical priority, the next chapter evaluates the reliability of early and cross-sectional cognitive screening in identifying those at risk of cognitive impairment.

Table 4-1: Demographic and clinical characteristics

	Cohort week 26 (N=66)
Demographics	
Age, years	63 (14)
Education, years	12 (4)
Sex, Female	26 (43%)
Clinical data	
Discharged before 30 days	38 (39%)
Admitted to ICU	3 (5%)
Days from admission to aciclovir	1.59 (2.88)
Received dexamethasone	33 (50%)
Acute symptoms	
Fever (>37·5)	58 (89%)
Headache	40 (53%)
Seizures	28 (46%)
Olfactory hallucinations	4 (11%)
Photophobia	12 (33%)
Neck stiffness/signs of meningism	10 (27%)
Dysphasia	23 (53%)

Data are mean (SD) or N (%).

Table 4-2: Comparison of Cognitive Test Scores to Normative Data

	N	Mean (SD)	Test statistic	p value [a]
Verbal memory	66	-1.54 (1.53)	-8.15	<0.0001
Visual memory	49	-1.38 (1.42)	-6.76	<0.0001
Immediate memory	49	-1.47 (1.42)	-7.25	<0.0001
Delayed memory	49	-1.69 (1.47)	-8.06	<0.0001
Working memory	58	-0.39 (1.04)	-2.87	<0.0057
Processing speed	51	-0.74 (1.04	-5.08	<0.0001
Attention	49	-1.1 (1.31)	-5.87	<0.0001
Executive function	48	-1.01 (1.39)	-5.01	<0.0001

Test statistics are one-sample t-test compared to normative data with a mean of zero and standard deviation of one. [a] all p values remained significant with Benjamini-Hochberg correction.

Table 4-3: Difference in cognitive outcomes between week 26 and week 78.

		Week 26	Week 78	Test statistic	p value
	N	Mean (SD)	Mean (SD)		
Verbal memory	32	-1.51 (2.00)	-1.43 (1.57)	-0.56	0.577
Visual memory	22	-1.19 (1.49)	-1 (1.41)	-0.99	0.333
Immediate memory	22	-1.4 (1.52)	-1.19 (1.36)	-1.45	0.163
Delayed memory	22	-1.72 (1.65)	-1.53 (1.65)	-0.99	0.336
Working memory	30	-0.23 (0.94)	-0.23 (1.05)	-0.027	0.979
Processing speed	25	-0.43 (0.91)	-0.37 (1.10)	63.5†	0.349
Attention	22	-0.89 (1.42)	-0.73 (1.43)	44.5†	0.234
Executive function	22	-0.74 (1.52)	-0.70 (1.64)	-0.15	0.884

Data are mean (SD) of z-scores on cognitive tests. Statistical tests are paired t-tests unless otherwise stated. † Wilcoxon signed-rank test.

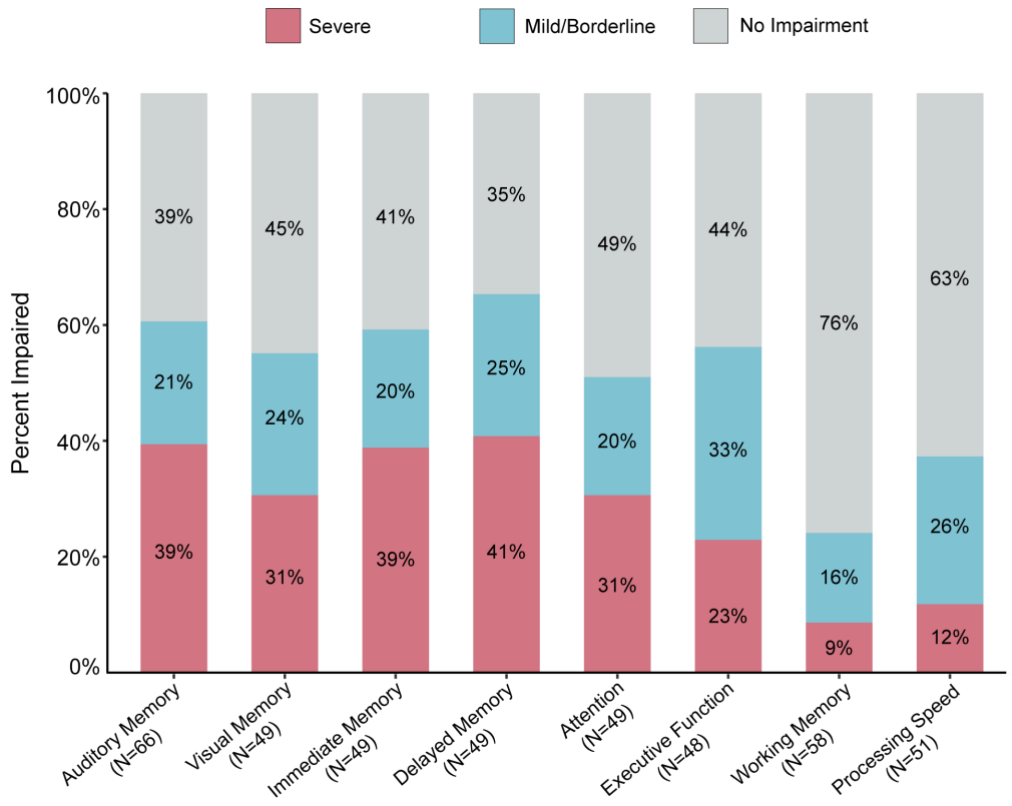

Figure 4-1: Stacked bar chart of impairment prevalence across cognitive domains

Severe impairment = score below 2nd percentile. Mild/borderline = scores below the 16th percentile and greater than the 2nd percentile. No impairment = scores greater than or equal to the 16th percentile compared to normative data. Percentages may not sum to 100% due to rounding.

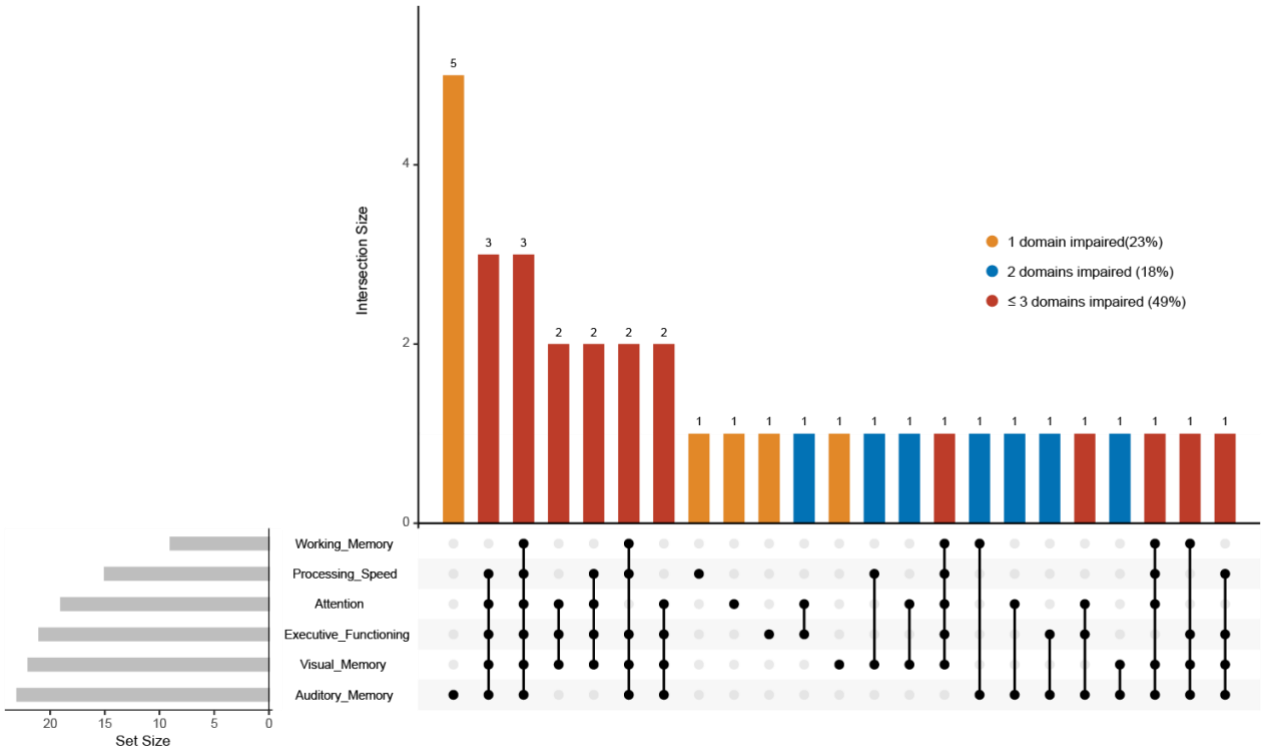

Figure 4-2: UpSet plot of the patterns of cognitive deficits at 26 week follow-up

Analysis was confined to 39 patients with complete neuropsychological data. Of these, four patients (10%) were not impaired in any cognitive domain. Set size (grey bars) is the number of patients with cognitive impairment in each specific domain ($z < -1$). For example, auditory memory impairment was the most frequently impaired domain and working memory was the least frequently impaired. Intersection size is the number of patients with intersecting impairments, highlighted by black dots below. For example, the first column shows there were 5 patients with a single domain impaired, and this was auditory memory; the second column shows three patients with five domains impaired (all domains except working memory); the third column shows three patients with all six domains impaired. The colour of the bars represents the number domains that were affected in each intersection orange bars indicate one domain affected, blue indicate two domains affected and red indicate three or more domains affected. For example, the cumulative number of patients with one domain affected (orange bars) was nine, which was 23% patients.

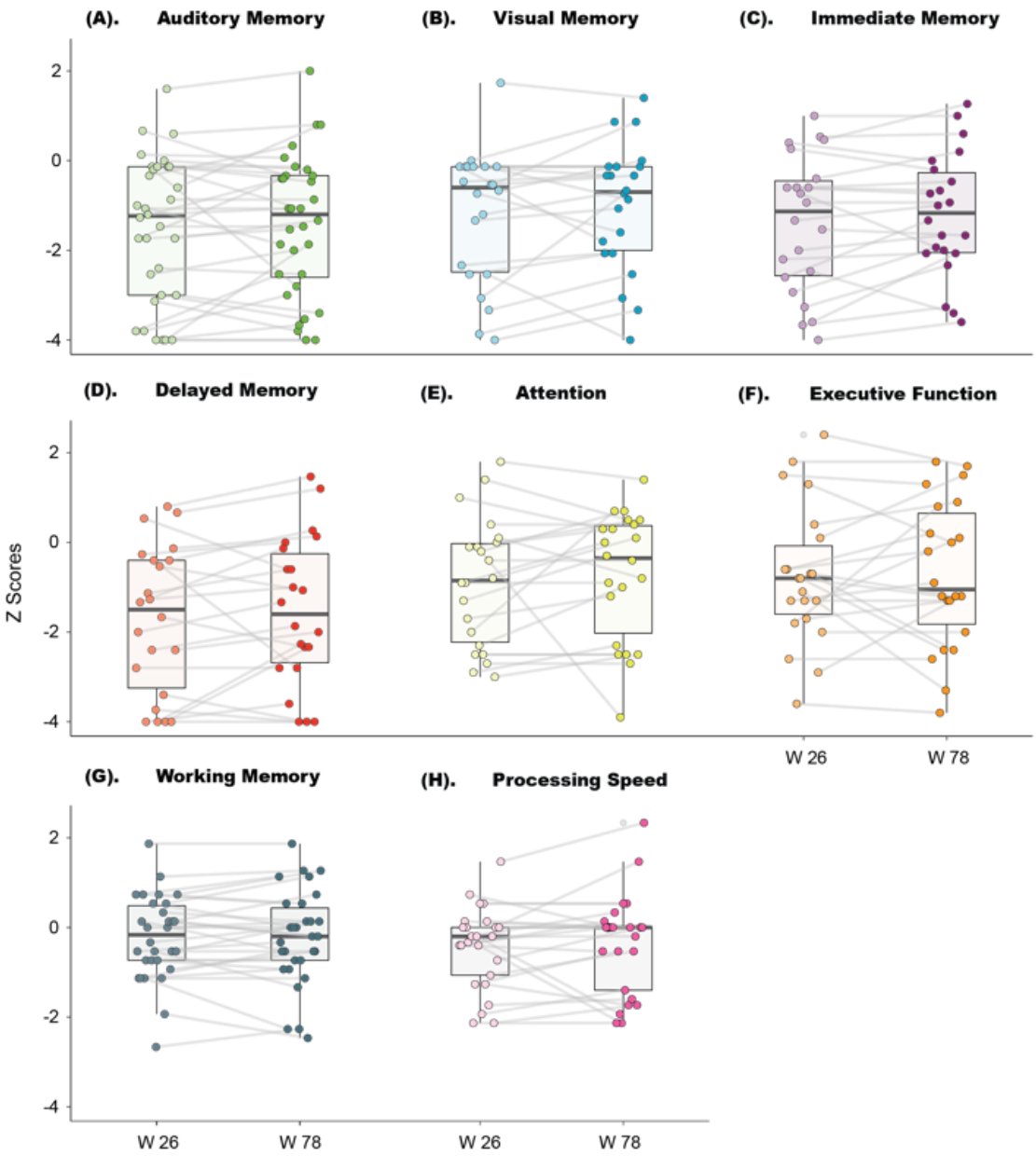

Figure 4-3: Recovery trajectories in HSV encephalitis patients between 26 week and 78 week follow-up

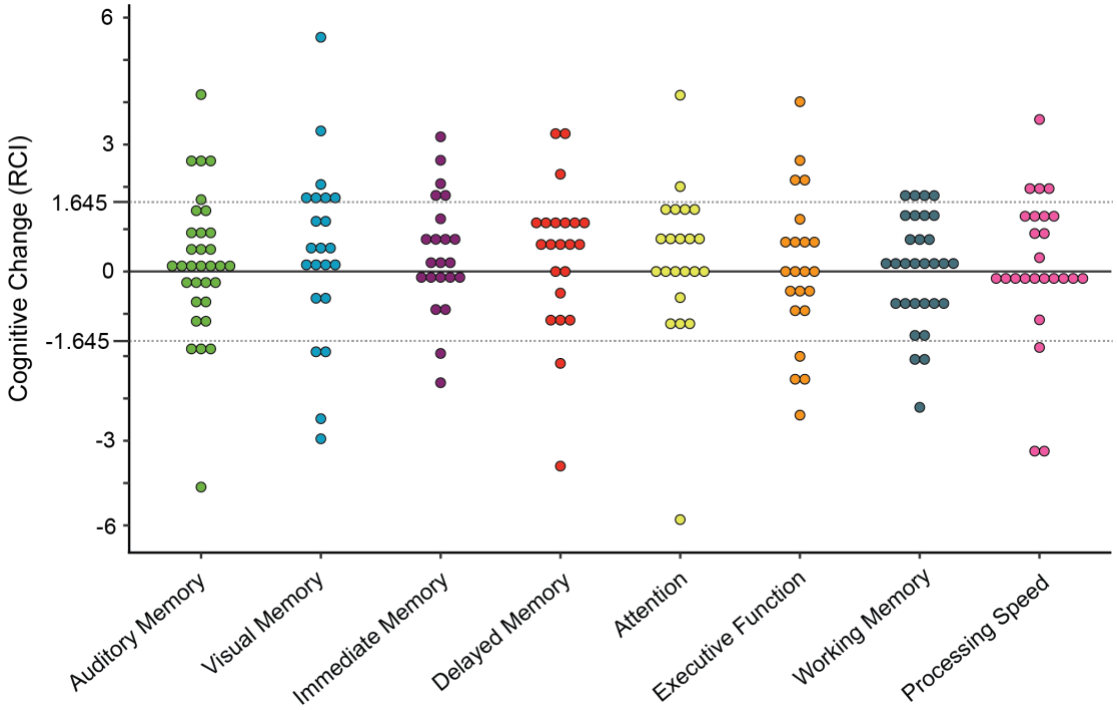

Figure 4-4: Reliable change index scores for individual patients between week 26 and week 78 across cognitive domains

RCI = reliable change index. Dotted lines are cut-offs for reliable improvement (>1.645) and reliable decline (<-1.645). i.e. values below the dotted bottom dotted line represent reliable decline in functioning between week 26 and week 78 and values above the top dotted line represent improvements in functioning between week 26 and week 78. Values falling between the two dotted lines show no reliable change in performance.

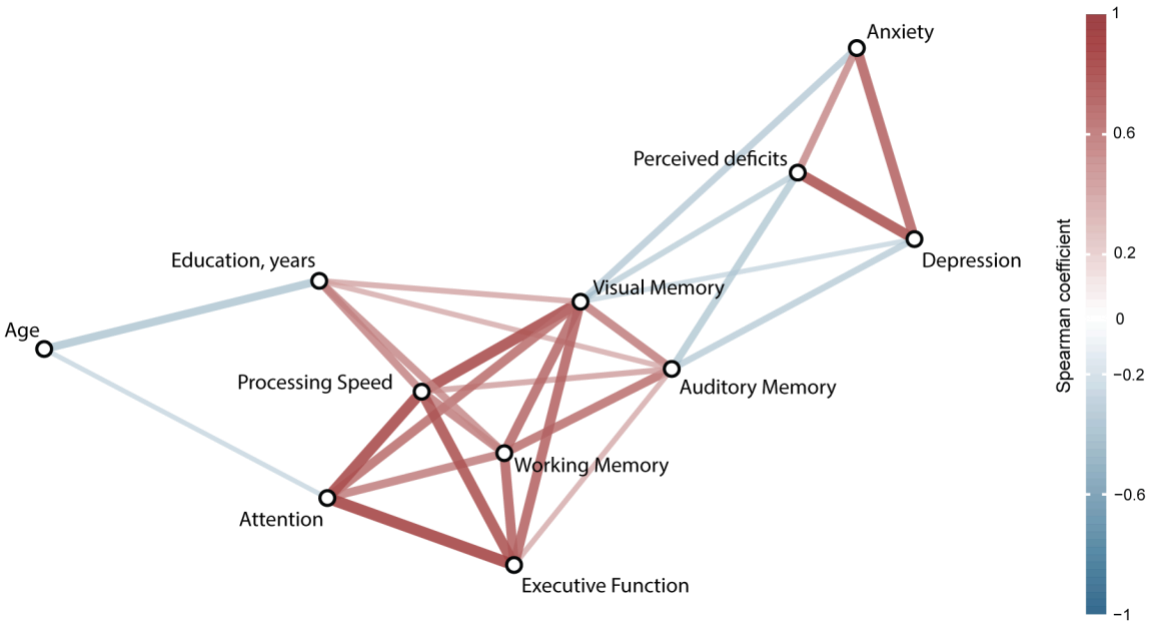

Figure 4-5: Network plot of the relationship between cognitive outcome, psychiatric functioning and cognitive reserve.

Force-directed network plot using the Fruchterman-Reingold algorithm. Circle nodes with black outlines are outcome variables. The strength of the Spearman correlation coefficient determines the thickness and opacity of the lines connecting nodes. Only significant correlations (p uncorrected) are shown. The figure shows, for example that performance in visual memory, processing speed, attention and executive function are all closely linked; and that perceived deficits are more closely associated with depression and anxiety than with objective performance on neuropsychological testing.

Chapter 5 Evaluating the Addenbrooke's Cognitive Examination-III for screening Memory and Executive Function impairment in HSV Encephalitis

5.1 Introduction

In the previous chapter, I demonstrated that cognitive recovery trajectories are variable. This non-linear recovery complicates post-acute care planning, as assessments at one time point may not reflect later cognitive functioning. Validation of a brief cognitive screening tool would enable rapid, repeated assessments, reducing the need for resource-intensive testing and support more flexible and responsive care planning. In this chapter, I analysed baseline cognitive screening data to assess its predictive value for later impairments in verbal memory and executive function and conducted cross-sectional analyses to evaluate its capacity to reliably identify concurrent deficits in these domains at 26 weeks.

Cognitive screening tests are widely employed in clinical practice, yet the principles of screening are often misunderstood. Many of these tools were originally developed to detect dementia in older adults and have not been validated in the populations they are subsequently used in (Arevalo-Rodriguez et al., 2021; Larner, 2017). This is important because misclassification can have serious consequences—labelling an individual as impaired when they are not may lead to unnecessary anxiety and a

self-perception of illness, while failing to identify a deficit may delay rehabilitation interventions.

In acute neurological conditions such as HSV encephalitis, the role of a screening tools could extend beyond detecting concurrent impairments; they also hold potential for prognostication (Bertolin et al., 2018). Accurate early cognitive assessments may help guide post-acute care and inform intervention strategies. However, the acute phase of CNS infections is characterised by transient factors—such as fatigue, fluctuating attention, and evolving clinical status—that can compromise test reliability. Moreover, recovery trajectories in these conditions are variable, as shown in chapter 4, with some patients improving and others declining. These observations emphasise why repeated, accurate screening is needed; to track ongoing recovery and to identify individuals at risk of long term cognitive impairment.

In this chapter, I evaluate the efficacy of the Addenbrooke's Cognitive Examination-III (ACE-III) for screening memory and executive function impairments in patients with HSV encephalitis. By examining the performance of the ACE-III both during the acute phase and later in recovery, I aim to determine the ACE scores validity in identifying present cognitive deficits also in identifying future impairment.

5.2 Methods

5.2.1 Patients and study design

This study is a secondary analysis of the 'DexEnceph' study cohort, a multicentre, randomised, controlled, open-label, observer-blind trial investigating the efficacy and safety of dexamethasone administration in adults with HSV encephalitis. The present study included adults aged greater than 16 years with Polymerase Chain Reaction (PCR) confirmed HSV encephalitis. I included patients between September 2016 and February 2022. Exclusion criteria were based on contraindication to dexamethasone treatment. Detailed description of data collection procedures is available in the published protocol online.

5.2.2 Cognitive outcome measures

I administered a cognitive screening assessment (Addenbrookes Cognitive Examination-III; ACE-III) at 30 days after encephalitis or discharge from hospital (whichever was sooner) and at 26 weeks after HSV encephalitis. The total score was calculated for the ACE-III total score, memory score (as an indicator of verbal memory impairment) and verbal fluency score (as an indicator of executive function impairment). Whilst other brief measures are available such as the MoCA and RBANS, we did not use them for this study. The MoCA is shorter but yields a largely global score without domain-specific indices aligned to our reference outcomes, limiting targeted interpretation. RBANS provides richer profiling but is a longer battery with training and logistical demands that are hard to standardise across multiple sites. The ACE-III therefore offered the best balance of administration time, sensitivity, and informative domain sub scores for discharge and follow-up use.

I also administered a comprehensive neuropsychological battery at 26 week follow up, with this study utilising tests in Verbal Memory and Executive Functioning. The reference standard used to determine patients with verbal impairment was the Auditory Memory Index of the Weschler Memory Scale-IV (WMS-IV) and Executive Function impairment with Part B of the Trail Making Test.

Normative data from test manuals were used to adjust the raw scores on the WMS-IV, producing age-adjusted standard scores for each patient. The Halstead-Reitan scoring manual for TMT was employed to produce age, sex, and education adjusted T scores. Adjusted scores based on normative data were converted to Z scores for each patient for ease of comparisons across domains. As described in chapter 4, I defined cognitive impairment separately for verbal memory and executive function as impaired (z score greater than - 1), mild/borderline (z score less than or equal to minus 1 and greater than or equal to minus 2), severe (z score less than minus 2).

5.2.3 Statistical Analysis

Analyses were conducted in R version 3.6.0 (package ‘pROC’). Continuous variables are presented as median (IQR range). Spearman’s correlation coefficients assessed associations between continuous variables. ROC curves were generated. Optimal cutoff was determined by maximizing Youden’s index. At the optimal threshold, sensitivity, specificity, PPV (Positive Predictive Value), and NPV (Negative Predictive Value) and the area under the curve (AUC) with bootstrapped 95% confidence intervals (200 replications) were calculated; all numeric values were rounded to two

decimal places. All tests were two-sided with significance set at 0.05. Due to pre-specified hypotheses, exploratory tests were minimal; thus, multiple comparisons corrections were deemed unnecessary.

5.3 Results

Of 94 patients recruited, 57 patients had a valid ACE total score (and at least one valid cognitive outcome (either verbal memory or executive functioning) and were therefore included in the 26-week (cross-sectional) analysis. In this subset, the mean ACE total score was 70.4 (SD = 29.1). All 57 patients had valid verbal memory scores, with a mean score of –1.61 (SD = 1.59), while 47 patients had valid executive functioning scores (mean = –1.01, SD = 1.41).

For the discharge analysis, 48 patients had a valid discharge ACE score and at least one valid verbal memory or executive function score. In this cohort, the mean discharge ACE total score was 65.7 (SD = 27.7). Cognitive outcomes in this group revealed a mean verbal memory of –1.44 (SD = 1.40) and a mean executive function score of –0.73 (SD = 1.36) (Table 5-1).

5.3.1 Longitudinal and Cross-Sectional Correlations

ACE-III scores correlated significantly with domain-specific measures of cognitive function at all timepoints. At discharge, the ACE-III total score showed moderate

correlations with auditory memory ($r = 0.41$, $p = 0.004$) and executive function ($r = 0.50$, $p = 0.002$) (Likewise, the memory and fluency subtests correlated with auditory memory ($r = 0.44$, $p = 0.003$) and executive function ($r = 0.46$, $p = 0.005$), respectively (Figure 5-1; Figure 5-2).

	N	Median (IQR)	Range
ACE Total score (baseline)	57	82 (46)	0 - 100
ACE Memory score (baseline)	57	18 (13)	0 - 26
ACE Fluency score (baseline)	58	9.5 (8.75)	0 - 14
ACE Total score (week 26)	50	75 (34)	0 - 100
ACE Memory score (week 26)	50	16 (14)	0 - 26
ACE Fluency score (week 26)	50	7 (7.75)	0 - 14
Verbal Memory (26 weeks)	66	-1.5 (2.6)	-4 - 1.6
Executive Function (26 weeks)	48	-1.2 (1.6)	-4.2 - 2.4

Table 5-1: Descriptive statistics for cognitive variables

By 26 weeks, associations for auditory memory increased (ACE total 26 weeks: $r = 0.75$, $p < 0.001$; ACE memory 26 weeks: $r = 0.78$, $p < 0.001$), whereas correlations for executive function remained moderate ($r=0.52$ and 0.48 for the total and fluency scores, respectively; Figure 5-1, Figure 5-2)

5.4 Predictive Performance at Discharge

Analyses at discharge demonstrated modest discriminative performance of the Addenbrooke's Cognitive Examination-III (ACE-III) in predicting 26-week cognitive impairment, with stronger accuracy for severe impairment compared to mild-to-moderate cases (Table 5-2).

Verbal Memory

The ACE-III total score at a threshold of 75.5 showed 70% sensitivity and 78% specificity (PPV 84%, NPV 61%; AUC 0.78, 95% CI 0.64–0.91) for identifying any cognitive impairment. Stratified analyses revealed divergent thresholds: a lower cutoff (72.5) optimized for severe impairment achieved 72% sensitivity and 82% specificity (PPV 81%, NPV 74%; AUC 0.83, 0.64–0.94), whereas the same threshold (75.5) for mild-to-moderate impairment yielded reduced sensitivity (54%) and specificity (76%; PPV 64%, NPV 68%; AUC 0.66, 0.47–0.83). The ACE-III memory subtest at 19.5 demonstrated 80% sensitivity and 61% specificity for total impairment (PPV 77%, NPV 65%; AUC 0.76, 0.62–0.89). Subgroup analyses showed improved sensitivity (92%) for mild-to-moderate impairment at a threshold of 20.5 (specificity

53%; PPV 60%, NPV 90%) but higher specificity (82%) for severe impairment at 12.5 (sensitivity 72%; PPV 81%, NPV 74%; AUC 0.80, 0.66–0.92).

Executive Function

For executive dysfunction, the ACE-III total score at 57.5 demonstrated 53% sensitivity and 95% specificity (PPV 90%, NPV 69%; AUC 0.73, 0.52–0.90). Stratified thresholds revealed 57% sensitivity and 100% specificity for severe impairment at 51 (PPV 100%, NPV 86%; AUC 0.80, 0.52–0.99), while mild-to-moderate impairment retained high specificity (95%) but low sensitivity (50%) at 57.5 (PPV 83%, NPV 78%; AUC 0.68, 0.44–0.87). The fluency subtest at 6.5 showed 59% sensitivity and 89% specificity for total impairment (PPV 83%, NPV 71%; AUC 0.76, 0.61–0.91), with severe impairment thresholds (3.5) achieving 57% sensitivity and 95% specificity (PPV 80%, NPV 86%; AUC 0.71, 0.44–0.90).

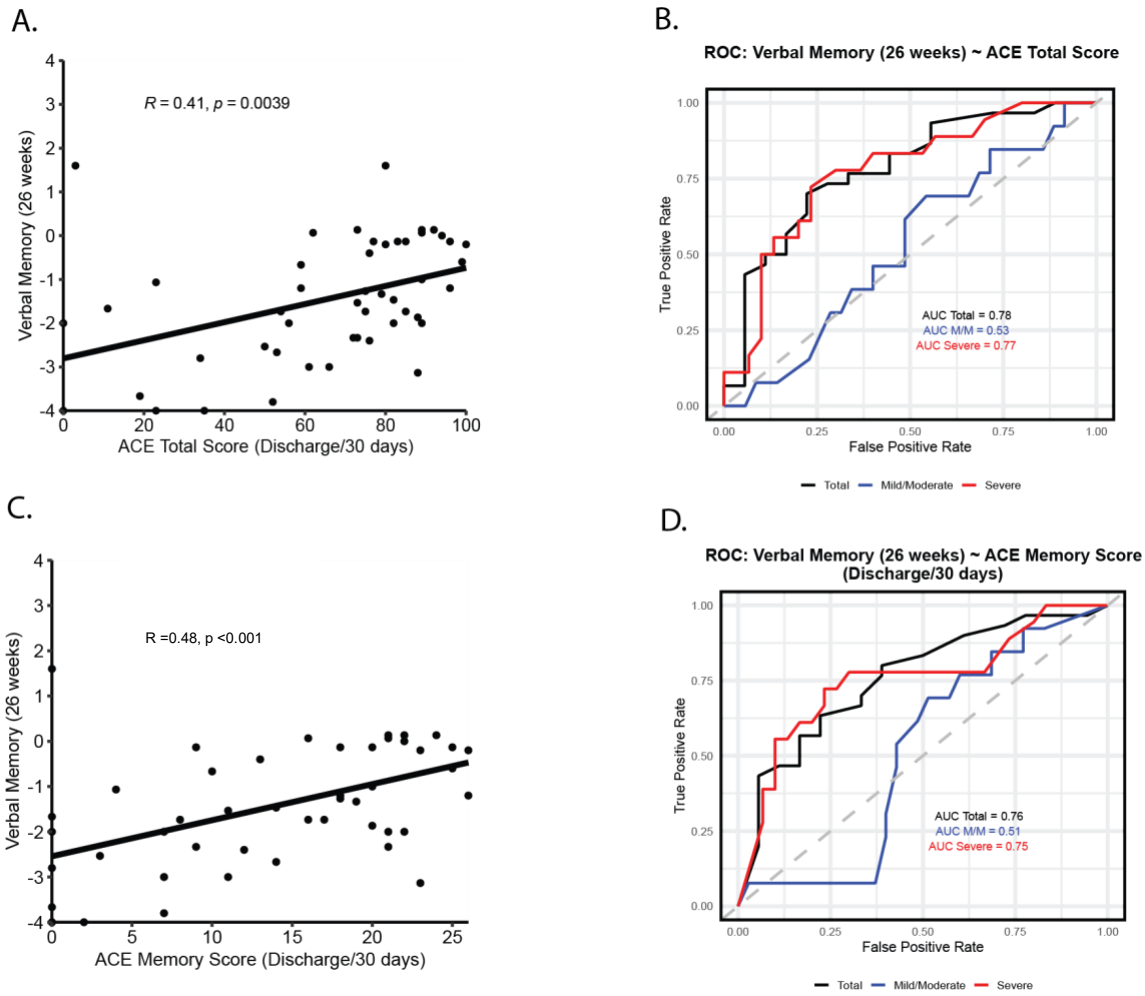

Figure 5-1: correlational and Receiver Operator Characteristic (ROC) analyses of ACE total and memory scores at discharge and verbal memory at 26 weeks

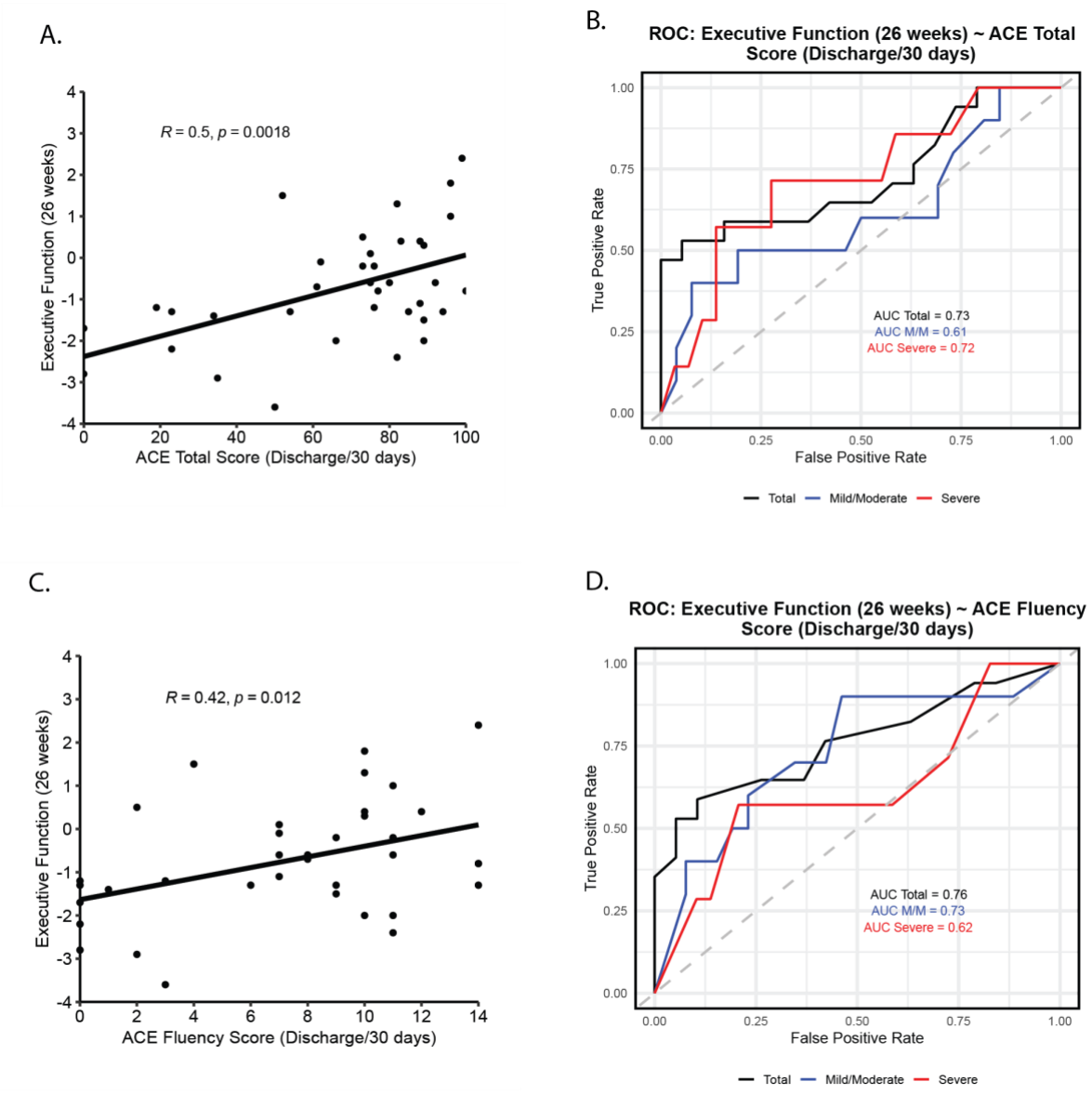

Figure 5-2: Correlational and Receiver Operator Characteristic (ROC) analyses for total ACE score at baseline and executive function at 26 weeks.

5.4.2 Enhanced Discrimination at 26 Weeks

Analyses at discharge demonstrated variable discriminative performance of the Addenbrooke's Cognitive Examination-III (ACE-III) in predicting 26-week cognitive impairment, with stronger accuracy for severe impairment compared to mild-to-moderate cases (Table 5-3).

Verbal Memory

The ACE-III total score at a threshold of 83.5 showed 81% sensitivity and 86% specificity (PPV 90%, NPV 76%; AUC 0.87, 95% CI 0.78–0.94) for identifying any cognitive impairment. When stratified, the same threshold (83.5) optimized for severe impairment achieved 95% sensitivity and 86% specificity (PPV 88%, NPV 95%; AUC 0.96, 0.87–0.99), while a marginally lower threshold (83) for mild-to-moderate impairment yielded reduced sensitivity (55%) despite retaining specificity (86%; PPV 67%, NPV 79%). The ACE-III memory sub score at a threshold of 16.5 demonstrated perfect specificity (100%) for total impairment (PPV 100%, NPV 65%) but poor sensitivity (36%) for mild-to-moderate impairment (AUC 0.69, 0.50–0.88). For severe impairment, the memory sub score at 19.5 achieved 95% sensitivity and 82% specificity (PPV 84%, NPV 95%; AUC 0.96, 0.91–1.00).

Executive Function

For total impairment, the ACE-III total score at a threshold of 88.5 showed 72% sensitivity and 75% specificity (PPV 78%, NPV 68%; AUC 0.79, 0.65–0.88). Stratified analyses revealed divergent thresholds: a lower total score cutoff (86) for severe impairment achieved 90% sensitivity and 75% specificity (PPV 64%, NPV 94%; AUC 0.85, 0.69–0.98), whereas the threshold for mild-to-moderate impairment (81.5) demonstrated 53% sensitivity and 85% specificity (PPV 73%, NPV 71%; AUC 0.74, 0.59–0.89). The fluency sub score at 10.5 showed balanced performance for total impairment (65% sensitivity, 80% specificity; PPV 81%, NPV 64%; AUC 0.73, 0.56–0.85). For severe impairment, the fluency sub score at 8.5 achieved 70% sensitivity and 85% specificity (PPV 70%, NPV 85%; AUC 0.80, 0.57–0.95).

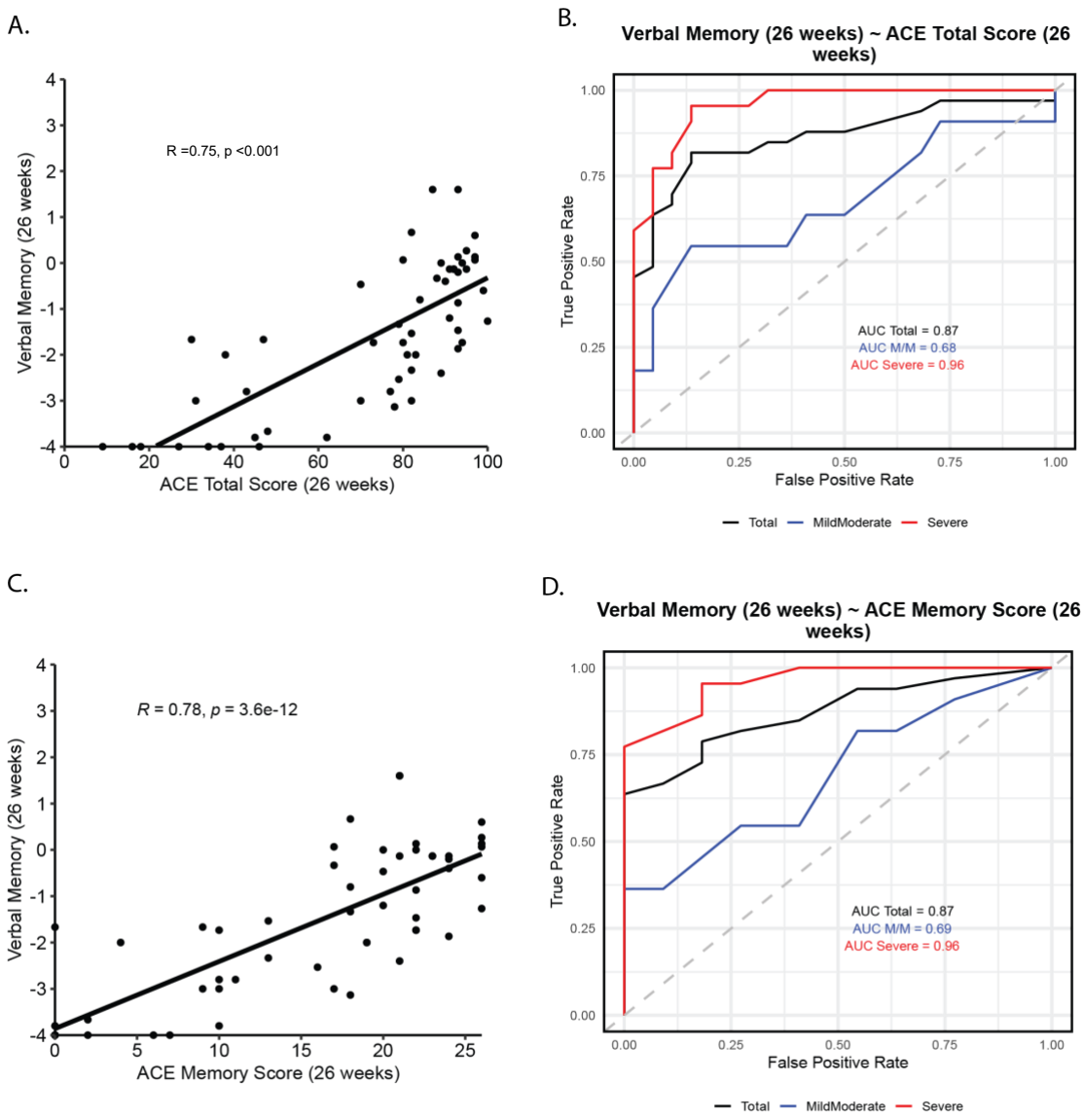

Figure 5-3: Correlational and Receiver Operator Characteristic (ROC) analyses for ACE-III scores and verbal memory scores at 26 weeks

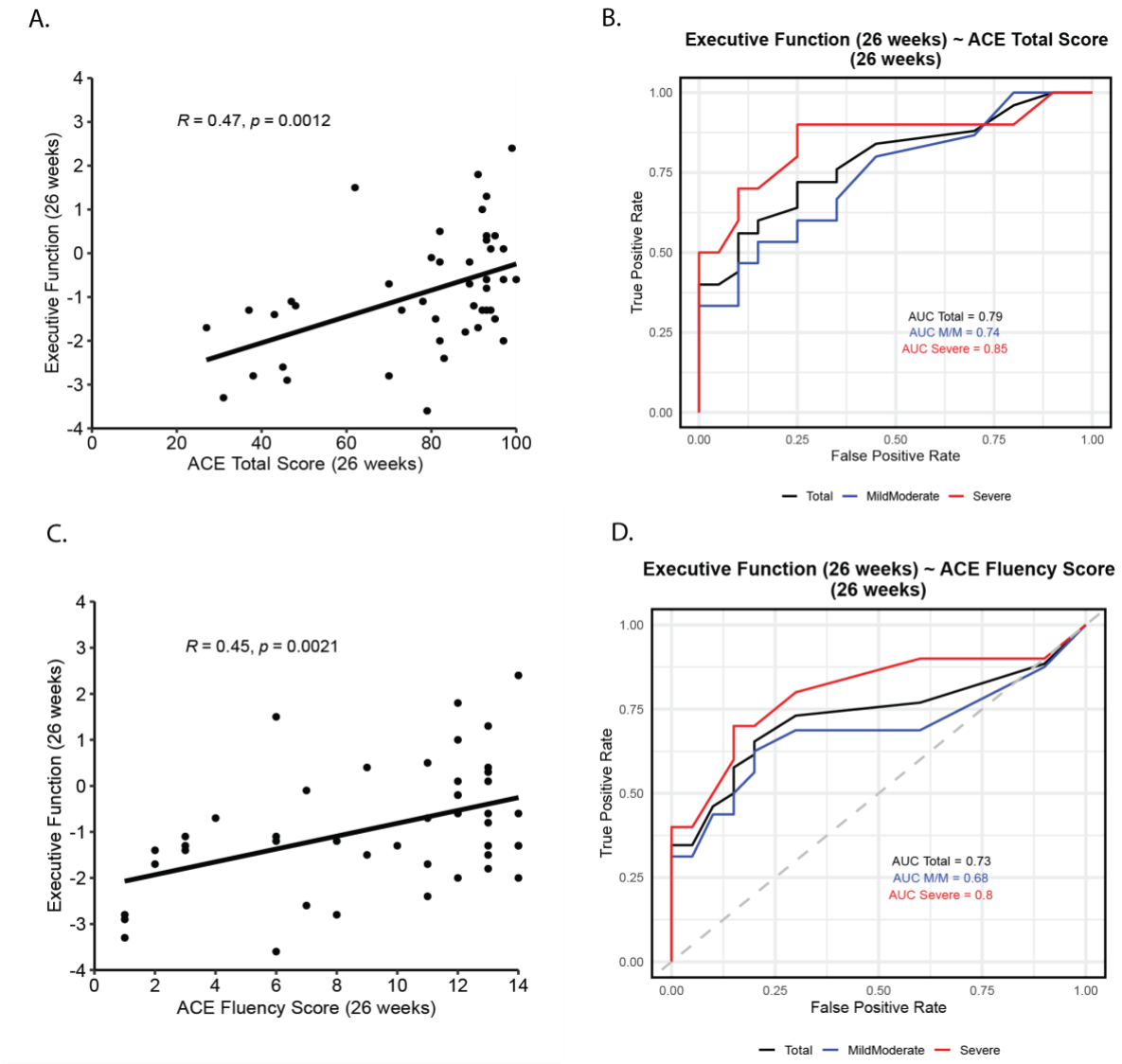

Figure 5-4: Correlational and Receiver Operator Characteristic (ROC) analyses for ACE scores and Executive Function at 26 weeks

Table 5-2: ACE-III scores at discharge for predicting verbal memory and executive functioning impairment at 26 weeks.

Condition	Predictor at discharge	Impairment Level	Impaired	Optimal Threshold	Sensitivity	Specificity	PPV	NPV	Youden Index	AUC (95% CI)
verbal memory	ACE Total score	Total impairment	30	75.5	70%	78%	84%	61%	1.48	0.78 (0.64-0.91)
verbal memory	ACE Total score	Mild/moderate impairment	13	75.5	54%	76%	64%	68%	1.3	0.66 (0.47-.83)
verbal memory	ACE Total score	Severe impairment	18	72.5	72%	82%	81%	74%	1.55	0.83 (0.64-0.94)
verbal memory	ACE memory score	Total impairment	30	19.5	80%	61%	77%	65%	1.41	0.76 (0.62-0.89)
verbal memory	ACE memory score	Mild/moderate impairment	13	20.5	92%	53%	60%	90%	1.45	0.67 (0.47-0.87)
verbal memory	ACE memory score	Severe impairment	18	12.5	72%	82%	81%	74%	1.55	0.8 (0.66-0.92)
executive functioning	ACE Total score	Total impairment	17	57.5	53%	95%	90%	69%	1.48	0.73 (0.52-0.90)
executive functioning	ACE Total score	Mild/moderate impairment	10	57.5	50%	95%	83%	78%	1.45	0.68 (0.44-0.87)
executive functioning	ACE Total score	Severe impairment	7	51	57%	100%	100%	86%	1.57	0.8 (0.52-0.99)
executive functioning	ACE fluency score	Total impairment	17	6.5	59%	89%	83%	71%	1.48	0.76 (0.61-0.91)
executive functioning	ACE fluency score	Mild/moderate impairment	10	6.5	60%	89%	75%	81%	1.49	0.79 (0.59-0.96)
executive functioning	ACE fluency score	Severe impairment	7	3.5	57%	95%	80%	86%	1.52	0.71 (0.44-0.9)

Table 5-3: ACE-III scores at 26 weeks for predicting verbal memory and executive functioning impairment at 26 weeks.

	Predictor at week 26	Impairment Level	Impaired	Optimal threshold	Sensitivity	Specificity	PPV	NPV	Youden Index	AUC (95% CI)
verbal memory	ACE Total score	Total impairment	33	83.5	81%	86%	90%	76%	1.68	0.87 (0.78-0.94)
verbal memory	ACE Total score	Mild/moderate impairment	11	83	55%	86%	67%	79%	1.41	0.68 (0.42-0.88)
verbal memory	ACE Total score	Severe impairment	22	83.5	95%	86%	88%	95%	1.82	0.96 (0.87-0.99)
verbal memory	ACE memory score	Total impairment	33	16.5	64%	100%	100%	65%	1.64	0.87 (0.79-0.95)
verbal memory	ACE memory score	Mild/moderate impairment	11	15	36%	100%	100%	76%	1.36	0.69 (0.50-0.88)
verbal memory	ACE memory score	Severe impairment	22	19.5	95%	82%	84%	95%	1.77	0.96 (0.91-1.00)
executive functioning	ACE Total score	Total impairment	25	88.5	72%	75%	78%	68%	1.47	0.79 (0.65-0.88)
executive functioning	ACE Total score	Mild/moderate impairment	15	81.5	53%	85%	73%	71%	1.38	0.74 (0.59-0.89)
executive functioning	ACE Total score	Severe impairment	10	86	90%	75%	64%	94%	1.65	0.85 (0.69-0.98)
executive functioning	ACE fluency score	Total impairment	26	10.5	65%	80%	81%	64%	1.45	0.73 (0.56-0.85)
executive functioning	ACE fluency score	Mild/moderate impairment	16	10.5	63%	80%	71%	73%	1.43	0.68 (0.48-0.88)
executive functioning	ACE fluency score	Severe impairment	10	8.5	70%	85%	70%	85%	1.55	0.8 (0.57-0.95)

5.5 Discussion

This study evaluated the utility of the Addenbrooke's Cognitive Examination-III (ACE-III) at hospital discharge for detecting cognitive impairment in patients recovering from HSV encephalitis, using 26-week neuropsychological assessments as the reference standard. While the ACE-III demonstrated moderate discriminative accuracy for severe cognitive impairment, its sensitivity for mild-to-moderate deficits in verbal memory and executive function was suboptimal. These findings align with prior studies in other neurological disease populations, where the cognitive screening missed milder deficits (Chan et al., 2014; Komadina et al., 2011). The instrument's limited utility in acute-phase assessments may reflect transient confounders (e.g., fatigue, attentional fluctuations) and variable recovery trajectories, which limit its prognostic value during early recovery. Weaker correlations could reflect that TMT-B and ACE-III fluency measure different aspects of executive control (speeded set-shifting versus verbal generation). Although these domains overlap and show moderate associations in prior work (Delis et al., 2012), lower agreement between specific executive tests is common (Lezak et al., 2012)

In our cohort, the optimal ACE-III total cut-off for detecting concurrent verbal-memory impairment at 26 weeks was 83.5, yielding 81% sensitivity and 86% specificity. In the original dementia validation, thresholds of 88 (sensitivity 0.94, specificity 0.89) and 82 (0.84, 1.00) were reported (Mioshi et al., 2006). Differences are expected because instrument version, target outcome (domain-specific impairment after HSV encephalitis vs dementia), and patient population shift optimal thresholds.

The ACE-III's reduced sensitivity for mild deficits likely stems from its limitations in higher-functioning cohorts. Originally calibrated for dementia detection in older adults, the tool exhibits a pronounced ceiling effect in working-age populations (Roebuck-Spencer et al., 2017). In this study, scores tended to cluster at the upper end of the scale, visible on scatter plots. This design bias diminishes its ability to discriminate between normal performance and clinically meaningful, but mild, impairment. Consequently, reliance on the ACE-III risks overlooking patients who retain functional independence yet experience deficits which are critical for occupational and social functioning.

Patients were classified as severely impaired if they fell below 2 standard deviations below the norm, equating to <2nd percentile. The ACE-III's ability to detect only severe impairment reliably, which may often already be apparent through clinical observation, limits its value as a standalone screening tool in HSV encephalitis. Patients with mild deficits, who may still benefit from early rehabilitative interventions, could remain undetected, risking delayed care. Thus, screening tools should be used cautiously.

Given the limitations associated with acute-phase cognitive testing—where factors such as fatigue may affect performance—it would be valuable to explore more objective biomarkers or tools that are less affected by these factors. For instance, almost all patients with encephalitis undergo an MRI as part of routine care, and MRI-based measures, which assess structural or functional brain integrity, may serve as more objective predictors of cognitive outcome. These biomarkers could

complement cognitive screening tools by providing an alternative method of early prognostication that is not confounded by the clinical state at the time of testing.

This study has several limitations, including a modest sample size. The ACE-III although overcomes some of the limitations of other cognitive screening tools, including multi-domain assessment, it shares the drawback that it is limited in its assessment of executive function. Future research should focus on refining existing screening instruments or developing novel tools that more effectively capture the full spectrum of cognitive impairment post-HSV encephalitis, especially during the early stages when comprehensive testing may be less feasible.

5.6 Conclusions

While the ACE-III showed reasonable ability at distinguishing severe verbal memory at 26 weeks, its poor predictive performance in the acute phase and limited sensitivity for mild-to-moderate deficits restricts its clinical utility as a standalone screening tool. These limitations highlight the need for objective biomarkers capable of identifying at-risk patients during the acute stages which could also help elucidate the neuroanatomical underpinnings of cognitive sequelae in HSV encephalitis. To address this gap, the next chapter investigates the prognostic potential of acute-phase MRI, focusing on neuroimaging correlates of cognitive outcomes and their implications for understanding disease progression in HSV encephalitis.

Chapter 6 MRI Biomarkers Are Associated with Domain-Specific Cognitive Outcomes in Herpes Simplex Encephalitis

6.1 Introduction

Previous studies and analysis of this cohort (chapter 4) show that HSV encephalitis is associated with severe neurocognitive impairment, with verbal memory particularly affected. Current cognitive screening tools did not reliably identify which patients will develop significant long-term deficits (chapter 5). Moreover, while early dexamethasone may improve verbal memory, as shown in chapter 3, the mechanisms underlying this benefit remain unclear. In a similar design to the previous chapter, I first quantified hippocampal and temporal lobe integrity and lesion volumes on acute-phase MRI scans and examined their association with later cognitive outcomes at 26 weeks. Second, I examined whether MRI changes at 26 weeks were associated with cognitive impairments at the same timepoint. I also explored whether treatment group affected these relationships.

Magnetic resonance imaging (MRI) is integral to the clinical management of HSV encephalitis. Current clinical guidelines recommend MRI for all suspected HSV encephalitis cases (Demaerel et al., 1992; Solomon et al., 2012). In the acute phase, MRI typically reveals hyperintense lesions on T2-weighted and FLAIR sequences, often associated with swelling and mass effect (Demaerel et al., 1992). DWI further

distinguishes cytotoxic from vasogenic oedema, offering insight into the underlying pathophysiological mechanisms (Küker et al., 2004; Renard et al., 2015). Yet, despite its widespread use, the prognostic utility of early MRI in HSV encephalitis remains unclear. While some studies suggest that a higher lesion burden or bilateral involvement may correlate with poorer outcomes, the evidence is inconsistent (Kapur et al., 1994; Sarton et al., 2021).

The hippocampus, a key structure for memory function, is particularly vulnerable to HSV-1 infection (Yong et al., 2021). Experimental models indicate that HSV-1 exhibits a strong predilection for hippocampal neurons, with viral fluorescence marking this region as a principal site of infection (Michael et al., 2020). Post-acute immune mechanisms may further exacerbate hippocampal injury, as seen in other encephalitic conditions such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, where hippocampal atrophy is correlated with cognitive impairment (Finke et al., 2016; Heine et al., 2015). Given the established role of the hippocampus in verbal memory and learning, it is plausible that early hippocampal damage in HSV encephalitis contributes directly to the verbal memory deficits observed in people post HSV encephalitis. Yet, the relationship between hippocampal pathology and long-term cognitive outcomes has not been systematically studied in HSV encephalitis.

The role of immunotherapy in mitigating hippocampal and medial temporal lobe damage in HSV encephalitis remains uncertain. Reduced hippocampal injury in response to picornavirus infection has been reported following inhibition of monocyte and neutrophil recruitment (Howe et al., 2012). In chapter 3, early adjunctive

corticosteroid use was associated with improved verbal memory. However, the relationship between corticosteroids administration, MRI findings, and long-term cognitive recovery remains unclear. Understanding whether advanced MRI analyses could detect hippocampal changes could provide a novel acute imaging marker to characterise disease progression and response to treatment.

Utilising a multi-modal imaging approach, I aimed to determine whether early MRI measures of hippocampal and temporal lobe integrity and vasogenic oedema predict long-term cognitive outcomes in HSV encephalitis. Specifically, I investigated (i) the relationship between early hippocampal and temporal lobe volumes and domain-specific cognitive performance at 26 weeks; (ii) the relationship between structural volumes at 26 weeks and cognitive outcomes; (iii) whether dexamethasone administration modifies these associations; and (iv) the impact of early cytotoxic and vasogenic oedema on long-term cognitive impairment.

6.2 Methods

Study design and participants

Neuroimaging and Cognitive data in this study were obtained from a prospective, multicentre, randomised trial at 53 National Health Service hospitals in the United Kingdom. Ninety-four adult patients with confirmed HSV encephalitis were enrolled and randomly assigned to receive either standard care (intravenous aciclovir) plus dexamethasone or standard care alone in a 1:1 ratio, as described in detail

previously (chapter 2 and 3). For the present secondary analysis, I included only those patients who had at least one MRI metric of interest (hippocampal volume, temporal lobe volume, total oedema, vasogenic oedema, or cytotoxic oedema) and who completed the Auditory Memory Index (Wechsler Memory Scale – Fourth Edition) at 26 weeks. Patients provided written informed consent in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was obtained from the University of Liverpool.

Procedures

MRI scans were obtained at Baseline, Week 2 (+/- 7 days), and Week 26 (+/- 4 weeks). Owing to the multicentre design, scanner models and acquisition protocols (including field strength) varied between sites. All centres acquired T1-weighted, T2 FLAIR, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) sequences. Two independent reviewers assessed scan quality; disagreements were resolved by consensus with a third reviewer. Scans with severe artefacts or insufficient slices to view temporal lobe boundaries, hippocampi or oedema were excluded. Neuropsychological assessments at 26 weeks included the Wechsler Memory Scale – Fourth Edition (WMS-IV; Auditory Memory Index (referred to as Verbal Memory) and the Visual Memory Index), the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV; Working Memory Index and Processing Speed Index), and Trail Making Tests Parts A and B (Attention and Executive Function). I converted all cognitive scores to Z scores for ease of comparison across domains and analysed these continuously except for oedema analyses, where cognitive outcomes were dichotomised as favourable or unfavourable, with unfavourable

defined as a z score below –2 in any single domain or below –1 in two or more domains, similar to an approach used previously (Heine et al., 2021).

Neuroimaging measures

Temporal lobe volumetry was done using the Cavalieri principle, a design-based stereological method that systematically overlays point-count grids onto coronal MRI slices (Dohertya et al., 2000; García-Fiñana et al., 2009), described in more detail in chapter 3. Briefly, the anterior and posterior boundaries of the temporal lobes were defined according to established anatomical landmarks (Defres et al., 2017; Mackay et al., 1998, 2000). Each temporal lobe was quantified by summing transect areas across approximately 24 systematically sampled slices, aiming for at least 300 point intersections per structure. Total oedema volume was measured on T2 FLAIR images, where hyperintense regions were considered oedematous. Cytotoxic oedema was identified by DWI hyperintensity with corresponding ADC hypointensity to exclude T2 shine-through effects, and vasogenic oedema was calculated by subtracting cytotoxic from total oedema volume. Whole-brain volume was also estimated from T2 FLAIR images, allowing all oedema measures to be expressed as a percentage of whole-brain volume.

Hippocampal volumes were quantified using SynthSeg (version 2.0), a convolutional neural network trained on synthetic MRI data and designed to segment heterogeneous clinical scans. Each patient's best available MRI scan, preferably three dimensional T1-weighted if available, was processed directly through SynthSeg without additional pre-processing. This approach provided volumetric

labels for the bilateral hippocampi and intracranial volume (ICV). Hippocampal volumes were then expressed as a percentage of ICV. An automated quality-control module in SynthSeg flagged potential segmentation failures, which were also checked through visual inspection and excluded if segmentation was deemed inadequate.

Lesion lateralisation and asymmetry

Lesion lateralisation was assessed using two complementary approaches. First, T2 FLAIR and DWI scans at baseline and Week 2 were visually inspected and categorised as predominantly left, predominantly right, bilateral, or undetermined if neither side was clearly more affected. Second, a continuous asymmetry index was calculated for the hippocampus and temporal lobe to capture incremental differences in left–right volumes. The formula commonly used in neuroimaging studies was applied:

$$\text{Asymmetry Index} = \frac{(\text{Left Volume} - \text{Right Volume})}{\frac{(\text{Left Volume} + \text{Right Volume})}{2}} \times 100$$

Positive values indicate relatively larger left-sided volumes, whereas negative values indicate relatively larger right-sided volumes. This quantitative measure allowed correlation of incremental left–right volume differences with cognitive outcomes, extending beyond the categorical classification.

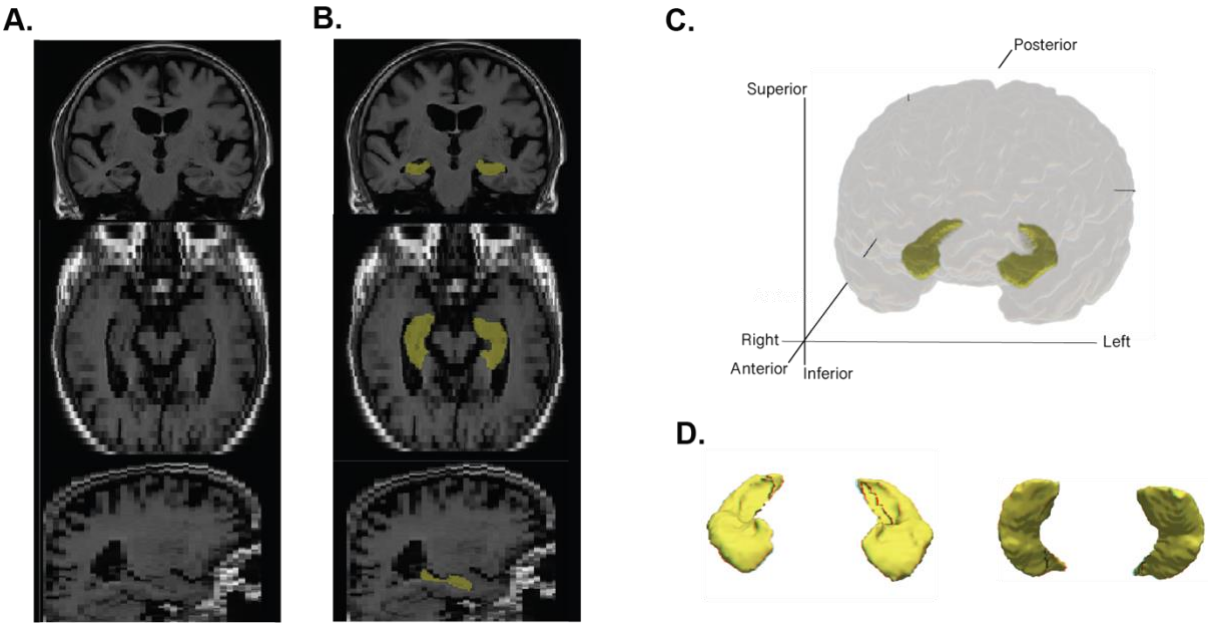

Figure 6-1: Illustrative hippocampal segmentation in one patient at baseline with 2D coronal T1 MRI.

(A) Coronal two-dimensional input T1 MRI scan. (B) Example mask of hippocampal segmentation following synthseg on the two-dimensional input image. (C) three-dimensional render of hippocampal segmentation in 'glass brain' cortical surface segmentation. (D) three-dimensional hippocampal segmentation from superior (left) and inferior (right) view.

Statistical analysis

The primary analyses were prespecified in a statistical analysis plan. All imaging and clinical data were analysed using R (version 4.4.3). All available data for each analysis was used, and the denominator for each analysis is reported throughout. Linear mixed-effects models were fitted on all available data to examine changes in

temporal lobe and hippocampal volumes over time (baseline, Week 2, and Week 26), with time as a fixed effect and participant as a random intercept. Pairwise contrasts compared baseline, week 2, and week 26 volumes. Spearman correlations assessed associations between early MRI measures (baseline, Week 2) and cognitive performance at 26 weeks. Additional subgroup analyses were performed to examine whether the relationship between hippocampal and temporal lobe volumes and verbal memory differed according to treatment allocation (dexamethasone vs control). Firth's penalised logistic regression was used to investigate whether early oedema volumes predicted the dichotomised cognitive outcome (favourable vs unfavourable) at 26 weeks, adjusting for age and sex. All p values were two-sided, statistical significance was set at 0.05.

Reliability assessments

Volumetric measures obtained via stereological methods were repeated by the same rater on ten randomly selected scans to assess intra-rater reliability. Inter-rater reliability was evaluated by having a second investigator independently measure volumes in a separate set of ten patients. Intraclass correlation coefficients (ICCs) were calculated for these repeated assessments. Additional validation was undertaken by comparing SynthSeg-based hippocampal segmentations from both 2D and 3D T1-weighted scans in five patients.

6.3 Results

Baseline Group Comparisons

A total of 47 participants were included, with a mean (SD) age of 63 (13) years and 47% female. The combined sample had a mean (SD) Glasgow Coma Score (GCS) of 12 (4.2) on admission, and the average delay in starting Aciclovir was 1.4 (2.9) days. Baseline volumetric measures showed mean (SD) left and right hippocampal volumes of 0.30 (0.06)% and 0.30 (0.06)% of intracranial volume (ICV), respectively, while left and right temporal lobe volumes were both 4.53% (approximately 0.75 SD overall). Mean (SD) total oedema was 5.41 (4.03)% of whole brain volume (WBV), predominantly vasogenic (4.57 (3.48%)), with lower cytotoxic oedema (0.85 (1.41)%). 9% of cases were classified as bilateral, 38% were mostly left, 49% mostly right affected. Overall, the baseline characteristics were similar between participants who received control treatment and those who received dexamethasone, with no marked differences in age, sex distribution, GCS, imaging measures, or side affected (Table 6-1). Interrater reliability analyses indicated excellent agreement between reviewers for manual segmentation and excellent agreement between automated segmentations (ICC ranging from 82-99, appendix C; p 284)

Volume trajectories of temporal lobe and hippocampus

Bilateral volumes for the temporal lobe and hippocampus were calculated by summing the left and right measurements. Temporal lobe volumes were stable from baseline to the two-week follow-up. However, a marked reduction was observed at the 26-week assessment (figure 6-2). Similarly, the hippocampal volume did not

differ substantially between baseline and Week 2, but a significant decline was evident by 26 weeks (figure 6-3).

Table 6-1: Baseline demographic, clinical and neuroimaging characteristics

	Combined		Control		Dexamethasone	
Variable	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Age, years	47	63 (13)	23	66 (12)	24	60 (14)
Sex, female	47	22 (47%)	23	10 (43%)	24	12 (50%)
Glasgow coma score at admission	37	12 (4.2)	17	11.8 (4.7)	20	12.2 (3.9)
Delay in Aciclovir, days	47	1.4 (2.9)	23	1.2 (2.1)	24	1.6 (3.5)
Left hippocampus (%ICV) Baseline	29	0.30 (0.06)	13	0.31 (0.06)	16	0.30 (0.06)
Right hippocampus (%ICV) Baseline	29	0.30 (0.06)	13	0.31 (0.06)	16	0.29 (0.05)
Left Temporal Lobe (% ICV) Baseline	29	4.53 (0.81)	13	4.78 (0.99)	16	4.33 (0.58)
Right Temporal Lobe (% ICV) Baseline	29	4.53 (0.69)	13	4.69 (0.84)	16	4.40 (0.53)
Total oedema (%WBV) Baseline	35	5.41 (4.03)	16	6.79 (3.64)	19	4.24 (4.06)
Vasogenic oedema (%WBV) Baseline	34	4.57 (3.48)	15	6.15 (3.52)	19	3.32 (2.97)
Cytotoxic oedema (%WBV) Baseline	35	0.85 (1.41)	15	0.79 (0.74)	20	0.89 (1.78)
Side Affected						
Bilateral	-	2 (9%)	-	1 (4.55%)	-	1 (4.2%)
Left	-	17 (38%)	-	10 (45%)	-	7 (30%)
Right	-	22 (49%)	-	11 (50%)	-	11 (48%)
Undetermined	-	4 (9%)	-	0 (0%)	-	4 (17%)

Baseline characteristics include all patients that had at least at least one of the MRI metrics and verbal score available. ICV = Intracranial Volume. WBV = Whole brain volume

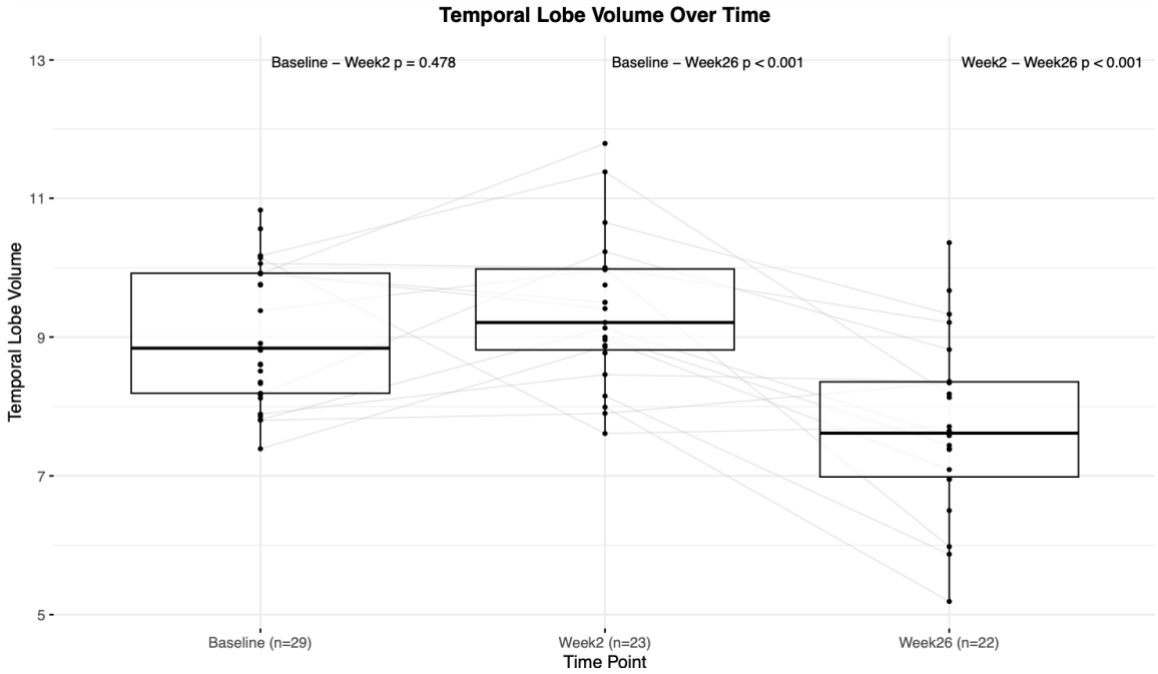

Figure 6-2: Changes in temporal lobe volume between baseline, week 2 and week 26 follow-up.

A linear mixed-effects model with time points as a fixed effect (Baseline, Week2, Week26) and participant as a random intercept was used to analyse bilateral volumes changes. For the temporal lobe, the estimated marginal means were 8.99 at Baseline, 9.38 at Week 2, and 7.78 at Week 26. Pairwise contrasts showed no significant change between Baseline and Week2 (contrast estimate = –0.39, p = 0.48) but a significant decrease at Week 26 relative to Baseline (estimate = 1.21, p = 0.0002) and Week2 (estimate = 1.60, p < 0.0001)

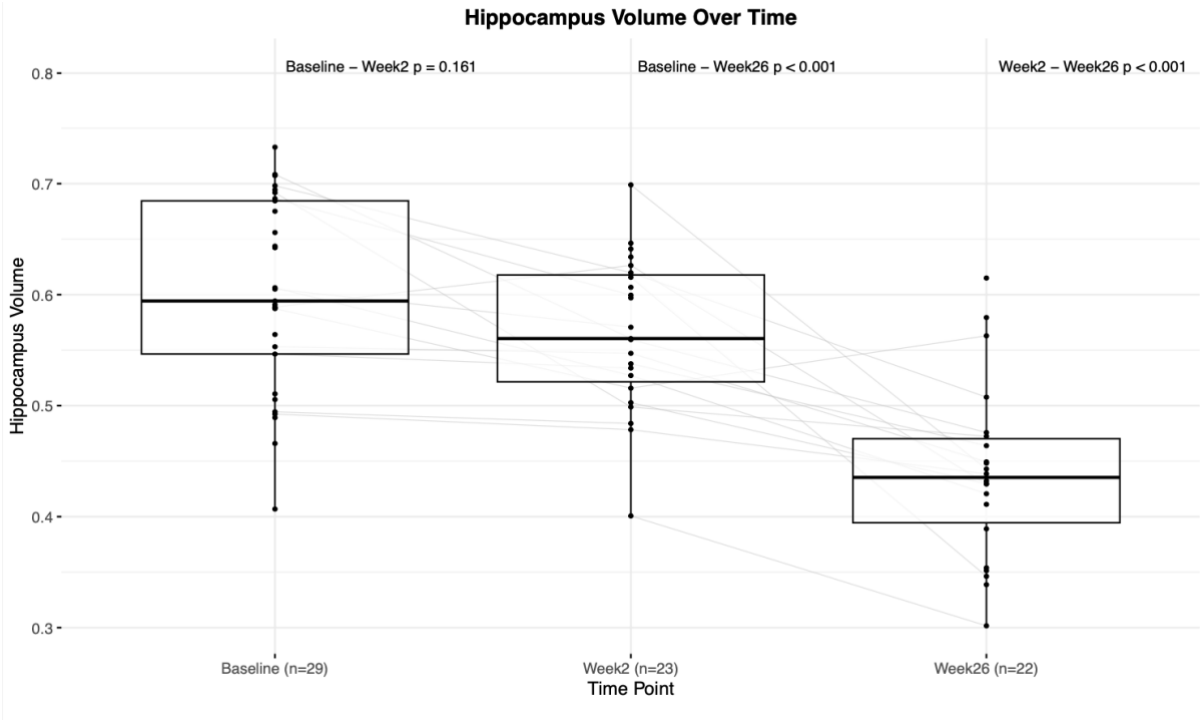

Figure 6-3:Changes in hippocampal volume between baseline, week 2 and week 26 follow-up.

A linear mixed-effects model with time points as a fixed effect (Baseline, Week2, Week26) and participant as a random intercept was used to analyse bilateral volume changes. Estimated marginal means were 0.60 at Baseline, 0.56 at Week2, and 0.45 at Week 26. The Baseline versus Week 2 difference was not significant (estimate = 0.037, p = 0.16), whereas both the Baseline versus Week26 (estimate = 0.151, p < 0.0001) and Week2 versus Week26 (estimate = 0.113, p < 0.0001) contrasts were significant.

Association between early structural MRI volumes (Baseline, Week 2) and 26-week cognitive performance

In the overall cohort, larger baseline left hippocampal ($r = -0.45$, $p < 0.05$) and left temporal lobe volumes ($r = -0.48$, $p < 0.01$) were associated with worse verbal memory at 26 weeks (Table 6-2; Figure 6-4). When I split these analyses by treatment group, the correlations persisted in the control group (left hippocampus: $r = -0.61$, $p = 0.035$; left temporal lobe: $r = -0.80$, $p = 0.002$) but were attenuated and nonsignificant in the dexamethasone group (left hippocampus: $r = -0.29$; left temporal lobe: $r = -0.18$; figure 6-6).

Baseline right hippocampal and temporal lobe volumes showed no associations with cognitive outcomes. By Week 2, the baseline volume-cognition relationships were no longer evident, and no new associations emerged for verbal memory or other domains (Table 6-2).

Cross-sectional association between structural MRI and cognition at 26 weeks

In contrast, larger left hippocampal ($r = 0.63$, $p < 0.01$) and left temporal lobe ($r = 0.69$, $p < 0.001$) volumes were associated with better verbal memory in the overall sample (Table 6-2). Similarly, a larger right hippocampus was linked to better attention ($r = 0.57$, $p < 0.05$). Figure 1 illustrates these contrasting associations

Table 6-2: Correlations between brain volumes at baseline, 2 weeks and 26 weeks, and cognitive functioning at 26 weeks

	Verbal Memory	Visual Memory	Working Memory	Processing Speed	Attention	Executive Function
Baseline						
Left Temporal Lobe	**-0.48****	0.11	-0.23	-0.14	0.13	0.02
Right Temporal Lobe	0.37	0.1	-0.08	0.06	-0.08	-0.03
Left Hippocampus	**-0.45***	0.26	-0.15	0.1	0.26	0.2
Right Hippocampus	0.34	0.22	-0.18	0.21	0	0
Week 2						
Left Temporal Lobe	-0.27	0.28	-0.01	0.27	0.31	0.03
Right Temporal Lobe	0.03	0.04	-0.08	-0.04	0.03	-0.03
Left Hippocampus	-0.07	0.21	0.13	-0.01	0.08	-0.26
Right Hippocampus	0.08	-0.16	-0.23	-0.11	-0.17	-0.39
Week 26						
Left Temporal Lobe	**0.69*****	0.44	0.16	0.12	0.03	0.34
Right Temporal Lobe	-0.22	0.26	-0.18	0.07	0.27	0.17
Left Hippocampus	**0.63****	0.2	0.04	0	-0.15	0.12
Right Hippocampus	-0.25	0.15	-0.22	0.12	**0.57***	0.25

*P<0.05; **P<0.01; ***P<0.001

Asymmetry Analyses

To assess whether left-right volumetric imbalances influenced cognitive outcomes, I calculated a hippocampal asymmetry index at each time point. The asymmetry index reflects the relative size of the left versus right hippocampus (positive values = larger left hippocampus).

At baseline, a higher asymmetry index (greater left-sided asymmetry) was associated with poorer verbal memory. By Week 26, however, this relationship reversed: lower left hippocampus volume compared to the right hippocampus, was associated with worse memory performance, paralleling the time based shift observed in raw left hippocampal volume measures (Figure 6-3). Similar asymmetry results were observed for temporal lobe volume (Figure 6-2). No significant asymmetry-cognition relationships were detected at Week 2, and no associations emerged with other cognitive domains at any time point ($p > 0.05$; appendix C, p 285-286).

Consistent with the hippocampal asymmetry findings, patients with predominantly left-hemisphere T2 FLAIR and DWI lesions exhibited significantly worse verbal memory compared to those with predominantly right-hemisphere lesions (Figure 6-7). Conversely, right-hemisphere lesions were associated with poorer attention ($p < 0.05$). No other lateralized lesion effects were statistically significant. These results reinforce the domain-specific vulnerability of left-hemisphere structures to verbal memory impairment, consistent with the earlier correlations between left hippocampal/temporal volumes and verbal memory performance.

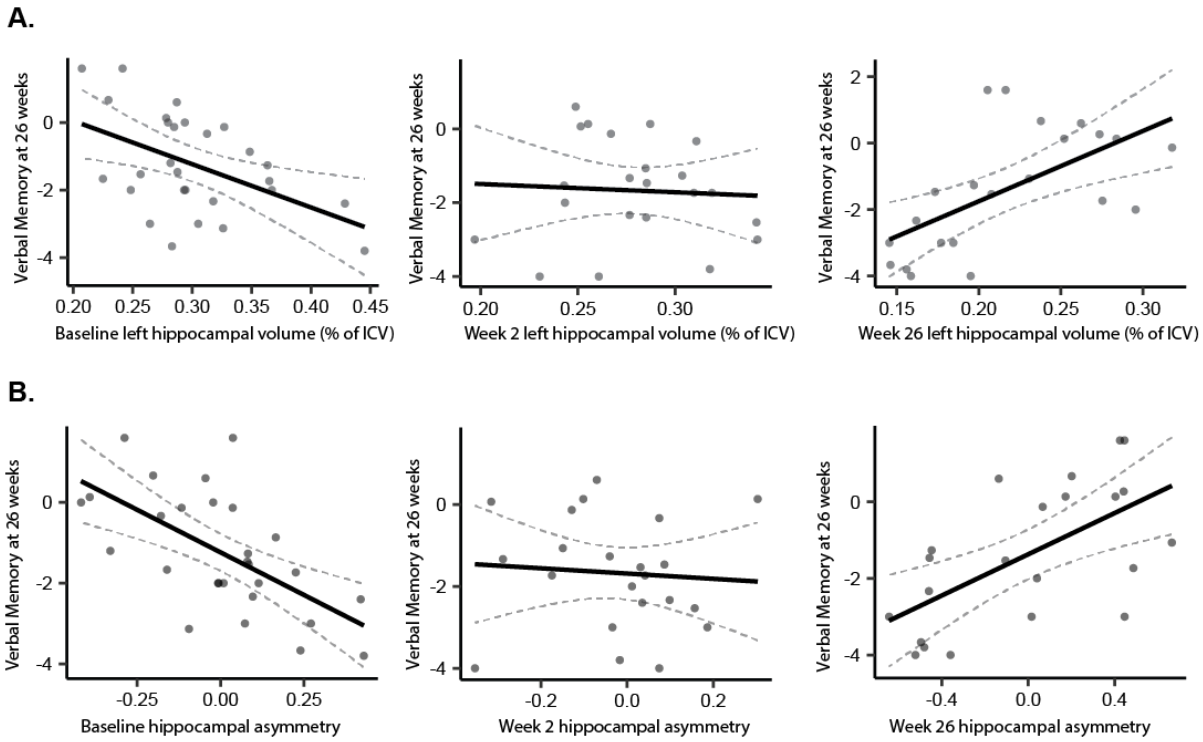

Figure 6-4: scatter plots showing the relationship between left temporal lobe volume, temporal lobe asymmetry and verbal memory at 26 weeks

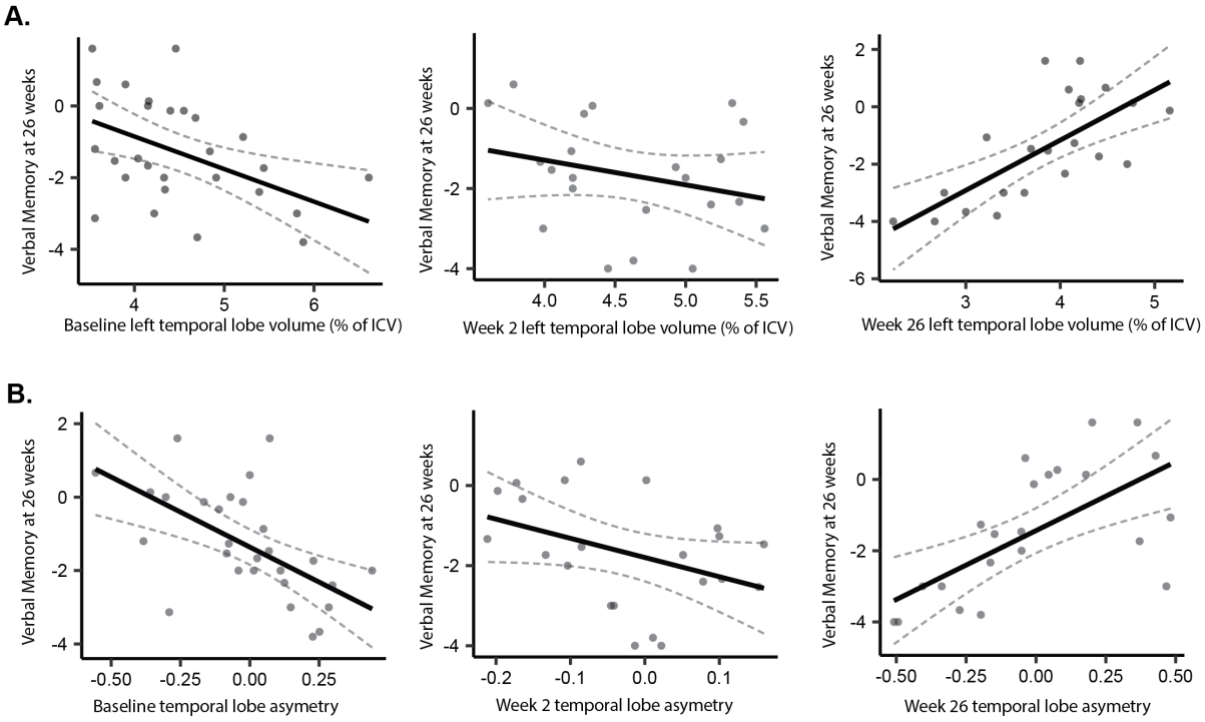

Figure 6-5:scatter plots showing the relationship between left temporal lobe volume, temporal lobe asymmetry and verbal memory at 26 weeks.

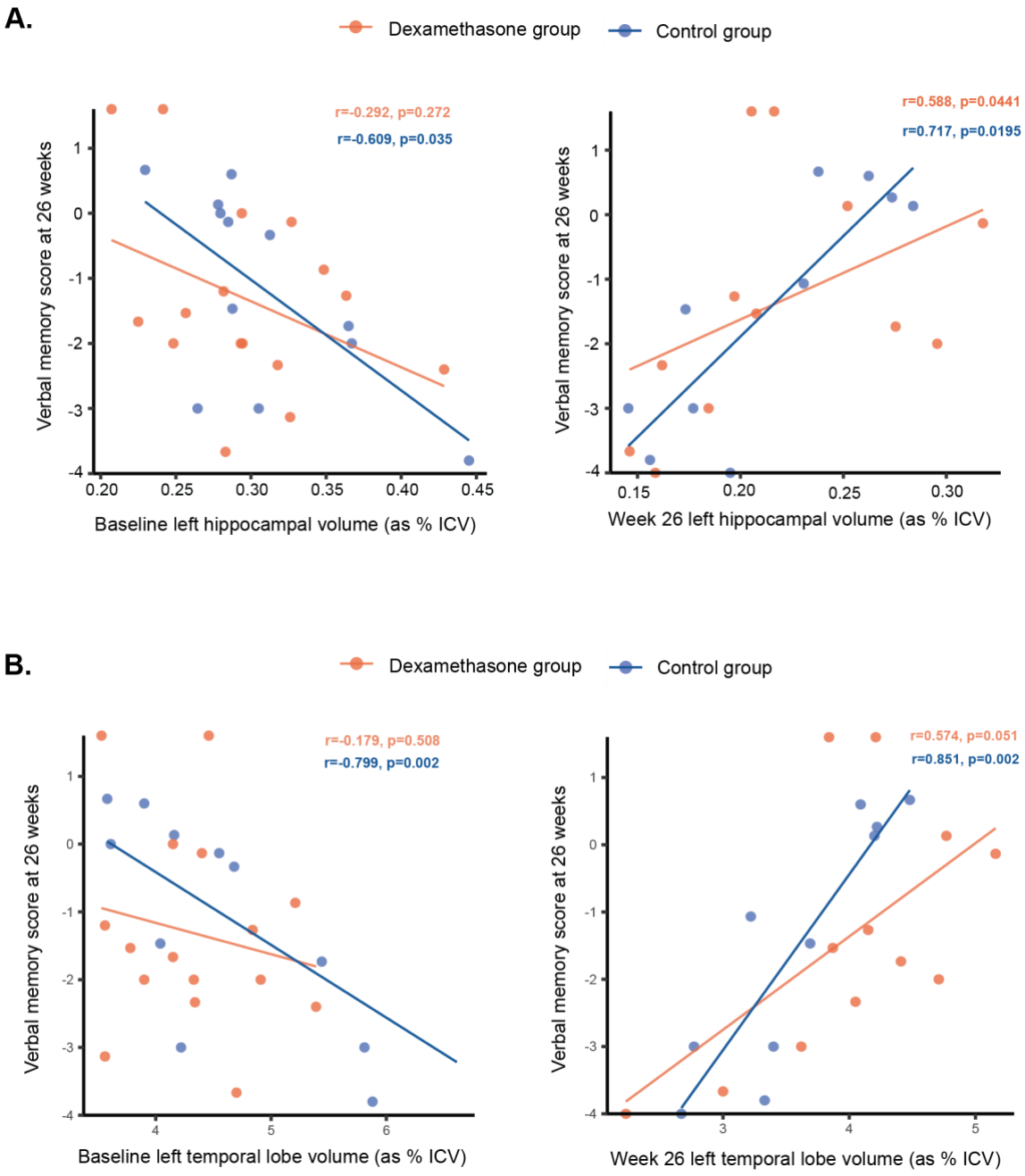

Figure 6-6: Relationship between left hippocampal volume at baseline/26 weeks and verbal memory

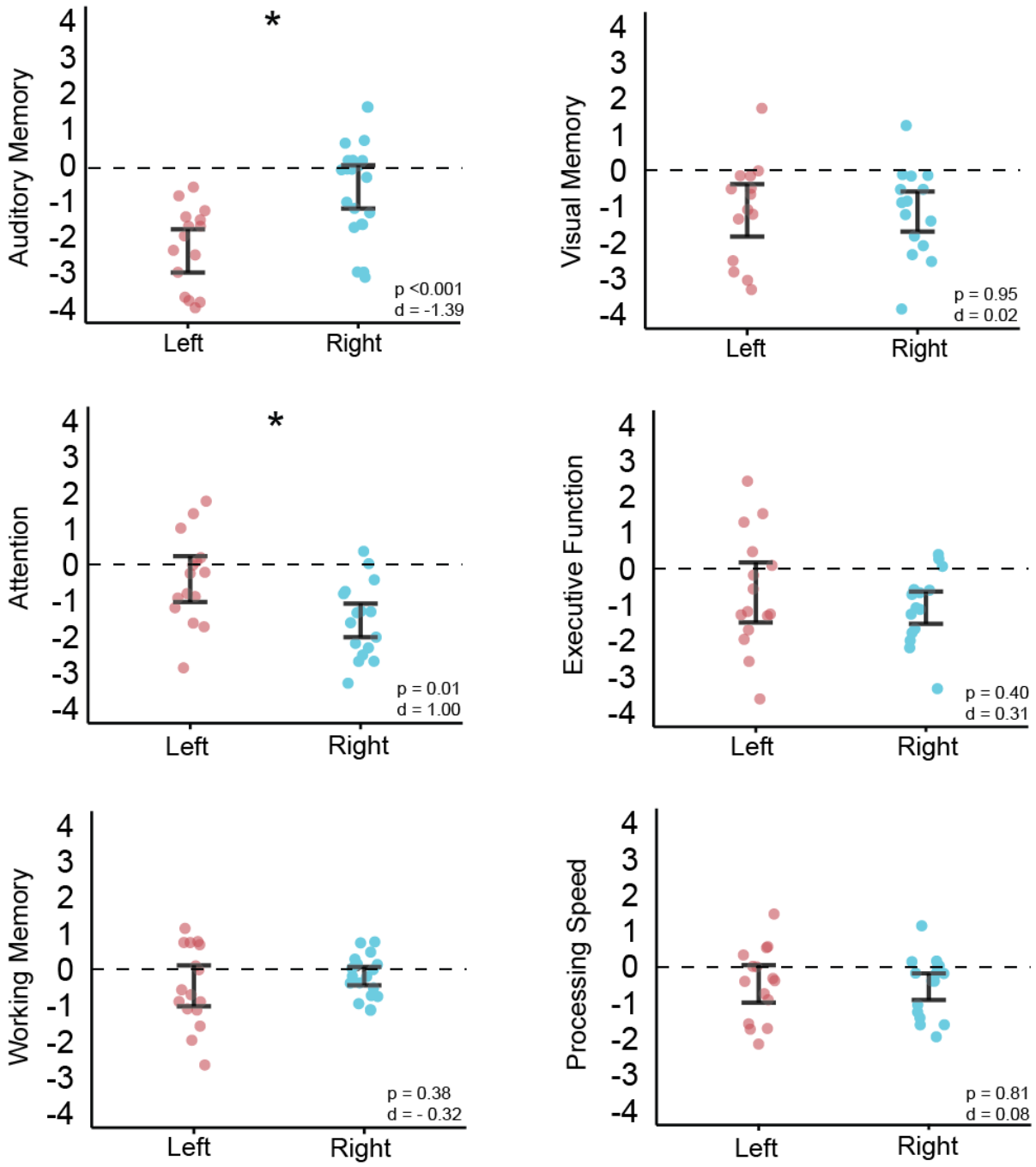

Figure 6-7: Comparison of cognitive functioning at 26 weeks between patients where the left or right hemisphere is most affected at baseline and/or week 2 scan.

Corresponding p values and Cohen's d effect size are reported in the bottom left corner of the respective plot. 6 patients were excluded as the damage was bilateral, and 4 were excluded as the lateralisation of damage could not be determined. Cognitive scores are age normalised scores converted to z-scores.

Table 6-3: Univariate logistic regression models predicting cognitive outcome at 26 weeks with early MRI oedema volumes at baseline and week 2.

	Favourable		Unfavourable			
	N	Median (IQR)	N	Median (IQR)	Odd ratio (95% CI)	P value
Baseline						
Total oedema	12	5.66 (4.97)	24	3.84 (5.32)	0.93 (0.78, 1.11)	0.42
Vasogenic oedema	12	4.98 (3.91)	23	3.39 (5.05)	0.95 (0.77, 1.17)	0.61
Cytotoxic oedema	12	0.42 (0.79)	24	0.35 (0.91)	0.84 (0.47, 1.28)	0.40
Week 2						
Total oedema	10	3.94 (2.18)	23	5.14 (4.38)	1.08 (0.84, 1.42)	0.84
Vasogenic oedema	6	2.90 (3.14)	20	5.06 (4.04)	1.15 (0.84, 1.69)	0.39
Cytotoxic oedema [a]	6	0.50 (1.00)	20	0.00 (1.00)	0.71 (0.11, 4.27)	0.71
Week 2 - adjusted for baseline [b]						
Total oedema	7	3.73 (5.23)	17	4.82 (3.40)	1.37 (0.82, 2.67)	0.24
Vasogenic oedema	6	2.90 (3.14)	14	4.23 (3.39)	1.48 (0.87, 3.12)	0.15
Cytotoxic oedema [a]	6	0.50 (1.00)	15	1.00 (1.00)	1.14 (0.17, 7.59)	0.89

All models used Firths penalised logistic regression and were adjusted for age and sex. Oedema volumes were included in logistic regression models as a percentage of whole brain volume. Median (IQR) volumes are as a percentage of whole brain volume. (a) Due to a larger number of patients showing no cytotoxic oedema in week 2, predictor values were binarised as low or high oedema with a median split.

6.4 Discussion

This prospective, multicentre study of adults with herpes simplex virus (HSV) encephalitis demonstrates that early volumetric changes in the hippocampus and temporal lobe are closely linked to long-term cognitive outcomes, particularly verbal memory at 26 weeks. At baseline, larger left-sided volumes—reflecting acute inflammatory swelling—were associated with poorer verbal memory at 26 weeks. By contrast, at follow-up, smaller hippocampal and temporal lobe volumes strongly correlated with persistent verbal deficits, suggesting that acute inflammation can evolve into atrophy in regions crucial for memory. Notably, these volume–cognition associations were diminished among patients receiving adjunctive dexamethasone, indicating that early immunomodulation may help mitigate hippocampal and temporal lobe damage

Acute HSV encephalitis is characterised by severe inflammation of temporal lobes structures. In this cohort, temporal lobe and hippocampal volumes were smaller at 26 weeks, consistent with tissue loss. Although we lacked age and sex matched control scans, prior studies have shown progressive post-encephalitic atrophy, and in our data smaller volumes tracked with poorer verbal memory, together supporting pathological atrophy rather than simple resolution of oedema (Frisch et al., 2015; Meyding-Lamadé et al., 1999; Yoneda et al., 2008). The absence of control imaging is a limitation; future studies should include matched healthy controls acquired on identical protocols, or apply normative modelling, to distinguish resolution of swelling from true atrophy more definitively. Additionally, the diminished association between volumetric changes and cognitive outcomes in patients receiving adjunctive

dexamethasone implies that early anti-inflammatory therapy may help mitigate subsequent structural damage, consistent with previous animal models, showing reduced MRI changes in mice receiving glucocorticoids as adjunct to aciclovir compared to aciclovir alone (U. K. Meyding-Lamadé et al., 2003). The association between left-sided involvement and poorer verbal memory is consistent with left medial temporal specialisation for verbally mediated episodic memory (Kapur et al., 1994; Frisch et al., 2015; Lezak et al., 2012). Right-sided involvement correlated with Trail Making Test Part A, which largely measures visual scanning and processing speed; this likely reflects broader right-hemisphere network effects rather than a specific attentional role for the right hippocampus and should be interpreted cautiously. Future studies should include attention-specific measures alongside right-leaning memory tasks to test right medial temporal structures more directly. Finally, the absence of a clear relation between visual memory performance and right hippocampal or temporal volumes probably reflects measurement limitations: the WMS-IV visual indices are not right-specific and depend on organisation, visuoconstruction and attention, with ceiling effects that dilute lateralised structure–function relations.

Population-based data from FINNGEN and the UK Biobank suggest that individuals with a history of HSV encephalitis have up to 30-fold increased risk of Alzheimer's disease (Levine et al., 2023). This association may reflect vulnerability of the hippocampus, which is notably atrophied in preclinical Alzheimer's disease and progressively declines throughout the disease course (Barnes et al., 2009). My finding, that changes in hippocampal volumes change over time and are associated with verbal memory impairment provide a potential link to longer term

neurodegeneration. Long-term studies are needed to clarify whether early inflammatory injury in HSV encephalitis precipitates Alzheimer's pathology and potentially leads to earlier or more severe cognitive decline.

These imaging biomarkers could inform immunotherapy strategies. Although the dexamethasone dosing in this study was guided by evidence from animal models and other neurological infections (de Gans & van de Beek, 2002; Sergerie, Boivin, et al., 2007), it remains unclear whether a higher dose might be more effective, or whether patients with greater swelling have an increased benefit. Future studies should consider stratifying participants based on baseline volumetric assessments to determine the optimal dose, timing, and patient selection for immunomodulation. With respect to rehabilitation, patients with pronounced left-sided involvement may benefit from memory-oriented memory interventions, while those with right-sided damage could require therapies focusing on attention.

A key strength of this study is its multimodal neuroimaging approach. I used stereology—the gold standard for volumetric assessment—alongside SynthSeg, an automated deep learning segmentation tool, to obtain robust and reliable measurements even in the presence of imaging artefacts. This combined methodology not only validates the volumetric results but also illustrates the feasibility of conducting detailed neuroimaging analyses with clinical MRI scans which is critical in a rare disease such as HSV encephalitis.

Several limitations warrant consideration. First, the modest sample size—though reasonable for a rare disease—reduced the ability to conduct subgroup analyses.

Second, the multicentre design introduced variability in imaging protocols may have influenced volumetric precision. Third, follow-up was restricted to 26 weeks; longer observation is needed to determine the potential role of early HSV-related hippocampal and temporal lobe injury in subsequent neurodegenerative processes. Future work should record handedness and, where feasible, language dominance, to enable stratified left–right analyses of hippocampal/temporal volumes and their relation to verbal and visual memory.

6.5 Conclusions

In this chapter, I demonstrate that acute volumetric changes in the hippocampus and temporal lobe are associated with domain-specific cognitive deficits following HSV encephalitis. Immunotherapy, potentially administered early in the disease course, may be pivotal in mitigating hippocampal and temporal lobe damage and subsequent memory impairments. Studies incorporating more complete longitudinal imaging, and immune profiling are needed to refine therapeutic windows and tailor interventions for patients at highest risk. Data collected in this cohort offers a unique opportunity to explore the imaging markers described here with biomarkers of the host immune response.

Chapter 7 General Discussion

The aim of this thesis was to improve, understand and predict cognitive outcomes in patients with HSV encephalitis. To achieve this, I set out to answer four key questions:

1) Does early adjunctive dexamethasone therapy improve outcomes as demonstrated in a multicentre randomised controlled trial?

2) What is the prevalence, nature, and long-term recovery trajectories of cognitive impairments in people post HSV encephalitis?

3) How effective are existing cognitive screening tools in identifying patients at risk for persistent deficits?

4) To what extent are MRI biomarkers associated with domain specific cognitive performance?

Having answered all four research questions, this chapter addresses each in turn, discusses their broader implications, situates the findings within the wider literature and evaluates the limitations of my research.

Does early adjunctive dexamethasone therapy improve outcomes as demonstrated in a multicentre randomised controlled trial?

In Chapter 3, dexamethasone alongside aciclovir produced no overall difference in the primary outcome of verbal memory at 26 weeks compared with aciclovir alone. A post-hoc analysis, however, revealed that within the dexamethasone group, earlier initiation significantly improved verbal memory outcomes. Safety outcomes showed that dexamethasone did not increase adverse events or lead to uncontrolled viral replication. These findings are consistent with previous retrospective studies (Kamei et al., 2005). Moreover, clinical studies in other neuroinflammatory conditions—such as bacterial meningitis—have demonstrated that early corticosteroid use can reduce complications and improve functional outcomes (Brouwer et al., 2015). The present work is a novel contribution to the field, showing that dexamethasone treatment for HSV encephalitis is safe, and while there was no benefit for patients overall, dexamethasone may be beneficial if given soon after hospital admission.

During the course of the clinical trial, advances emerged in understanding the immune pathways driving HSV encephalitis pathology. For instance, in a mouse model CXCL1-mediated recruitment of neutrophils disrupts the blood–brain barrier and propagates tissue damage, and while dexamethasone treatment reduced overall inflammation it did not fully suppress key chemokine signals such as CXCL1 (Michael et al., 2020). Thus, although dexamethasone's broad immunosuppressive

effect proves beneficial if given early in patients with HSV encephalitis, its non-specificity may limit optimal outcomes; therapies that target these key pathways may ultimately prove more effective.

What is the prevalence, nature, and long-term recovery trajectories of cognitive impairments in people post HSV encephalitis?

The data I collected in the clinical trial offered a unique opportunity to explore this in the largest, prospective, longitudinal neuropsychology study in HSV encephalitis to date. I found that cognitive deficits were both widespread and severe in people post HSV encephalitis. Verbal memory was the most affected domain, however I also found substantial impairments in all domains assessed, with relatively lower levels in processing speed and working memory. Importantly, these deficits were persistent with limited evidence of improvement over time. Some patients showed improvement in specific domains (such as immediate and visual memory), whereas others experienced further decline.

Many patients exhibited high levels of depression and anxiety symptoms, with symptom levels more strongly correlated with subjective rather than objective measures of cognitive functioning. This dissociation aligns with findings with Harris et al., (2020), who showed that in encephalitis patients' subjective cognitive complaints often persisted long term, even after improved objective performance. These results are also consistent with findings observed in traumatic brain injury and other

acquired brain injuries, where patients' self-reported cognitive difficulties often diverge from performance-based test scores (Nijsse et al., 2017; Zlatar et al., 2018).

Cognitive outcomes after HSV encephalitis range from profound amnesia and executive dysfunction to subtler deficits that will likely impact everyday activities, return to work, and social participation. Future studies should therefore include brief patient- and carer-reported outcomes alongside neuropsychological testing to capture lived impact and participation; in this thesis, health-related quality of life was collected with the SF-36 and will be reported separately (Ware & Sherbourne, 1992). Neuropsychological rehabilitation has demonstrated benefits after acquired brain injury, with strategy-based memory and executive interventions and goal-oriented programmes improving functional outcomes and goal attainment; such approaches should be offered routinely to people post HSV encephalitis (Cicerone et al., 2019a; Cicerone et al., 2019b)

The role of psychological functioning in shaping outcomes is increasingly recognised as important. A recent global survey on mental health outcomes in encephalitis revealed that 37.5% of respondents had experienced suicidal ideation, while 4.4% had attempted suicide (Butler et al., 2024). Notably, more than half of the patients reported inadequate or no access to appropriate mental healthcare, highlighting a significant gap in post-encephalitis care that demands urgent attention.

How effective are existing cognitive screening tools in identifying patients at risk for persistent deficits?

While cognitive screening provides a useful initial evaluation, the ACE-III was less effective in identifying patients with milder deficits and executive functioning. This aligns with findings in other neurological conditions, where the sensitivity of brief screening tools is often limited by ceiling effects (Kourtesis et al., 2020). The need for more refined and sensitive instruments, or possibly the development of encephalitis-specific screening protocols, is evident from both the present work and the wider literature. Psychometrically sound measures, such as the NIH Toolbox Brief Cognitive Battery, have been validated across a wide range of neurological disorders, including traumatic brain injury and stroke (Carlozzi et al., 2017; Holdnack et al., 2017). This brief, multi-domain tool may prove more effective than instruments like the ACE-III, as it is specifically designed to capture nuanced impairments.

Encephalitis outcomes research currently lacks a unified, disease-specific toolset; in a systematic review I co-authored during my PhD we found that cognitive functioning is not routinely assessed with appropriate measures (Tooren et al., 2022). Developing encephalitis-specific screening tools or adapting existing measures to more accurately capture the unique cognitive deficits in HSV encephalitis would have benefits for both clinical assessment and research.

To what extent are MRI biomarkers associated domain-specific cognitive outcomes?

I looked at whether MRI biomarkers, measured both acutely and during follow-up, correlate with domain-specific cognitive outcomes. I found that, at baseline,

increased volumes in the left hippocampus and temporal lobe—presumably reflecting acute inflammatory swelling—were associated with poorer auditory–verbal memory at 26 weeks. Conversely, at 26 weeks, reduced volumes in these regions, suggestive of post-inflammatory atrophy, were linked with impaired verbal memory. The concurrent association between verbal memory and hippocampal/temporal at 26 weeks confirms results from previous studies in HSV encephalitis with smaller sample sizes, as well as animal studies showing progressive neuronal loss in the hippocampus (Frisch et al., 2015; Kapur et al., 1994; U. K. Meyding-Lamadé et al., 1999).

One of the key novel finding from this study is that the magnitude of acute swelling in memory-critical structures was a determinant of later memory impairment. Previous studies examining the prognostic value of MRI have shown inconsistent results, likely due to small sample sizes and selective designs. In one larger retrospective study, Sarton et al., (2021) described radiological features, showing that diffuse injury, and specifically left thalamic lesions, predicted poor global outcomes measured using the modified Rankin Scale. Taken together, both studies highlight the importance of left-sided damage in HSV encephalitis. However, Sarton et al. examined only severe ICU-admitted patients, suggesting that left thalamic lesions may mark particularly severe disease. Indeed previous reports have suggest that thalamic lesions in HSV encephalitis are rare (Chow et al., 2015).

7.2 Clinical and policy implications

The safety and potential benefits of early adjunctive dexamethasone therapy have immediate clinical relevance. HSV encephalitis has seen few therapeutic advancements beyond aciclovir since its introduction, despite accumulating evidence regarding the role of inflammation in its pathogenesis. Because dexamethasone is inexpensive and globally available, its benefit in HSV encephalitis represents a practical and immediately translatable intervention. The RECOVERY trial, for example, demonstrated how rapidly dexamethasone can be integrated into treatment protocols worldwide (The RECOVERY Collaborative Group, 2021).

Furthermore, the benefits of early dexamethasone administration extend beyond HSV encephalitis. In current clinical practice, steroid therapy is often delayed until HSV is excluded via PCR testing, a delay that may adversely affect patients with autoimmune encephalitis such as anti-NMDAR encephalitis (Defres et al., 2023; Solomon et al., 2012). By demonstrating that dexamethasone use is safe supports a change shift in clinical practice, wherein immunotherapy may be initiated sooner in patients with suspected encephalitis, potentially improving outcomes in both viral and autoimmune cases.

Biomarkers that predict clinical outcome at presentation could be valuable in guiding early immune therapy for HSV encephalitis. This is particularly relevant given the findings in chapter 3, indicating that early dexamethasone administration is both beneficial and safe, although the dose was based on the proven efficacy in other neurological infections (de Gans & van de Beek, 2002; Thwaites et al., 2004). Clinically, HSV encephalitis patients exhibit more pronounced cerebral swelling than patients with these other infections, and concerns about uncontrolled viral replication

precluded the use of higher steroid doses. Future trials should aim to integrate imaging data with clinical and cognitive outcomes to explore whether MRI-based biomarkers could help stratify patients according to the extent of swelling and thus tailor the intensity of immunotherapy. Furthermore, given that higher dexamethasone doses have been effective in other neurological infections without causing undue harm (Nosadini et al., 2021), future studies could explore whether increased steroid dosing could further improve outcomes, potentially guided by imaging markers of inflammation.

The broader literature on acquired brain injuries, including traumatic brain injury, has led to a reconceptualisation of these conditions as chronic diseases. This perspective is directly applicable to HSV encephalitis, where recovery is not simply a linear process but may involve phases of improvement and decline, influenced by both neurobiological and psychological factors. The evidence of persistent cognitive deficits and significant psychiatric morbidity highlights the necessity for a comprehensive, multidisciplinary follow-up approach. Although recent National Clinical Guidelines for the Management of Viral Encephalitis recommend outpatient follow-up and rehabilitation planning at discharge, these guidelines often lack detailed implementation strategies. My findings highlight the need for structured neuropsychological assessments at multiple time post-discharge—to identify patients requiring cognitive rehabilitation and psychological support. Given that subjective cognitive complaints correlate more strongly with affective symptoms than with objective test scores, routine screening for depression and anxiety should be incorporated into follow-up care, allowing for timely and effective interventions.

7.3 Future research

Mounting evidence links viral encephalitis with increased dementia risk: FinnGen and UK Biobank analyses suggest up to a 30-fold higher risk of an Alzheimer's diagnosis, 13% of people post encephalitis develop dementia-level memory impairment, and the adjusted dementia rate ratio is 2.66 versus controls (Granerod et al., 2017; Hokkanen & Launes, 1997b; Levine et al., 2023). However, Alzheimer's disease is a pathological or biomarker-defined diagnosis, and registry studies often rely on clinical codes without gold standard diagnosis, so some cases may reflect age-related decompensation after limbic injury, vascular disease, or other neurodegenerative processes. In this cohort I observed decline and medial temporal change with hippocampal changes reminiscent of Alzheimer's disease, but this does not establish Alzheimer's pathology. Future work should apply gold standard diagnostic criteria with biomarker confirmation, for example CSF Aβ42/40 and phosphorylated tau, amyloid and tau PET, or validated plasma p-tau with confirmatory imaging to distinguish true biomarker-positive Alzheimer's disease from alternatives and to test whether early hippocampal injury modifies later risk (Sperling & Johnson, 2010).

Recent advancements in artificial intelligence (AI) have significantly expanded the capabilities of neuroimaging, promising substantial benefits for patients with HSV encephalitis as well as for broader neurological conditions. While my work utilised SynthSeg to quantify hippocampal volumes from clinical MRI scans, new deep learning models are emerging that enhance segmentation and classification capabilities. For example, studies in dementia, stroke, and brain tumour research

have successfully employed these techniques to improve the detection and characterisation of brain lesions (El-Assy et al., 2024; Feng et al., 2019; Guerrero et al., 2018; Liu et al., 2020). In HSV encephalitis, developing accurate and automated lesion volume mapping should be a research priority, which, with advances in AI could be translated from research tools to being routinely used in clinical practice. Such tools would allow for the precise characterisation of the type, volume, and location of oedematous lesions, which is crucial for assessing disease severity and guiding treatment strategies. Translating these imaging advances into clinical practice requires integrating AI-derived biomarkers with other clinical data to enhance diagnostic accuracy and support reliable clinical prediction. I have demonstrated that clinical scans can be used for advanced imaging; consequently, future studies should utilise these scans to augment datasets, a critical consideration given the low incidence of HSV encephalitis.

Although machine-learning methods hold potential in standardising volumetry and automating lesion quantification, the priority is to improve treatment pathways and cognitive outcomes. Given the largely static post-acute cognitive profiles in this cohort, efforts should focus on earlier recognition and timely antiviral therapy, evaluation of targeted anti-inflammatory or neuroprotective strategies, structured longitudinal neuropsychological follow-up with rehabilitation referral, and routine capture of patient- and carer-reported outcomes

The COVID-19 pandemic led to a significant increase in the use of telemedicine, highlighting the potential value of remote assessment methods in clinical research. However, conducting longitudinal studies in acute and rare CNS disorders remains

challenging, largely because traditional neuropsychological evaluations are resource-intensive and time-consuming. For example, considerable travel was required in the present study for data collection, making it impractical to establish a research programme solely focused on in-person neuropsychological testing.

Tele-cognitive assessments could help overcome these logistical barriers by enabling larger and longer-term studies of neuropsychological outcomes without necessitating frequent, in-person visits, as shown in the COVID CNS study which collected cognitive data in 351 patients over a 20 month period (Wood et al., 2025). Evidence also supports the validity of tele-neuropsychology. Previous studies reported good agreement between videoconference and in-person neuropsychological testing across memory, language and executive measures, with verbally mediated tasks showing the closest correspondence, which supports remote assessment as both feasible and psychometrically acceptable in clinical research. This argues for remote follow-up in HSE while emphasising the need for standardised equipment, quiet testing conditions and clear protocols for identity verification and test security (Cullum et al., 2014).This approach would improve feasibility and reduce costs, facilitating the collection of larger datasets over extended follow-up periods.

It would be advantageous to develop a standardised assessment protocol for patients with HSV encephalitis. Such a protocol could be integrated with current NHS clinical databases, allowing for systematic and comprehensive monitoring of cognitive outcomes. By using a telemedicine infrastructure and established data repositories, researchers and clinicians could more efficiently track disease

progression and treatment efficacy, ultimately improving patient care and advancing our understanding of HSV encephalitis.

7.4 Limitations

There are several limitations that warrant consideration. First, survivorship bias may have influenced the findings. Some patients were lost to follow-up, which could skew results if those with worse outcomes were disproportionately underrepresented. To mitigate this, an independent committee assigned scores for missing data in the clinical trial, and multiple imputation techniques were used to assess the robustness of findings. Additionally, in Chapter 4, I conducted sensitivity analyses to test for differences between those with complete and incomplete neuropsychological batteries, as well as between those who were followed up and those who were not. These analyses provided further insight into the potential impact of missing data and helped assess the reliability of the observed trends. Despite these efforts, there remains a possibility that the cognitive outcomes observed do not fully capture the most severe cases, since the worst-affected individuals might be among those not represented in the follow-up data.

Second, sample size constraints limited statistical power. The relatively low incidence of HSV encephalitis poses inherent challenges in recruiting large patient cohorts, precluding analyses of subgroups in this cohort. While the power calculation ensured an adequate sample for the clinical trial in Chapter 3, subsequent analyses, such as those assessing MRI biomarkers and long-term cognitive outcomes, were

based on smaller sample sizes and require validation in independent cohorts. Encouragingly, an ongoing ‘sister’ study in France, with a similar study design and procedures, presents an opportunity to merge datasets and enhance statistical power for future analyses.

Third, the absence of a control group in later chapters presents further limitations. Without a control group, it was not possible to assess practice effects or adjust reliable change indices based on control performance. Moreover, an exploration of the extent of atrophy in Chapter 6 would have provided valuable insights, potentially strengthening the interpretation of the imaging findings. Also, factors such as rehabilitation interventions, socioeconomic status, and co-morbidities may have influenced recovery trajectories but were not fully controlled for in my analyses. Future work should aim to include these variables to better understand their impact if adequate sample sizes to assess this can be achieved.

7.5 Conclusion

When I set out on this project, 6 years ago, I wanted to better understand the long-term cognitive outcomes in HSV encephalitis and see how they might be improved. The trial of dexamethasone (chapter 3) showed no benefit overall, although this may have been a fault of the trial design which allowed patients to be included up to 21 days after hospital admission. A post hoc analysis showed that patients in the dexamethasone group who received prompt treatment experienced improved outcomes, suggesting that early dexamethasone administration may be beneficial

without causing harm. One way to improve longer term outcomes is with prompt and targeted intervention through neuropsychological rehabilitation, but this requires a better understanding of what those outcomes are, and accurate identification and prognosis of poor cognitive outcome. I described the full range and extent of outcomes (chapter 4) and examined the potential of the ACE-III screening tool in predicting poor outcomes (chapter 5). However, this tool was not useful for mild and moderate impairment. I found acute imaging biomarkers were associated with neuropsychological outcomes (chapter 6); with rapid advances in imaging analysis, especially using AI, with further research such approaches could be incorporated into routine clinical care to guide neuropsychological rehabilitation and immunomodulatory treatments.

C.P. Cavafy wrote in his wonderful poem, “hope your road is a long one, full of adventure, full of discovery.” Although the road, or roads in my case, felt long at times, I have certainly enjoyed and learnt from my journey, and I am pleased that my discoveries are meaningful and that they point the way towards improving long-term outcomes for patients with HSV encephalitis.

Chapter 8 References

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Chapter 9 Appendices

9.1 Appendix A - Chapter 3.

The content of this paper has been submitted to The Lancet.

Adjunct dexamethasone in adults with herpes simplex virus encephalitis: a Phase III multicentre, observer-blind, randomised controlled trial.

Tom Solomon, Cory Hooper, Ava Easton, Anna Rosala-Hallas, Bethany Facer, Perry Moore, Simon Keller, Thomas Whitfield, Cristina Fernandez, Rachel Kneen, Michael Griffiths, Kumar Das, Shona C Moore, Kelly Davies, Dianne Wheatley, Jean Paul Stahl, Ben Hardwick, Sylviane Defres, Benedict D Michael, DexEnceph Study Group[†], *Girvan Burnside, *Mark A Ellul.

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7th February 2025

Dear Sir/Madam,

RE: Incorporation of publications in Cory Hooper's doctoral thesis

This letter is written in support of incorporation of the following paper, currently under submission, in Cory Hooper's doctoral thesis:

1. Solomon, T., Hooper, C., Easton, A., Rosala-Hallas, A., Facer, B., Moore, P., Keller, S., Whitfield, T., Fernandez, C., Kneen, R., Griffiths, M., Das, K., Moore, S. C., Davies, K., Wheatley, D., Stahl, J. P., Hardwick, B., Defres, S., Michael, B. D., … Mark. (Under Submission). Adjunct dexamethasone in adults with herpes simplex virus encephalitis: A phase III multicentre, observer-blind, randomised controlled trial

As corresponding author for this publication, I can confirm that I have discussed with all co-authors who have given their permission for the publication to appear in Cory Hooper's thesis, therefore I am signing on behalf of all of co-authors.

As declared in the author declarations for the publication and under responsibilities of the work section of this thesis, I can confirm that Cory Hooper contributed to collection of data, analysis and interpretation of results and writing the initial draft as well as reviewing and approving the final draft of submission.

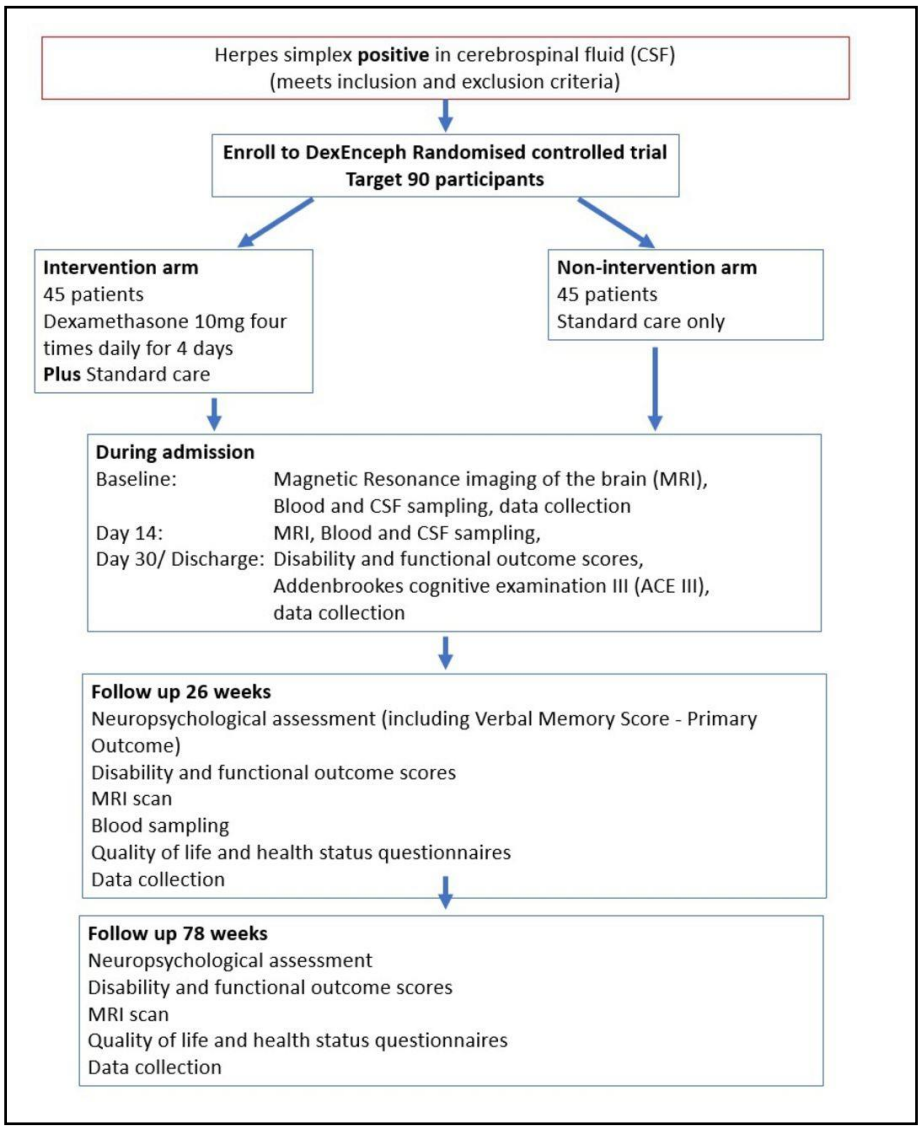
With best wishes,

Professor Tom Solomon CBE FRCP FMedSci
- Director, The Pandemic Institute
- Director, NIHR Health Protection Research Unit in Emerging and Zoonotic Infections
- Chair, Neurological Science, University of Liverpool
- Honorary Consultant Neurologist, Walton Centre NHS Foundation Trust.
- Vice President (International), Academy of Medical Sciences
- Academic Vice President, Royal College of Physicians of London

A member of the Russell Group

Trial timeline and interventions

Figure SA1: schematic of study design



Standard care was according to UK guidelines.1

All patients received intravenous acyclovir (10 mg/kg three times daily or reduced according to renal function) for a minimum of 14 days. Patients were randomised within seven days of initial lumbar puncture, and the intervention group received intravenous dexamethasone 10 mg four times daily for four days from ward stock, starting within 24 hours of randomisation. Clinicians were free to modify or discontinue dexamethasone or give alternative treatments if in the best interest of the patient. After 14

days (+/- three days) acyclovir treatment we repeated the lumbar puncture, unless clinically contraindicated; If HSV DNA was detected by CSF PCR, acyclovir was continued with weekly lumbar punctures until the CSF was clear. IgG antibodies to NMDAR were measured through modifications of an established assay.2 Data were collected at baseline, 14 days, discharge or 30 days (whichever was sooner), six and 18 months.

Inclusion and exclusion criteria

Inclusion criteria: Enrolled patients must fulfil ALL the following criteria (1-5):

1. Suspected encephalitis criteria: New onset seizure OR, new focal neurological signs OR alteration in consciousness, cognition, personality, or behaviour*.
2. A positive HSV PCR result from CSF, reported not more than 7 days prior to randomisation.
3. Receiving intravenous aciclovir dosed at 10mg/kg TDS or at a reduced dose if clinically indicated.
4. Age ≥ 16 years.
5. Written informed consent has been given by the patient or their legal representative.

* Personality / behaviour change includes agitation, psychosis, somnolence, insomnia, catatonia, mood lability, altered sleep pattern.

Exclusion Criteria: Patients are excluded if ANY criteria are present:

1. Having received oral or injectable corticosteroid therapy in the 30 days prior to the day of admission to hospital**

.

2. History of hypersensitivity to corticosteroids.
3. Immunosuppression secondary to:

a. Known HIV infection AND CD4 count under 200cell/mm3.
b. Currently taking biologic therapy or other immunosuppressive agents [azathioprine, methotrexate, ciclosporin].
c. Previous solid organ transplant and currently on immunosuppression.
d. Previous bone marrow transplant.
e. Currently undergoing a course of chemotherapy or radiotherapy.
f. Known primary immunodeficiency syndrome.
g. Known current hematological malignancy.

4. Pre-existing indwelling cerebroventricular drain/shunt
5. Peptic ulcer disease in the last 6 months: defined as a peptic ulcer seen at endoscopy or an upper gastrointestinal bleed causing ≥ 2-unit hemoglobin drop in the last 6 months.
6. Antiretroviral regime containing rilpivirine as current treatment.

**Participants are not excluded if steroids are administered after admission prior to randomisation.

List of outcomes

Primary Outcome: Verbal memory score, as determined by the Wechsler Memory Scale (WMS-IV): Auditory Memory Index at 26 weeks after randomisation.

Secondary Outcomes: (Time points given are from randomisation)

Neuropsychological Outcome Measures [26 weeks and 78 weeks]

Visual, immediate and delayed memory (WMS-IV), Processing speed and working memory(WAIS-IV), & Higher executive function (Trail Making Tests Parts A and B)

Anxiety and Depression (BDI & BAI) Subjective cognitive complaints (Perceived Deficits Questionnaire) **Cognitive Outcome Measures** [at 30 days/discharge, 26 weeks and 78 weeks] Addenbrooke's Cognitive Assessment revised (ACE-III)

Clinical Outcomes

Incidence of epilepsy

Time to hospital discharge

Requirement of HDU/ITU admission up to 30 days post randomisation

Time to reach 14 days without ventilatory support [if any]

Time to reach maximum recorded GCS

Survival

Disability & Functional Outcomes [at 30 days/discharge, 26 weeks and 78 weeks]

Modified Rankin Score, Barthel Index, Liverpool Outcome Score and Glasgow Outcome Score Extended

Imaging Outcomes [Baseline, 2 weeks, 26 weeks and 78 weeks]

Temporal lobe volume (as % of intra-cranial volume).

Whole brain volume (as % of intra-cranial volume).

Volume of affected region as seen on FLAIR image (as % of intra-cranial volume).

Volume of affected region as seen on diffusion-weighted image (as % of intra-cranial volume).

Safety Outcomes

Proportion of patients with detectable HSV in CSF by PCR at 2 weeks

Health Status and Quality of Life [at 26 and 78 weeks]

Measured by the EuroQOL-5D-5L and SF-36 self-completed questionnaires

Exploratory Outcomes:

Biomarker Outcomes

HSV Viral Load in CSF

Transcriptomic and proteomic profiling on CSF at baseline and 2 weeks in HSV and non-HSV cohort; on blood at baseline, 2 weeks, and 26 weeks in HSV cohort

Anti NMDA receptor antibody testing at 26 weeks

Additional autoantibody testing at 2 and 26 weeks

Safety Outcomes

White blood cell function at baseline and 26 weeks

Sample Size Calculation

The sample size was estimated with the following considerations. Firstly, we anticipated a 10% mortality rate before the primary outcome could be assessed (24 weeks). Secondly, verbal memory scores were expected to average 88·9 (SD 18·9), based on a published series of adult who survived HSV encephalitis4, which was adjusted to a population mean of 84·8, (SD 23·1), adjusting for the expected 10% mortality rate. Thirdly, a difference of 15·5 on the verbal memory score would represent a clinically meaningful difference. A final sample size of 36 participants per group would allow us to detect a clinically meaningful difference of 15·5 on the verbal memory score with 80% power, at a two-sided significance level of 0·05. Allowing for up to 20% dropout gave a target sample size of 45 participants per group, for a total of 90.

MRI Analysis

First, we quantified hyperintense regions on T2-weighted-Fluid-Attenuated Inversion Recovery (FLAIR) scans, considered total oedema. Second, we quantified cytotoxic and vasogenic oedema separately to explore the treatment effect on each type. Cytotoxic oedema was quantified by measuring hyperintense regions on DWI, and corresponding Apparent Diffusion Coefficient (ADC) scans were used to identify hypointense regions, eliminating T2 shine through (high signal on DWI that is not due to restricted diffusion)[3]. Vasogenic oedema was calculated by subtracting the volume of cytotoxic oedema from the volume of total oedema. Third, we used the same T2 FLAIR scan to quantify the whole-brain volume, adjusting the total, cytotoxic and vasogenic oedema as a percentage of whole-brain volume. Temporal lobe volume was quantified on the coronal images of the best available scan, using the same anatomical boundaries as defined previously.[4] We used SynthSeg, a deep learning tool for segmentation validated for its robustness to poor contrast, resolution and diseased brains[5], to quantify intracranial volume (ICV). Temporal lobe volume was calculated as a percentage of ICV.

Screening data

Table SA1: screening and eligibility for recruiting sites

Hospital	Date of site opening	Screenings [a]	Eligible (% of [a]) [b]	Eligible and consented (% of [b]) [c]	Randomised (% of [c])
Blackpool Victoria Hospital	07/19/2016	52	7 (13.5%)	3 (42.9%)	3 (100.0%)
St James Hospital Leeds	08/05/2016	59	13 (22.0%)	8 (61.5%)	7 (87.5%)
Bradford Teaching Hospital	09/01/2016	71	3 (4.2%)	0 (0.0%)	NA
Leicester Royal Infirmary	09/05/2016	22	3 (13.6%)	2 (66.7%)	2 (100.0%)
The James Cooke University Hospital	09/14/2016	82	1 (1.2%)	1 (100.0%)	1 (100.0%)
North Cumbria	09/26/2016	8	5 (62.5%)	1 (20.0%)	1 (100.0%)
Royal Preston Hospital	10/04/2016	234	3 (1.3%)	1 (33.3%)	1 (100.0%)
Royal Bolton Hospital	10/07/2016	15	1 (6.7%)	1 (100.0%)	1 (100.0%)
Northumbria	11/02/2016	20	5 (25.0%)	2 (40.0%)	2 (100.0%)
North Tees	11/17/2016	14	4 (28.6%)	2 (50.0%)	2 (100.0%)
St Peter's, Surrey	11/22/2016	2	2 (100.0%)	2 (100.0%)	2 (100.0%)
Walton Centre	12/20/2016	3	2 (66.7%)	2 (100.0%)	2 (100.0%)
Royal Cornwall	01/26/2017	9	5 (55.6%)	3 (60.0%)	3 (100.0%)
Royal Stoke	01/31/2017	2	1 (50.0%)	0 (0.0%)	NA
Heartlands	02/16/2017	3	3 (100.0%)	2 (66.7%)	2 (100.0%)
Royal London (Barts)	03/21/2017	5	3 (60.0%)	3 (100.0%)	3 (100.0%)
Salford Royal	03/23/2017	25	0 (0.0%)	NA	NA
Royal Victoria Infirmary, Newcastle	04/06/2017	21	3 (14.3%)	3 (100.0%)	3 (100.0%)
John Radcliffe, Oxford	04/06/2017	11	3 (27.3%)	3 (100.0%)	3 (100.0%)
Royal Liverpool university	04/27/2017	97	6 (6.2%)	6 (100.0%)	6 (100.0%)
Wythenshawe Hospital	05/11/2017	3	0 (0.0%)	NA	NA
Countess of Chester	06/06/2017	21	2 (9.5%)	1 (50.0%)	1 (100.0%)
King's College London	07/04/2017	7	6 (85.7%)	4 (66.7%)	4 (100.0%)
Western General	07/18/2017	20	9 (45.0%)	8 (88.9%)	8 (100.0%)

Hospital	Date of site opening	Screenings [a]	Eligible (% of [a]) [b]	Eligible and consented (% of [b]) [c]	Randomised (% of [c])
Plymouth NHS Trust	07/27/2017	199	1 (0.5%)	1 (100.0%)	1 (100.0%)
Addenbrookes	08/31/2017	26	5 (19.2%)	2 (40.0%)	2 (100.0%)
Northwick Park	10/06/2017	12	3 (25.0%)	1 (33.3%)	1 (100.0%)
Royal Hallamshire	10/20/2017	41	5 (12.2%)	3 (60.0%)	3 (100.0%)
Queen Elizabeth Hospital, Birmingham	11/21/2017	4	2 (50.0%)	2 (100.0%)	2 (100.0%)
QA Hospital, Portsmouth	11/23/2017	24	2 (8.3%)	1 (50.0%)	1 (100.0%)
Devon & Exeter	01/31/2018	10	7 (70.0%)	1 (14.3%)	1 (100.0%)
Southend Hospital	02/27/2018	6	2 (33.3%)	1 (50.0%)	1 (100.0%)
Calderdale and Huddersfield	03/29/2018	23	2 (8.7%)	2 (100.0%)	2 (100.0%)
Coventry and Warwickshire	04/19/2018	3	3 (100.0%)	3 (100.0%)	3 (100.0%)
Charing Cross Hospital	04/30/2018	31	4 (12.9%)	2 (50.0%)	2 (100.0%)
Norfolk and Norwich	06/12/2018	5	4 (80.0%)	2 (50.0%)	2 (100.0%)
Lincoln County Hospital	06/12/2018	9	3 (33.3%)	1 (33.3%)	1 (100.0%)
Musgrove Park	07/10/2018	138	3 (2.2%)	2 (66.7%)	2 (100.0%)
Nottingham University Hospitals Trust	02/13/2019	19	5 (26.3%)	4 (80.0%)	4 (100.0%)
Romford	02/20/2019	8	4 (50.0%)	4 (100.0%)	4 (100.0%)
County Durham	03/26/2019	7	1 (14.3%)	1 (100.0%)	1 (100.0%)
Royal Lancaster Infirmary	06/05/2019	40	0 (0.0%)	NA	NA
Aberdeen Royal Infirmary	06/14/2019	13	5 (38.5%)	2 (40.0%)	2 (100.0%)
St Georges London	07/04/2019	2	2 (100.0%)	2 (100.0%)	2 (100.0%)
Hull	08/02/2019	1	0 (0.0%)	NA	NA
	Total	**1427**	**153 (10.7%)**	**95 (62.1%)**	**94 (98.9%)**

Table SA2: Reasons for ineligibility of screened patients

	Participant did not have suspected encephalitis	Participant not aged 16+	PCR negative	Currently receiving oral or injectable corticosteroid therapy	Immunosuppression secondary to [1]	Pre-existing indwelling ventricular devices
Total Number of patients	128	60	1149	23	13	2

[1] - Known HIV infection & CD4 count under 200cell/mm3; Biologic therapy or other immunosuppressive [azathioprine, methotrexate, ciclosporin]; Solid organ transplant on immunosuppression'; Bone marrow transplant; Currently undergoing a course of chemotherapy or radiotherapy; Known immunodeficiency syndrome [other than HIV]; Known hematological malignancy.

Neuropsychological tests

Table SA3: Summary of neuropsychological assessment battery.

Test	Cognitive domain/Index	Subtest
Weschler Memory Scale-IV (WMS-IV)[6]	*Auditory Memory Index (AMI)	Logical Memory I & II Verbal Paired Associates I & II
	Visual Memory Index (VMI)	Visual reproduction I & II Designs[d] I & II
	Immediate Memory Index (IMI)	Logical Memory I Verbal Paired Associates I Visual Reproduction I Designs I*
	Delayed Memory Index (DMI)	Logical Memory II Verbal Paired Associates II Visual Reproduction II Designs II*
Weschler Adult Intelligence Scale (WAIS-IV)[7]	Working Memory Index (WMI)	Digit Span Arithmetic
	Processing Speed Index (PSI)	Symbol Search Coding
Trail Making Test[8]	Psychomotor Speed/Attention	Trail Making Test A
	Executive Function	Trail Making Test B
Test of Premorbid Functioning (TOPF)[9]	Estimation of premorbid memory abilities	-
Addenbrookes Cognitive Examination (ACE-III)[10]	Brief cognitive screening	-
Perceived Deficits Questionnaire (PDQ)[11]	Self-report cognitive difficulties	-
Beck Depression Questionnaire[12]	Self-report symptoms of depression	-
Beck Anxiety Questionnaire[13]	Self-report symptoms of anxiety	-

* Auditory memory index and verbal memory score are the same thing; the former term is used by neuropsychologists, but in the manuscript, we use the latter term, which is more accessible to the general reader.

If inability to complete testing was related to encephalitis, the patient was attributed a score of 40, the lowest possible score.

Baseline measurements

Table SA4: additional baseline characteristics and measurements

Baseline characteristic		Dex	Control	Overall
Age (years)	N	47	47	94
	Mean (SD)	64.10 (13.44)	66.71 (15.40)	65.40 (14.43)
	Median (IQR)	66.20 (56.34,73.91)	68.84 (57.91,80.88)	67.19 (57.77,76.06)
	Min, Max	19.38,85.32	19.28,94.07	19.28,94.07
Gender				
	Female	20 (43%)	24 (51%)	44 (47%)
	Male	27 (57%)	23 (49%)	50 (53%)
	Missing			
Ethnicity				
	Asian or Asian British	2 (4%)	1 (2%)	3 (3%)
	Black/African/Caribbean/Black British	0 (0%)	1 (2%)	1 (1%)
	Mixed/multiple ethnic groups	1 (2%)	0 (0%)	1 (1%)
	Other ethnic group	0 (0%)	2 (4%)	2 (2%)
	White	43 (93%)	43 (91%)	86 (92%)
	Unobtainable	2 (4%)	1 (2%)	3 (3%)
Age categorical (years)				
	65+	25 (53%)	28 (60%)	53 (56%)
	<65	22 (47%)	19 (40%)	41 (44%)
Glasgow Coma Score at randomisation				
	9+	39 (83%)	38 (81%)	77 (82%)
	<=8	8 (17%)	9 (19%)	17 (18%)
Steroid use prior to randomisation				
	No	40 (85%)	39 (83%)	79 (84%)
	Yes	7 (15%)	8 (17%)	15 (16%)
Number of days of delay in receiving aciclovir				
	3+	8 (17%)	7 (15%)	15 (16%)
	<=2	39 (83%)	40 (85%)	79 (84%)
Days from hospital to	N			
	Mean (SD)	8.13 (4.00)	8.53 (3.30)	8.33 (3.66)

randomisation	Median (IQR)	7.00 (5.00,10.00)	8.00 (6.00,11.00)	8.00 (6.00,10.00)
	Min, Max	3.00,21.00	3.00,19.00	3.00,21.00

Continued		Dex	Control	Overall
On day of randomisation was patient in ITU/HDU?				
	No	36 (77%)	35 (74%)	71 (76%)
	Yes	11 (23%)	12 (26%)	23 (24%)
Reason(s) for admission	Uncontrolled seizures/status epilepticus	5 (45%)	5 (42%)	10 (43%)
	Requirement of ventilator support	5 (45%)	9 (75%)	14 (61%)
	Decreased conscious level	9 (82%)	7 (58%)	16 (70%)
	Requirement of cardiovascular support	1 (9%)	0 (0%)	1 (4%)
	Closer monitoring required due to altered personality or behaviour	3 (27%)	2 (17%)	5 (22%)
	Seizure then respiratory arrest	1 (9%)	0 (0%)	1 (4%)
	Worsening encephalitis	0 (0%)	1 (8%)	1 (4%)
On day of randomisation was patient receiving ventilator support				
	No	40 (85%)	38 (81%)	78 (83%)
	Yes	7 (15%)	9 (19%)	16 (17%)
Previous episodes of encephalitis *****				
	No	45 (96%)	46 (98%)	91 (97%)
	Yes	2 (4%)	1 (2%)	3 (3%)
If yes, etiology				
	HSV-2 encephalitis	1 (50%)	0 (0%)	1 (33%)
	Other	1 (50%)	1 (100%)	2 (67%)
Previous diagnosis of dementia and/or cognitive impairment				
	No	46 (98%)	46 (98%)	92 (98%)
	Yes	1 (2%)	1 (2%)	2 (2%)
Diagnosis				
	Vascular dementia	1 (100%)	1 (100%)	2 (100%)
Previous diagnosis of epilepsy				
	No	45 (96%)	44 (94%)	89 (95%)
	Yes	2 (4%)	3 (6%)	5 (5%)
Patient on at least one antiepileptic drug prior to admission				
	No	44 (94%)	45 (96%)	89 (95%)
	Yes	3 (6%)	2 (4%)	5 (5%)

Continued		Dex	Control	Overall
CSF PCR Result from LP - HSV1	Positive	41 (87%)	47 (100%)	88 (94%)
	Negative	6 (13%)	0 (0%)	6 (6%)
CSF PCR Result from LP - HSV2				
	Positive	6 (13%)	0 (0%)	6 (7%)
	Negative	40 (87%)	44 (100%)	84 (93%)
	Unobtainable	1	3	4
Peripheral white blood cell count (10^9/L)	N	47	46	93
	Mean (SD)	10.41 (3.37)	12.70 (20.15)	11.54 (14.34)
	Median (IQR)	10.29 (8.00,11.70)	9.62 (8.00,11.70)	10.00 (8.00,11.70)
	Unobtainable	0	1	1
Sodium (mmol/L)	N	47	46	93
	Mean (SD)	131.17 (6.41)	132.80 (4.50)	131.98 (5.58)
	Median (IQR)	133.00 (126.00,135.00)	132.50 (130.00,136.00)	133.00 (129.00,136.00)
	Min, Max	113.00,142.00	123.00,142.00	113.00,142.00
	Unobtainable	0	1	1
Prior to admission was patient in paid employment?				
	No	24 (55%)	31 (69%)	55 (62%)
	Yes	20 (45%)	14 (31%)	34 (38%)
	N/A	3	0	3
	Unobtainable	0	2	2
If not in work, was patient a student?	Unobtainable	0 (0%)	1 (3%)	1 (2%)
	No	22 (92%)	30 (97%)	52 (95%)
	Yes	2 (8%)	0 (0%)	2 (4%)
Is the patient known to take recreational drugs?				
	No	39 (98%)	38 (100%)	77 (99%)
	Yes	1 (3%)	0 (0%)	1 (1%)
	N/A	7	7	14
	Unobtainable	0	2	2

Continued		Dex	Control	Overall
Does the patient drink alcohol?				
	No	16 (42%)	16 (41%)	32 (42%)
	Yes	22 (58%)	23 (59%)	45 (58%)
	N/A	7	7	14
	Unobtainable	2	1	3
Fever (>37.5)				
	No	9 (19%)	4 (9%)	13 (14%)
	Yes	38 (81%)	43 (91%)	81 (86%)
Headache				
	No	12 (32%)	14 (33%)	26 (33%)
	Yes	26 (68%)	28 (67%)	54 (68%)
	Not recorded in the notes	9	5	14
Seizures				
	No	23 (53%)	22 (49%)	45 (51%)
	Yes	20 (47%)	23 (51%)	43 (49%)
	Not recorded in the notes	4	2	6
Olfactory hallucinations				
	No	23 (92%)	23 (82%)	46 (87%)
	Yes	2 (8%)	5 (18%)	7 (13%)
	Not recorded in the notes	22	19	41
Abbreviated mental test (AMT) done				
	No	39 (83%)	36 (77%)	75 (80%)
	Yes	8 (17%)	11 (23%)	19 (20%)
Abbreviated mental test (AMT) score	N	8	10	18
	Mean (SD)	6.63 (3.07)	7.10 (1.85)	6.89 (2.40)
	Median (IQR)	7.00 (4.00,9.50)	7.00 (5.00,9.00)	7.00 (5.00,9.00)
	Min, Max	2.00,10.00	5.00,10.00	2.00,10.00
	N/A	39	37	76
Shortened AMT score	N	0	1	1
	Mean (SD)		2.00 (.)	2.00 (.)
	Median (IQR)		2.00 (2.00,2.00)	2.00 (2.00,2.00)
	Min, Max		2.00,2.00	2.00,2.00
	N/A	47	46	93
Photophobia				
	Absent	18 (69%)	17 (68%)	35 (69%)
	Present	8 (31%)	8 (32%)	16 (31%)

Continued		Dex	Control	Overall
Neck stiffness/signs of meningism				
	Absent	24 (75%)	19 (86%)	43 (80%)
	Present	8 (25%)	3 (14%)	11 (20%)
Dysphasia				
	Absent	14 (45%)	13 (38%)	27 (42%)
	Present	17 (55%)	21 (62%)	38 (58%)
CSF white blood cells (mm^3)	N	43	41	84
	Mean (SD)	195.81 (252.84)	135.28 (224.12)	166.27 (239.75)
	Median (IQR)	100.00 (17.00,271.00)	52.00 (11.00,121.00)	69.50 (11.80,235.50)
	Min, Max	1.00,1150.00	1.00,1200.00	1.00,1200.00
	Missing	1	0	1
	N/A	3	6	9
CSF red blood cells (mm^3)	N	44	42	86
	Mean (SD)	174.16 (365.32)	900.26 (4632.78)	528.77 (3248.59)
	Median (IQR)	20.00 (4.50,105.50)	19.50 (1.00,90.00)	19.50 (3.00,93.00)
	Min, Max	0.00,1721.00	0.00,30000.00	0.00,30000.00
	Unobtainable	1	0	1
	N/A	2	5	7
CSF lymphocytes (%)	N	34	25	59
	Mean (SD)	86.91 (21.82)	81.32 (25.42)	84.54 (23.36)
	Median (IQR)	95.00 (90.00,100.00)	90.00 (75.00,100.00)	92.00 (81.00,100.00)
	Min, Max	18.00,102.00	4.00,100.00	4.00,102.00
	Unobtainable	2	2	4
	N/A	11	17	28
CSF neutrophils (%)	N	13	13	26
	Mean (SD)	4.85 (5.60)	5.14 (4.34)	4.99 (4.91)
	Median (IQR)	4.00 (0.00,5.00)	4.00 (1.00,10.00)	4.00 (0.00,10.00)
	Min, Max	0.00,17.00	0.00,10.00	0.00,17.00
	N/A	34	34	68
CSF glucose (mmol/L)	N	41	40	81
	Mean (SD)	3.41 (0.75)	3.59 (0.87)	3.50 (0.81)
	Median (IQR)	3.40 (3.00,3.80)	3.55 (2.90,4.25)	3.40 (2.90,3.90)
	Min, Max	1.90,5.80	1.90,5.70	1.90,5.80
	N/A	6	7	13
Paired serum glucose (mmol/L)	N	15	17	32
	Mean (SD)	5.73 (1.05)	6.42 (2.10)	6.10 (1.70)
	Median (IQR)	5.20 (4.90,6.50)	5.80 (5.00,6.80)	5.80 (4.95,6.65)

	Min, Max	4.30,7.90	4.30,11.70	4.30,11.70
	N/A	32	30	62
Opening pressure (mm)	N	13	13	26
	Mean (SD)	39.90 (56.65)	33.00 (45.96)	36.45 (50.67)
	Median (IQR)	18.00 (15.00,21.00)	23.00 (20.00,24.50)	20.50 (15.00,24.50)
	Min, Max	7.50,190.00	11.00,185.00	7.50,190.00
	Unobtainable	3	2	5
	N/A	31	32	63
MRI scan				
	No	6 (13%)	4 (9%)	10 (11%)
	Yes	41 (87%)	43 (91%)	84 (89%)
MRI scan contraindicated				
	No	4 (67%)	2 (50%)	6 (60%)
	Yes	2 (33%)	2 (50%)	4 (40%)
	N/A	41	43	84

- Although theoretically patients could have been included in the study more than

Treatment compliance

Table SA5: aciclovir compliance summary by treatment group

	Control (N=46)		Dexamethasone (N=46)	
	Days on treatment	Doses missed	Days on treatment	Doses missed
Mean (SD)	21.60 (5.73)	0.78 (1.72)	21.31 (5.35)	1.07 (2.11)
Median (IQR)	22 (18, 25)	0 (0, 1)	21 (17, 23)	0 (0, 2)
Range	9 to 45	14 to 41	0 to 8	0 to 11

Table SA6: dosage information for control patients receiving dexamethasone before randomisation

Patient	Dose	Frequency	day started (relative to day of randomisation)	day stopped (relative to day of randomisation)	Number of days from start to stop (inclusive)
1	8mg	Twice daily	-6	0	7
2	3.3mg	three times daily	-5	-4	2
3	6.6mg	single dose	-6	-6	1
4	6.6mg	single dose	-5	-5	1
5	4mg	four times daily	-4	-2	3
6	9.9mg	four times daily	-3	-3	1
7	9.9mg	four times daily	-6	-5	2

Table SA7: number of doses of dexamethasone received in those randomised to dexamethasone.

Number of doses (16 specified in protocol)	Number of participants
0	1 (2.1%)
12	1 (2.1%)
13	3 (6.4%)
14	1 (2.1%)
15	6 (12.8%)
16	32 (68.1%)
17	2 (4.3%)
19	1 (2.1%)

Additional safety data

Table SA8: Notable events

Notable Event	Control		Dexamethasone	
	Number of events	Number of participants (% of 47)	Number of events	Number of participants (% of 45)
Gastrointestinal Bleed	2	2 (4.3%)	1	1 (2.2%)
Severe or unexpected neuropsychiatric events	6	5 (10.6%)	3	2 (4.4%)
New onset severe depression or worsening depression	2	2 (40.0%)	1	1 (50.0%)
New onset severe paranoia or worsening paranoia	0	-	0	-
New onset suicidal thoughts	2	2 (40.0%)	1	1 (50.0%)
New onset delusions	1	1 (20.0%)	1	1 (50.0%)
New visual or auditory hallucinations	1	1 (20.0%)	0	-
New onset psychosis	0	-	0	-
Event lead to:				
Addition or increase in dose of neuropsychiatric medication	2	2 (40.0%)	0	-
Decrease in the dose/stopping of dexamethasone	0	-	0	-
Referral for psychiatry review	1	1 (20.0%)	1	1 (50.0%)
Hyperglycemia requiring change in medical management	3	2 (4.3%)	3	2 (4.4%)
Increased insulin dose	1	1 (50.0%)	1	1 (50.0%)
Prescribe new insulin (either regular or STAT dose/s)	2	2 (100.0%)	1	1 (50.0%)
Increased dose of oral hypoglycemics	0	-	0	-
Prescribing of new oral hypoglycemics	0	-	1	1 (50.0%)
Decrease in dexamethasone dose in response to hypergycemia	0	-	0	-
Dexamethasone stopped early in response to hyperglycemia	0	-	0	-
Gastrointestinal infection	0	-	0	-
Culture result				
Negative	0	-	0	-
Positive	0	-	0	-
Not done	0	-	0	-
Antibiotics prescribed				
Yes	0	-	0	-
No	0	-	0	-
Intraabdominal infection	0	-	0	-
Culture result				
Negative	0	-	0	-
Positive	0	-	0	-
Not done	0	-	0	-
Antibiotics prescribed				

Notable Event	Control		Dexamethasone	
	Number of events	Number of participants (% of 47)	Number of events	Number of participants (% of 45)
Yes	0	-	0	-
No	0	-	0	-
Pneumonia	5	5 (10.6%)	9	9 (20.0%)
Culture result				
Negative	1	1 (20.0%)	3	3 (33.3%)
Positive	3	3 (60.0%)	3	3 (33.3%)
Not done	0	-	3	3 (33.3%)
Missing	1	1 (20.0%)	0	-
Antibiotics prescribed				
Yes	1	5 (100%)	9	9 (100%)
No	0	-	0	-
Blood stream infection	1	1 (2.1%)	1	1 (2.2%)
Blood stream infection of unknown origin	1	1 (100%)	1	1 (100%)
Secondary blood stream infection	0	-	0	-
Intravascular catheter related sepsis	0	-	0	-
Culture result				
Negative	0	-	1	1 (100%)
Positive	1	1 (100%)	0	-
Not done	0	-	0	-
Antibiotics prescribed				
Yes	1	1 (100%)	0	-
No	0	-	1	1 (100%)
Soft tissue	2	2 (4.3%)	2	2 (4.4%)
Culture result				
Negative	1	1 (50.0%)	0	-
Positive	1	1 (50.0%)	0	-
Not done	0	-	2	2 (100%)
Antibiotics prescribed				
Yes	2	2 (100%)	1	1 (50.0%)
No	0	-	1	1 (50.0%)
Clostridium Difficile Infection	1	1 (2.1%)	0	-
Culture result				
Negative	0	-	0	-
Positive	1	1 (100%)	0	-
Not done	0	-	0	-
Antibiotics prescribed				
Yes	1	1 (100%)	0	-
No	0	-	0	-
Urinary system	1	1 (2.1%)	0	-
Culture result				
Negative	0	-	0	-
Positive	1	1 (100%)	0	-
Not done	0	-	0	-
Antibiotics prescribed				
Yes	1	1 (100%)	0	-

Notable Event	Control		Dexamethasone	
	Number of events	Number of participants (% of 47)	Number of events	Number of participants (% of 45)
No	0	-	0	-
Urinary tract infection	5	5 (10.6%)	6	6 (13.3%)
Culture result				
Negative	0	-	1	1 (16.7%)
Positive	5	5 (100.0%)	4	4 (66.7%)
Not done	0	-	1	1 (16.7%)
Antibiotics prescribed				
Yes	5	5 (100.0%)	6	6 (100.0%)
No	0	-	0	-
Herpes	1	1 (2.1%)	0	-
Type: Herpes zoster (shingles)	1	1 (100.0%)	0	-
Type: Chicken pox	0	-	0	-
Type: Herpes liabilis (cold sores) or genital herpes	0	-	0	-
Total	27	18 (38.3%)	25	18 (40.0%)

Table SA9: Serious Adverse events in the control group

Participant	System Organ Class	Preferred Term	Date of event / Weeks since randomisation	Severity	Seriousness	Expectedness	PI/CI assessment of relationship to drug	Outcome
R000460059	Nervous system disorders	Seizure	20APR2020 / 26	Moderate	Required Hospitalisation	N/A	N/A	Completed trial
R000500007	Nervous system disorders	Hepatic encephalopathy	02FEB2017 / 0	Mild	Medically significant / important	N/A	N/A	Withdrew from trial on 07APR2017 / Date of last visit 07APR2017
R000500007	Metabolism and nutrition disorders	Dehydration	02FEB2017 / 0	Moderate	Medically significant / important	N/A	N/A	Withdrew from trial on 07APR2017 / Date of last visit 07APR2017
R000820009	Injury, poisoning and procedural complications	Fall	19DEC2017 / 24	Moderate	Required Hospitalisation	N/A	N/A	Completed trial
R000820009	Nervous system disorders	Frontotemporal dementia	24SEP2017 / 12	Severe	Required Hospitalisation	N/A	N/A	Completed trial
R001610052	Psychiatric disorders	Suicidal ideation	26MAY2019 / 5	Mild	Required Hospitalisation	N/A	N/A	Participant deceased on 22APR2020
R001610052	Psychiatric disorders	Cognitive disorder	21MAY2019 / 4	Mild	Required Hospitalisation	N/A	N/A	Participant deceased on 22APR2020

R001610052	Injury, poisoning and procedural complications	Fall	28DEC2019 / 35	Mild	Required Hospitalisation	N/A	N/A	Participant deceased on 22APR2020

Table SA10: Serious Adverse Events (SAEs) in the dexamethasone group

Participant	System Organ Class	Preferred Term	Date of event / Weeks since randomisation	Severity	Seriousness	Expectedness	PI/CI assessment of relationship to drug	Outcome
R000210002	Vascular disorders	Deep vein thrombosis	24OCT2016 / 1	Moderate	Prolonged existing hospitalisation	Unexpected	Unrelated / Unrelated	Completed trial
R000210002	Vascular disorders	Deep vein thrombosis	27JAN2017 / 14	Mild	Medically significant / important	Unexpected	Unrelated / Unrelated	Completed trial
R000210002	Nervous system disorders	Encephalitis autoimmune	20FEB2017 / 18	Severe	Required Hospitalisation;Prolonged existing hospitalisation	Unobtainable	Unrelated / Unrelated	Completed trial
R000310006	Infections and infestations	Meningoencephalitis herpetic	12JUN2017 / 22	Severe	Required Hospitalisation	Unexpected	Probably / Unlikely	Completed trial
R000310006	Nervous system disorders	Headache	03MAY2017 / 16	Mild	Required Hospitalisation	Unexpected	Possibly / Unlikely	Completed trial
R000360039	Nervous system disorders	Status epilepticus	18DEC2018 / 4	Severe	Required Hospitalisation	Unobtainable	Unlikely / Unlikely	Withdrew from trial on 04NOV2020 / Date of last visit 17DEC2018
R000360039	Nervous system disorders	Seizure	22JAN2019 / 9	Moderate	Required Hospitalisation	Unobtainable	Unlikely / Unrelated	Withdrew from trial on 04NOV2020 / Date of last visit 17DEC2018

R000360039	Nervous system disorders	Partial seizures	26MAR2019 / 18	Moderate	Required Hospitalisation	Unobtainable	Unlikely / Unlikely	Withdrew from trial on 04NOV2020 / Date of last visit 17DEC2018
R000360039	Nervous system disorders	Partial seizures	07MAY2019 / 24	Severe	Required Hospitalisation	Unobtainable	Unrelated / Unlikely	Withdrew from trial on 04NOV2020 / Date of last visit 17DEC2018
R000360039	Nervous system disorders	Seizure	05AUG2019 / 36	Severe	Required Hospitalisation	Unobtainable	Unlikely / Unlikely	Withdrew from trial on 04NOV2020 / Date of last visit 17DEC2018
R000500012	Infections and infestations	Lower respiratory tract infection	05OCT2017 / 1	Moderate	Prolonged existing hospitalisation	Unexpected	Unrelated / Unrelated	Participant deceased on 22JAN2018
R000500012	Renal and urinary disorders	Acute kidney injury	18OCT2017 / 3	Moderate	Medically significant / important	Unexpected	Unrelated / Unrelated	Participant deceased on 22JAN2018
R000890026	Nervous system disorders	Peroneal nerve palsy	02JUL2018 / 2	Severe	Persistent or significant disability / incapacity	Unobtainable	Unlikely / Unlikely	Completed trial
R002130090	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	29SEP2021 / 2	Severe	Prolonged existing hospitalisation;Medically significant / important	Unexpected	Unlikely / Unrelated	Completed trial

R003500083	Nervous system disorders	Encephalitis autoimmune	17AUG2021 / 9	Moderate	Prolonged existing hospitalisation;Persistent or significant disability / incapacity	Unobtainable	Unrelated / Unobtainable	Completed trial

Sensitivity analyses

Sensitivity analysis 1

Table SA11: model estimates adjusting for estimates of premorbid functioning (immediate memory and delayed memory) using the test of premorbid functioning (TOPF) scale.

Variable	Estimate (SE)	95% CI	P-value
Intercept	-20.56 (109.93)	-241.48, 200.36	-
Dexamethasone vs Control	**-0.16 (4.46)**	**-9.11, 8.8**	**0.9723**
Age (<65 vs 65+)	-3.48 (6.23)	-15.99, 9.03	-
Steroid use since admission (yes vs no)	9.73 (5.73)	-1.79, 21.24	-
Glasgow Coma Score (≤8 vs 9+)	-20.04 (6.86)	-33.84, -6.25	-
Delay in acyclovir administration (≤2 vs 3+ days)	1.68 (6)	-10.38, 13.73	-
Estimate of premorbid delayed memory	9.17 (29.97)	-51.06, 69.4	
Estimate of premorbid immediate memory	-7.92 (30.98)	-70.18, 54.34	

Note: 57 participants were included within the model

Sensitivity analysis 2

Table SA12: model estimates exploring the subgroup of participants who did not receive dexamethasone between admission and randomisation.

Variable	Estimate (SE)	95% CI	P-value
Intercept	68.91 (8.75)	51.42, 86.41	-
Dexamethasone vs Control	**-0.94 (5.8)**	**-12.54, 10.65**	**0.8716**
Age (<65 vs 65+)	-10.54 (5.86)	-22.24, 1.17	-
Steroid use since admission (yes vs no)	8.66 (11.31)	-13.95, 31.26	-
Glasgow Coma Score (≤8 vs 9+)	8.13 (7.76)	-7.37, 23.64	-
Delay in acyclovir administration (≤2 vs 3+ days)	3.48 (7.96)	-12.43, 19.39	-

Note: 69 participants were included within the model

Sensitivity analysis 3

Table SA13: Sensitivity analysis 3 excluding control participants who received dexamethasone in the first 30 days since randomisation.

Variable	Estimate (SE)	95% CI	P-value
Intercept	65.15 (9.39)	46.42, 83.88	-
Dexamethasone vs Control	**4.14 (5.78)**	**-7.38, 15.65**	**0.4763**
Age (<65 vs 65+)	-7.85 (5.92)	-19.64, 3.95	-
Steroid use since admission (yes vs no)	4.95 (7.48)	-9.97, 19.87	-
Glasgow Coma Score (≤8 vs 9+)	6.11 (8.05)	-9.94, 22.17	-
Delay in acyclovir administration (≤2 vs 3+ days)	1.95 (7.44)	-12.89, 16.79	-

Note: 77 participants were included within the model

Sensitivity analysis 4

Sensitivity analysis 4: those who were judged by the neuropsychologist as too ill to complete the assessment had their primary outcome imputed using ACE-III and GOS scores. Sensitivity analysis 4 was not carried out, as none of the participants judged as too ill had both valid GOS and ACE scores.

Sensitivity analysis 5

Multiple imputation to assess robustness of results to missing data, under the assumption of missing at random. Variables included in the imputation model included all stratification factors, outcomes from WMS-IV and WAIS-IV, ACE-III, Glasgow Outcome Score, and

estimates of premorbid functioning. 1000 data sets were imputed using PROC MI in SAS, and results combined using PROC MIANALYZE.

Table SA14: Combined estimate of treatment effect from multiple imputation analysis

Variable	Estimate (SE)	95% CI	P-value
Dexamethasone vs Control	**1.36 (5.70)**	**-9.81, 12.54**	**0.811**

Table SA15: Further sensitivity analyses

Analysis	Participants included in analysis (Dexamethasone/Control	Estimate (SE) Dexamethasone vs Control	95% CI	P-value
Primary analysis	39/42	1.77 (5.70)	-9.57, 13.12	0.7564
Pre-specified sensitivity analyses				
Adjusting for estimates of premorbid functioning	30/27	-0.16 (4.46)	-9.11, 8.80	0.9723
Excluding those receiving dexamethasone between admission and randomisation	33/36	-0.94 (5.80)	-12.54, 10.65	0.8716
Excluding control participants who received dexamethasone in the first 30 days since randomisation	39/38	4.14 (5.78)	-7.38, 15.65	0.4763
Multiple imputation model	47/47	1.36 (5.70)	-9.81, 12.54	0.8110
Post-hoc sensitivity analyses				
Excluding all patients with imputed PO scores	33/33	-1.35 (5.85)	-13.04, 10.34	0.8181
Excluding control participants who received dex before or after randomisation, and dexamethasone patient who did not receive dexamethasone	38/33	0.17 (6.07)	-11.97, 12.30	0.9783
Excluding patients who died before PO	35/38	2.21 (5.91)	-9.57, 14.01	0.7093

Post-hoc analysis

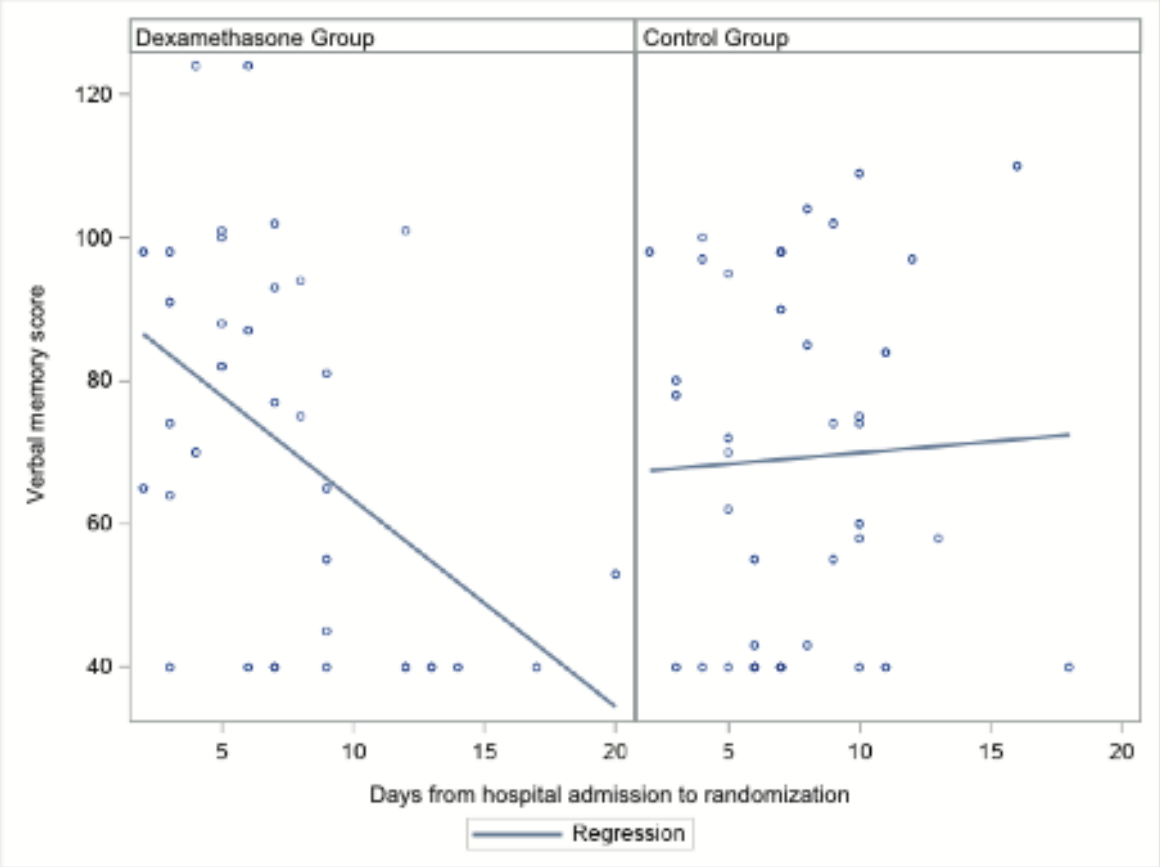


Figure SA2: Scatterplot showing the association between time to randomisation and verbal memory score for patients in the dexamethasone group (left) and placebo group (right)

post-hoc regression analyses explored the association between primary outcome and time to dexamethasone and time to randomisation. Left, patients in the dexamethasone arm and right, patients in the control arm, showing the association between time to randomisation and verbal memory score. Adjusting for known prognostic factors (time to aciclovir treatment (≤2 vs 3+ days), age (<65 vs 65+ years), and Glasgow Coma Scale score at admission (≤8 vs 9+)) and time to randomisation, the estimated effect of dexamethasone vs control on verbal memory was 7.74 points, (95%CI: -4·26–19·74, p=0.20).

Additional neuropsychology, Quality of Life, and functional outcomes

Table SA16: Secondary outcomes at week 26 and week 78.

	Dexamethasone		**Control**		**difference, hazard ratio or odds ratio (95% CI)***	**p value**
	N		N			
Secondary neuropsychology outcomes at 78 weeks						
Verbal memory (WMS-IV) at 78 weeks	18	70 (30)	23	71 (24)	-2.31 (19.04, 14.42)	0.78
Visual memory (WMS-IV)	15	70 (29)	19	78 (23)	-8.59 (-25.7, 8.52)	0.31
Immediate memory (WMS-IV)	15	71 (29)	19	74 (22)	-4.46 (-22.2, 13.27)	0.61
Delayed memory (WMS-IV)	15	69 (32)	19	69 (22)	-0.34 (-18.5, 17.82)	0.97
Working memory (WAIS-IV)	17	83 (29)	21	86 (26)	-3.99 (-22.33, 14.34)	0.66
Processing speed (WAIS-IV)	14	77 (29)	20	86 (27)	-10.28 (-28.82, 8.27)	0.27
Trail Making Test A (seconds)	14	120 (121)	20	101 (106)	22.65 (-48.19, 93.49)	0.52
Trail Making Test B (seconds)	14	176 (119)	20	176 (98)	0.99 (-72.00, 73.98)	0.98
ACE-III	10	78 (22)	15	80 (14)	-0.18 (-16.2, 15.84)	0.98
Perceived deficits questionnaire	10	34 (15)	15	26 (14)	9.63 (-3.79, 23.04)	0.15
Beck Anxiety Inventory	11	13 (10)	16	5 (4)	8.45 (2.34, 14.56)	0.009
Beck Depression Inventory	11	17 (13)	16	10 (9)	8.05 (-1.98, 18.08)	0.11
Clinical outcomes						
Frequency of seizures 78 weeks	23	8 (35%)	25	6 (24%)	1.63 (0.43, 6.22)	0.47
Quality of Life outcomes						
SF-36						

Physical functioning	18	61 (34)	19	72 (38)	-13.86 (-37.15, 9.43)	0.23
Physical role limitations	18	55 (35)	19	70 (34)	-18.88 (-45.74, 7.98)	0.16
Bodily pain	18	61 (27)	19	80 (27)	-18.98 (-39.31, 1.34)	0.066
General health perceptions	18	47 (25)	19	70 (23)	-22.66 (-40.70, -4.61)	0.015
Energy/vitality	18	45 (28)	19	61 (22)	-15.05 (-34.13, 4.04)	0.12
Social functioning	18	56 (33)	19	72 (32)	-15.88 (-39.82, 8.06)	0.19
Emotional role limitations	18	61 (38)	19	80 (28)	-18.06 (-43.15, 7.02)	0.15
Mental health	18	63.33 (22.36)	19	72.65 (17.6)	-11.24 (-25.53, 3.05)	0.12
EQ-5D-5L	17	63 (20)	16	78 (24)	-15.81 (-32.84, 1.22)	0.068

*Models adjusted for age (<65 vs 65+), steroid use since admission, Glasgow Coma Score (≤8 vs 9+), and delay in aciclovir treatment (≤2 vs 3+ days)

Table SA17: Functional outcomes at 30 days/discharge, week 26 and week 78.

	Dexamethasone		Control		Difference (95% CI)*	p value
	N		N			
30 day/discharge functional outcome						
Modified Rankin Scale	43	2.51 (1.70)	41	2.85 (1.49)	-0.40 (-0.95, 0.14)	0.14
Barthel index	43	13.47 (8.17)	41	13.63 (7.53)	0.34 (-2.03, 2.70)	0.78
Liverpool Outcome Score	39	2.74 (0.79)	41	2.68 (0.72)	0.07 (-0.24, 0.38)	0.65
Week 26 functional outcome						
Modified Rankin Scale	35	1.86 (1.33)	33	1.85 (1.56)	-0.02 (-0.68, 0.72)	0.96
Barthel index	35	17.17 (5.16)	33	17.06 (5.34)	0.39 (-2.00, 2.78)	0.75
Liverpool Outcome Score	35	3.20 (0.96)	30	3.43 (1.04)	-0.23 (-0.73, 0.26)	0.35
Week 78 functional outcome						
Modified Rankin Scale	22	1.59 (1.18)	22	1.64 (1.53)	0.05 (-0.77, 0.88)	0.89
Barthel index	22	18.91 (1.63)	22	16.77 (5.74)	1.84 (-0.62, 4.30)	0.14
Liverpool Outcome Score	21	3.57 (0.98)	22	3.36 (1.14)	0.15 (-0.55, 0.84)	0.67

*Models adjusted for age (<65 vs 65+), steroid use since admission, Glasgow Coma Score (≤8 vs 9+), and delay in aciclovir treatment (≤2 vs 3+ days)

Kaplan Meier plots of clinical outcomes

Figure SA3: Time to hospital discharge

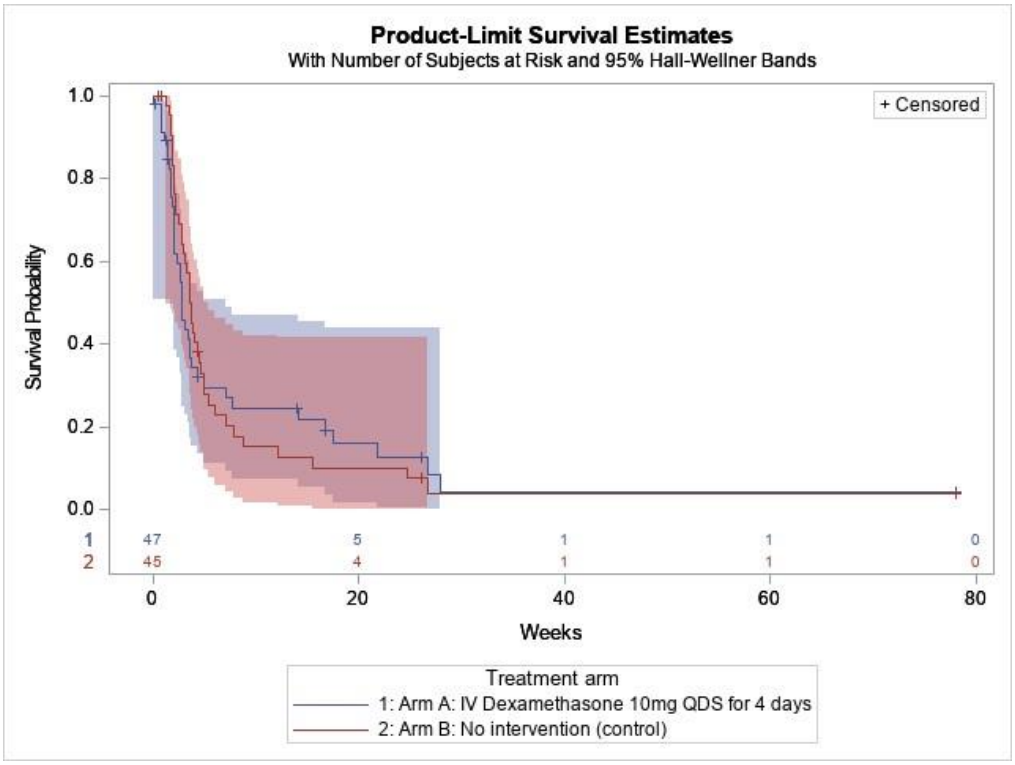
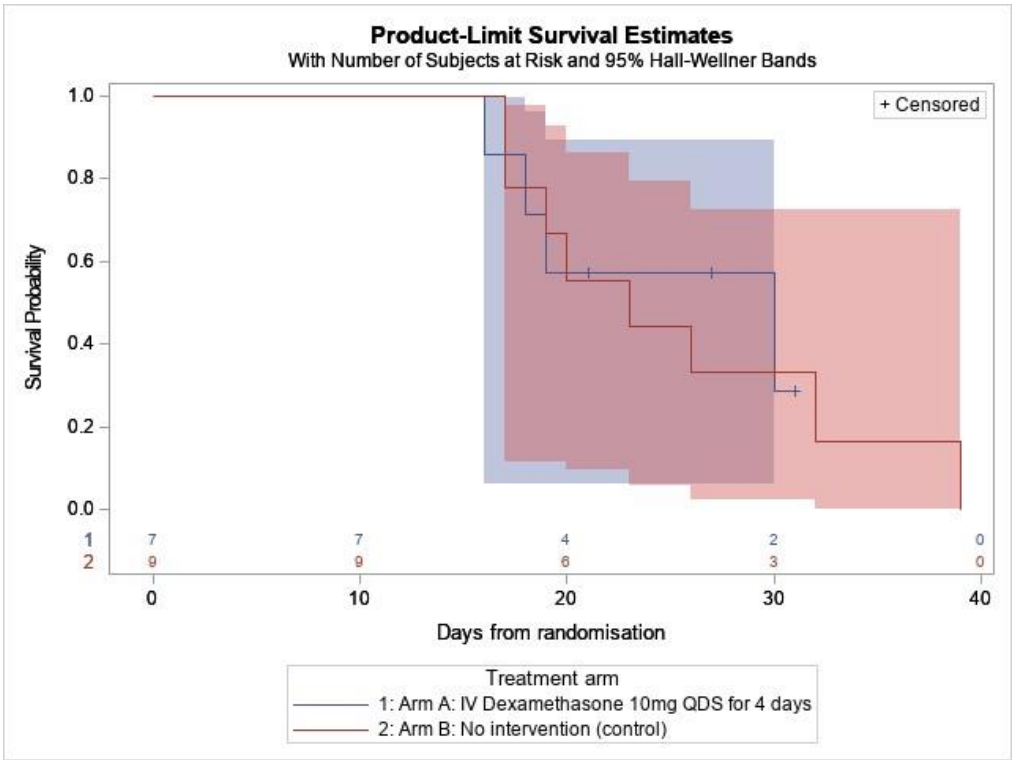
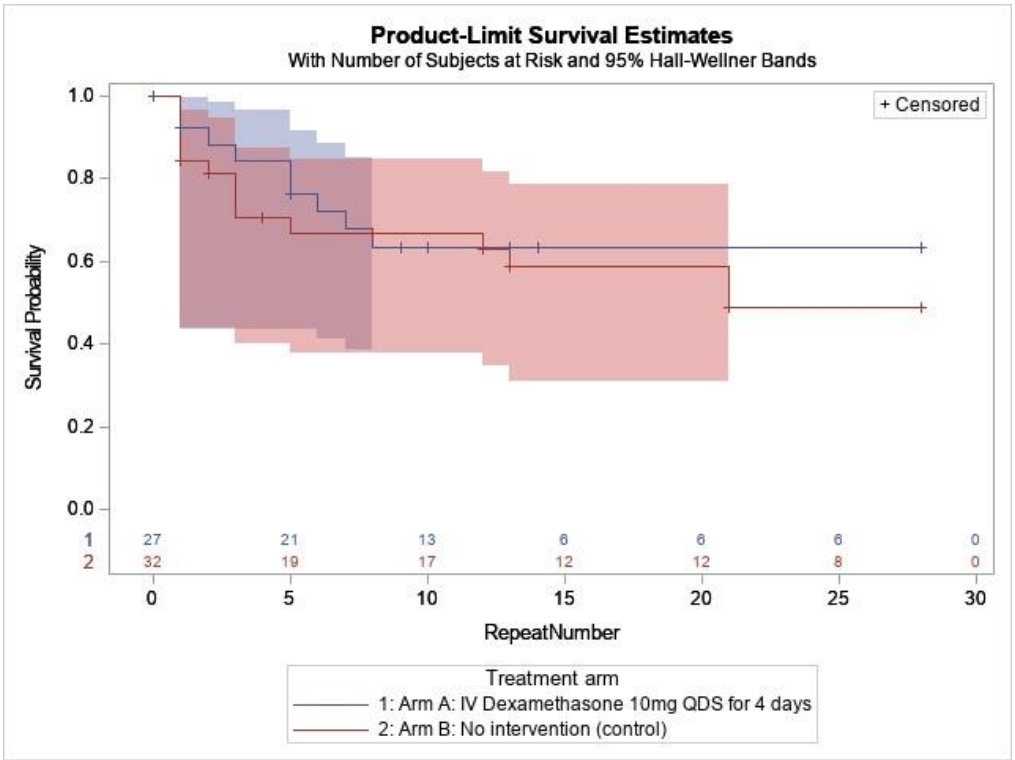


Figure SA4: Time to reach 14 days without ventilator support.



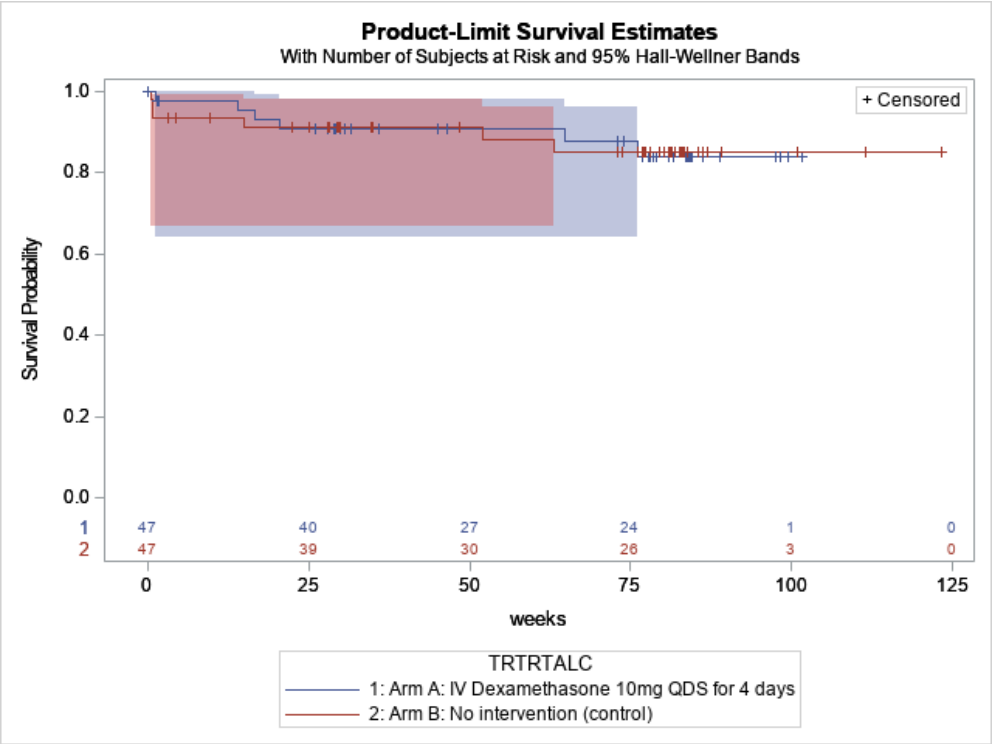
This analysis includes the subset of patients on ventilator support at the time randomisation. Curves cross several times, so Cox PH model not fitted

Figure SA5: Time to reach maximum recorded Glasgow Coma Score.



Curves cross several times, so Cox PH model is not fitted

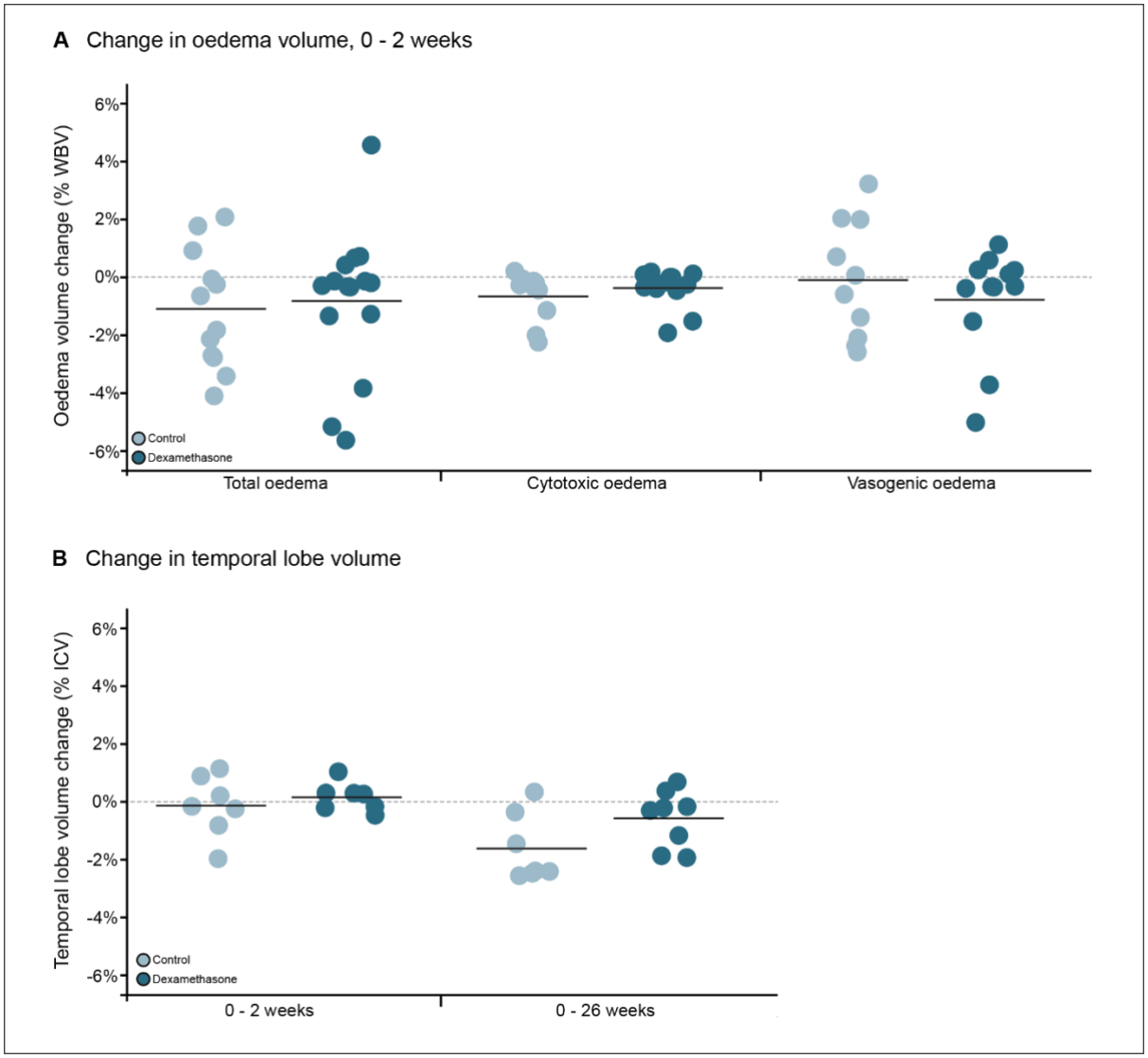
Figure SA6: Survival



As survival curves overlap several times, no further analysis was carried out.

MRI outcomes

Figure SA7: Secondary MRI outcomes



The mean and individual patient values are shown for volume change in total oedema, cytotoxic oedema and vasogenic oedema (left to right) between baseline and week two magnetic resonance imaging (MRI) scans (A).

change in volume of the most affected temporal lobe between baseline and two weeks and baseline and 26 weeks (B). The mean is indicated by a solid bar, and individual patient values are light blue for

control group and dark blue for dexamethasone group. Percentages are presented as percentage points. WBV = whole brain volume. ICV = intracranial volume.

Between baseline and week two total oedema decreased by 1·1% (SD 2.0) in the control group and by 0·8% (SD 2·5) in the dexamethasone group (adjusted difference, -0·31; 95% CI, -2·17, 1.55; P=0·73); cytotoxic oedema decreased on average by 0·7% in the control group and by 0·4% in the dexamethasone group (adjusted difference, 0.14; 95% CI, -0.12, 0.41; P=0·27); vasogenic oedema reduced by 0·1% (SD 2.0) in the control group, and 0·8% (SD 1·8) in the dexamethasone group (adjusted difference, -1.83; 95% CI, -4.27, 0.62; P=0·13).

Quantitative longitudinal analysis of MRI scans between baseline and week two showed a decrease in temporal lobe volume of the most affected side by 0·1% (SD 1·1) in the control group and an increase in the dexamethasone group by 0·2% (SD 0·5), however, there were no significant differences between the two groups (adjusted difference, -0·21; 95% CI, -1·11, 0·69; P=0·57). At 26 weeks, temporal lobe volume in the control group decreased by 0·6% (SD 1·2) compared to baseline, and by 0·6% (SD 1.0) in the dexamethasone (adjusted difference, 0·42; 95% CI, -0·65, 1·49; P=0·38).

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10.2 Appendix B – Chapter 4

Table SB1: sensitivity analysis: difference between patients with and without 78 week assessment

variable	26 Only	26 and 78	P value
total number	34	32	
Age (IQR)	16	17.5	0.216592976
Age (Mean)	65.79310345	60.8125	
Age (Median)	67	62.5	
Age (SD)	11.32437103	15.46992399	
Not admitted to ICU, %	93.33333333	96.875	0.606557377
Admitted to ICU, %	6.666666667	3.125	
Discharged before 30 days, %	53.33333333	68.75	0.297548478
Inpatient after 30 days, %	46.66666667	31.25	
Male, %	55.17241379	59.375	0.799135723
Female, %	44.82758621	40.625	
No seizures, %	83.33333333	90.625	0.466720554
Had Seizures, %	16.66666667	9.375	
Education, years, IQR	3.5	4.25	
Education, years, Mean	12.06896552	12.48214286	
Education, years, Median	11	12	0.532929981
Education, years, SD	2.658289387	2.492515251	
AMI Z (IQR) at 26 weeks	2.333333333	2.866666667	
AMI Z (mean) at 26 weeks	-1.566666667	-1.5125	
AMI Z (median) at 26 weeks	-1.666666667	-1.233333333	0.862294261
AMI Z (SD) at 26 weeks	1.471731384	1.613779153	
VMI Z (IQR) at 26 weeks	2	2.25	
VMI Z (mean) at 26 weeks	-1.565079365	-1.24047619	
VMI Z (median) at 26 weeks	-1.4	-0.8	0.292511361
VMI Z (SD) at 26 weeks	1.418390175	1.428843302	
IMI Z (IQR) at 26 weeks	1.866666667	1.95	
IMI Z (mean) at 26 weeks	-1.485714286	-1.457142857	
IMI Z (median) at 26 weeks	-1.266666667	-1.233333333	0.855565
IMI Z (SD) at 26 weeks	1.382291633	1.45751514	
DMI Z (IQR) at 26 weeks	2	2.45	

DMI Z (mean) at 26 weeks	-1.631746032	-1.730952381	
DMI Z (median) at 26 weeks	-1.6	-1.5	0.919398887
DMI Z (SD) at 26 weeks	1.394850697	1.539866078	
WMI Z (IQR) at 26 weeks	1.483333333	1.166666667	
WMI Z (mean) at 26 weeks	-0.5	-0.308333333	
WMI Z (median) at 26 weeks	-0.266666667	-0.166666667	0.588584591
WMI Z (SD) at 26 weeks	1.08324615	1.037193622	
PSI Z (IQR) at 26 weeks	1.366666667	1.15	
PSI Z (mean) at 26 weeks	-1.072463768	-0.471428571	
PSI Z (median) at 26 weeks	-0.933333333	-0.266666667	0.044284463
PSI Z (SD) at 26 weeks	1.138652942	0.912812967	
TRAIL A Z (IQR) at 26 weeks	1.8	1.8	
TRAIL A Z (mean) at 26 weeks	-1.368181818	-0.874074074	
TRAIL A Z (median) at 26 weeks	-1.3	-0.8	0.165056928
TRAIL A Z (SD) at 26 weeks	1.271813989	1.317512981	
TRAIL B Z (IQR) at 26 weeks	1.8	1.65	
TRAIL B Z (mean) at 26 weeks	-1.276190476	-0.8	
TRAIL B Z (median) at 26 weeks	-1.3	-0.8	0.360017587
TRAIL B Z (SD) at 26 weeks	1.339367299	1.425320477	

Table SB2: differences between patients with complete and incomplete cognitive outcomes at 26 weeks.

Characteristic	Complete_Median_or_Percentage	Complete_Range	Incomplete_Median_or_Percentage	Incomplete_Range	p_value
Age	61	19-87	70	19-88	0.026
Years of education	12	8-18	11	8-17	0.688
Sex (Female)	36%	.	50%	NA	0.270
Sex (Male)	64%	.	50%	NA	0.270
Discharged Before 30 Days	75%	.	44%%	NA	0.006
Admitted to ITU, yes	3.4%	.	5.6%%	NA	1
Seizures, yes	8.5%	.	19.4%	NA	0.214

Table SB3: All correlation results between cognitive functioning and psychological and patient characterisitics.

		AMI_Z	VMI_Z	WMI_Z	PSI_Z	TRAILA_Z	TRAILB_Z	pdq	bai	BDI	age	Years of Education
AMI_Z	Spearman Corr.	1	0.51835*	0.55573*	0.37742*	0.20243	0.33486*	-0.45153*	-0.23174	-0.41345*	-0.04804	0.33823*
	p-value	--	1.3611E-4	<0.0001	0.00633	0.16304	0.02	6.10112E-4	0.09178	0.00256	0.71315	0.00879
VMI_Z	Spearman Corr.	0.51835*	1	0.5957*	0.68114*	0.57123*	0.60715*	-0.37796*	-0.43026*	-0.31233*	-0.15028	0.35948*
	p-value	1.3611E-4	--	<0.0001	<0.0001	1.18297E-4	<0.0001	0.01246	0.00398	0.04681	0.33019	0.01308
WMI_Z	Spearman Corr.	0.55573*	0.5957*	1	0.51925*	0.51991*	0.61272*	-0.27624	-0.24139	-0.18072	0.02257	0.47455*
	p-value	<0.0001	<0.0001	--	<0.0001	1.80083E-4	<0.0001	0.05215	0.09127	0.22414	0.87129	2.88569E-4
PSI_Z	Spearman Corr.	0.37742*	0.68114*	0.51925*	1	0.69948*	0.65477*	-0.16152	-0.28037	-0.16224	-0.24172	0.49243*
	p-value	0.00633	<0.0001	<0.0001	--	<0.0001	<0.0001	0.27274	0.05103	0.28136	0.10165	2.4199E-4
TRAILA_Z	Spearman Corr.	0.20243	0.57123*	0.51991*	0.69948*	1	0.71364*	-0.04425	-0.10854	0.07947	-0.30294*	0.27013
	p-value	0.16304	1.18297E-4	1.80083E-4	<0.0001	--	<0.0001	0.77027	0.47274	0.61247	0.03635	0.06049
TRAILB_Z	Spearman Corr.	0.33486*	0.60715*	0.61272*	0.65477*	0.71364*	1	-0.04668	-0.24427	0.04123	-0.07336	0.23235
	p-value	0.02	<0.0001	<0.0001	<0.0001	<0.0001	--	0.76073	0.10585	0.79544	0.62411	0.11203
pdq	Spearman Corr.	-0.45153*	-0.37796*	-0.27624	-0.16152	-0.04425	-0.04668	1	0.46459*	0.65383*	-0.06287	-0.19475
	p-value	6.10112E-4	0.01246	0.05215	0.27274	0.77027	0.76073	--	5.21106E-4	<0.0001	0.66445	0.16229

bai	Spearman Corr.	-0.23174	-0.43026*	-0.24139	-0.28037	-0.10854	-0.24427	0.46459*	1	0.61898*	-0.2362	-0.0095
	p-value	0.09178	0.00398	0.09127	0.05103	0.47274	0.10585	5.21106E-4	--	<0.0001	0.10227	0.94617
BDII	Spearman Corr.	-0.41345*	-0.31233*	-0.18072	-0.16224	0.07947	0.04123	0.65383*	0.61898*	1	-0.23659	-0.12222
	p-value	0.00256	0.04681	0.22414	0.28136	0.61247	0.79544	<0.0001	<0.0001	--	0.10935	0.39779
age	Spearman Corr.	-0.04804	-0.15028	0.02257	-0.24172	-0.30294*	-0.07336	-0.06287	-0.2362	-0.23659	1	-0.50789*
	p-value	0.71315	0.33019	0.87129	0.10165	0.03635	0.62411	0.66445	0.10227	0.10935	--	<0.0001
Years of Education	Spearman Corr.	0.33823*	0.35948*	0.47455*	0.49243*	0.27013	0.23235	-0.19475	-0.0095	-0.12222	-0.50789*	1
	p-value	0.00879	0.01308	2.88569E-4	2.4199E-4	0.06049	0.11203	0.16229	0.94617	0.39779	<0.0001	--

2-tailed test of significance is used
*: Correlation is significant at the 0.05 level

10.3 Appendix C – Chapter 6

Table SC1: Intraclass correlation coefficient between automated neuroimaging methods for ICV

Analysis	ICC	Lower_CI	Upper_CI	p_value
Synthseg 3D T1 ICV vs Free surfer 3D T1 ICV	0.83	0.51	0.95	<0.001
Synthseg Dimensions	0.99	0.78	1	0.001

Table SC2: Inter and Intraclass correlation coefficient between and within raters for stereological methods

Measure	ICC	p_value	CI_lower	CI_upper
Intra Total Oedema	0.99	<0.001	0.96	1
Intra DWI Oedema	0.98	<0.001	0.82	1
Intra Orientation Oedema	0.97	<0.001	0.73	1
Inter T1 vs T2 WBV	0.92	<0.001	0.70	0.98
Inter Total Oedema	0.91	<0.001	0.69	0.98
Inter DWI Oedema	0.96	<0.001	0.85	0.99

Table SC3: Temporal lobe asymmetry Spearmans's correlations

Variable	Cognitive_Variable	Spearman_rho	p_value
temporal_lobe_AI_Baseline	Auditory Memory	-0.622	4E-04
temporal_lobe_AI_Baseline	Visual Memory	-0.06	0.7899
temporal_lobe_AI_Baseline	Trail A	0.127	0.5548
temporal_lobe_AI_Baseline	Trail B	-0.035	0.8715
temporal_lobe_AI_Baseline	Working Memory	-0.158	0.4514
temporal_lobe_AI_Baseline	Processing Speed	-0.103	0.6389
temporal_lobe_AI_Baseline	Ace Total	-0.385	0.0521
temporal_lobe_AI_Week2	Auditory Memory	-0.38	0.0807
temporal_lobe_AI_Week2	Visual Memory	0.261	0.2667
temporal_lobe_AI_Week2	Trail A	0.33	0.1443
temporal_lobe_AI_Week2	Trail B	0.181	0.4456
temporal_lobe_AI_Week2	Working Memory	0.092	0.684
temporal_lobe_AI_Week2	Processing Speed	0.258	0.2579
temporal_lobe_AI_Week2	Ace Total	-0.089	0.6921
temporal_lobe_AI_Week26	Auditory Memory	0.682	5E-04
temporal_lobe_AI_Week26	Visual Memory	0.155	0.5265
temporal_lobe_AI_Week26	Trail A	-0.274	0.2556
temporal_lobe_AI_Week26	Trail B	0.178	0.467
temporal_lobe_AI_Week26	Working Memory	0.296	0.1928
temporal_lobe_AI_Week26	Processing Speed	0.03	0.9028
temporal_lobe_AI_Week26	Ace Total	0.229	0.305

AI= Asymmetry Index

Table SC4: Hippocampus asymmetry Spearman's correlations

Variable	Cognitive_Variable	Spearman_rho	p_value
hippocampus_AI_Baseline	Verbal Memory	-0.641	2E-04
hippocampus_AI_Baseline	Visual Memory	0.071	0.7533
hippocampus_AI_Baseline	Trail A	0.19	0.3749
hippocampus_AI_Baseline	Trail B	0.194	0.364
hippocampus_AI_Baseline	Working Memory	-0.051	0.81
hippocampus_AI_Baseline	Processing Speed	-0.093	0.6732
hippocampus_AI_Baseline	Ace Total	-0.264	0.192
hippocampus_AI_Week2	Verbal Memory	-0.223	0.3191
hippocampus_AI_Week2	Visual Memory	0.289	0.2157
hippocampus_AI_Week2	Trail A	0.192	0.4047
hippocampus_AI_Week2	Trail B	0.053	0.8228
hippocampus_AI_Week2	Working Memory	0.372	0.0879
hippocampus_AI_Week2	Processing Speed	0.058	0.803
hippocampus_AI_Week2	Ace Total	0.115	0.6105
hippocampus_AI_Week26	Verbal Memory	0.588	0.004
hippocampus_AI_Week26	Visual Memory	-0.033	0.8941
hippocampus_AI_Week26	Trail A	-0.493	0.0318
hippocampus_AI_Week26	Trail B	-0.101	0.6805
hippocampus_AI_Week26	Working Memory	0.119	0.607
hippocampus_AI_Week26	Processing Speed	-0.004	0.9857
hippocampus_AI_Week26	Ace Total	0.103	0.6475

AI = Asymmetry Index

10.4 Appendix D – Systematic Review

Figure SD1: Search strategy

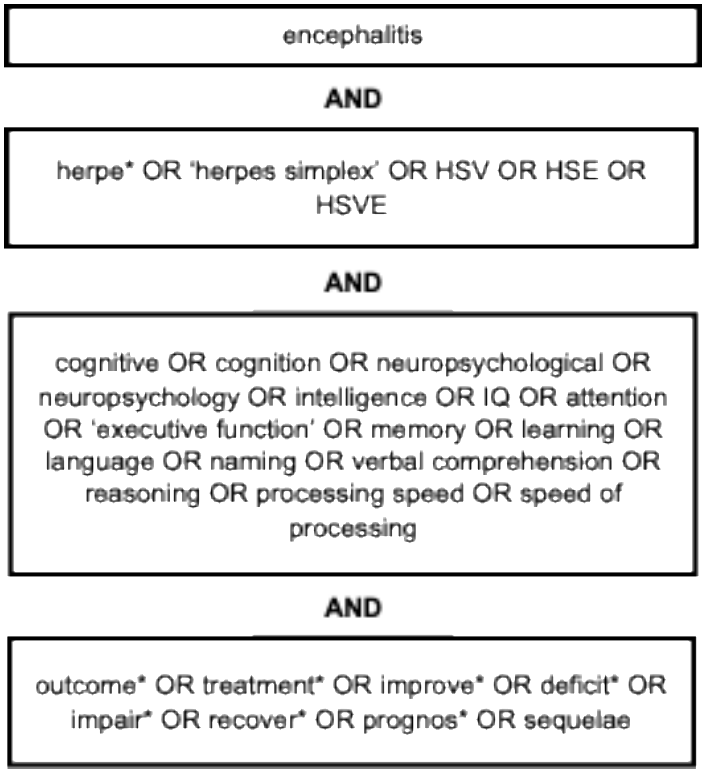

Figure SD2: Prisma Flow Diagram

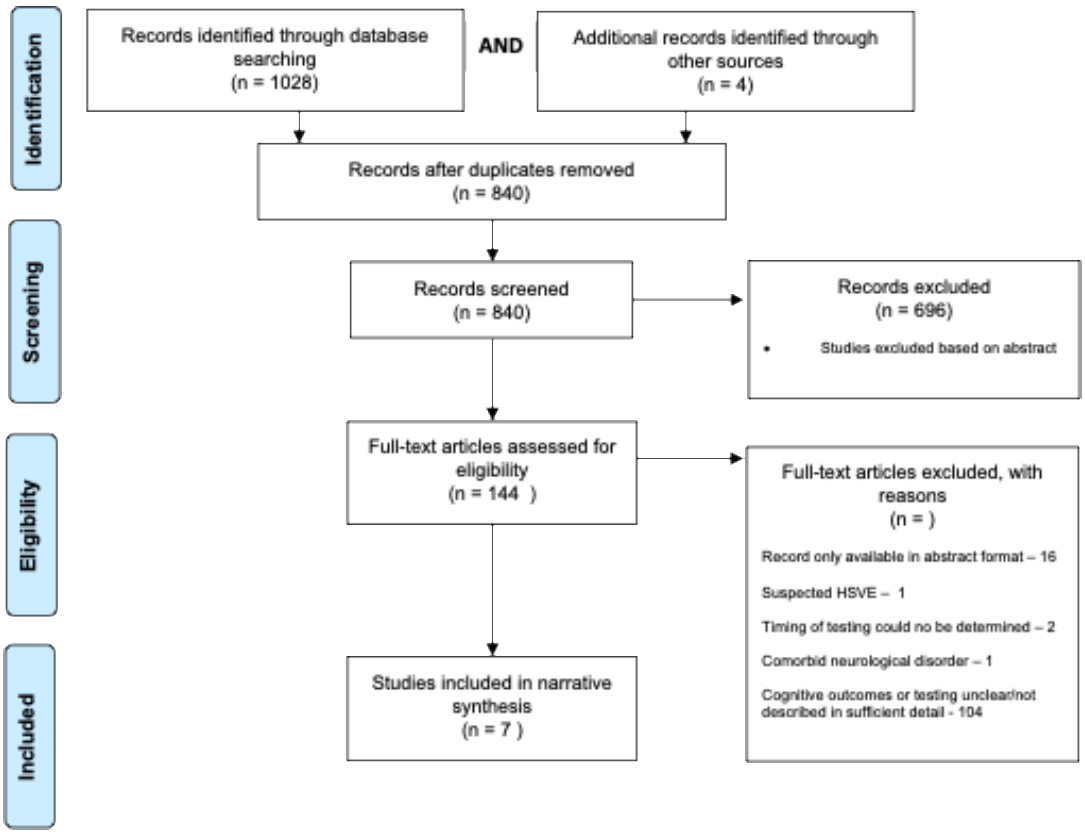

Table SD3: Summary table of studies included

Reference	**Setting**	**Participant Information**	**Time assessed**	**Data presentation**	**Deficit definition**	**Domains assessed**	**Tests administered**	**cognitive deficits reported**	**Psychological functioning**
Harris et al. (2020)	Patients identified at ENCEPH-UK hospital sites. Referred for formal neuropsychology testing at KCL or Walton centre, Liverpool.	HSV encephalitis - 11M 9F mean age 53.05. Case controls - (matched for age, gender distribution & premorbid IQ) 23M 22F, mean age 51.16.	4 Months - short term cohort	Group Level	Significant difference compared to controls. Not always clear.	Premorbid IQ, Full scale IQ, anterograde memory, retrograde memory, executive function, language, visual semantic access, perception, psychiatric functioning, perceived cognitive functioning-	WTAR, WASI-II, doors and people (verbal, visual, recall and recognition), AMI (personal, semantic and autobiographical incidents memory), verbal fluency (FAS) TMT A-B, Hayling test, Rule detection, Brixton test, GNT, PPTT. VOSP, BFRT, BAI, BDI, ABNAS.	significant impairment on visual recall and recognition. Personal semantic memory and autobiographical incidents memory, executive function impairment, severe naming impairment.	Raised levels of depression

	separate long-term cohort. Recruited through ENCEPH-UK sites, PHE database or self-referral in response encephalitis society notice.	HSV encephalitis - 10M 20F mean age 48.37 Case controls - (matched for age, gender and premorbid IQ) 32M 38F, mean age 50.80.	12M - Long term cohort	Group Level	As Before.	As before.	As before.	Verbal & visual recall and verbal recognition impairment. Impaired autobiographical incidents memory.	Raised Depression and Anxiety
Hokkanen et al. (1996a)	Referred for neuropsychological examination at the Department of Neurology, Helsinki University Central Hospital.	HSV encephalitis group - 8M 9F mean age 50.2. Controls - 11M 18F age 44.4 no	Post-acute' as soon as initial confusion subsided, and patient could cooperate.		VIQ & PIQ - score below 95 (Finnish norms). For other tests deficit defined as ≤2 SD below mean of controls.	Verbal Logical thinking, Visual logical thinking, Verbal memory, Visual memory, verbal-semantic, visuo-perceptual, voluntary motor functions	WAIS (sub-tests adequate to calculate VIQ and PIQ), WMS (logical memory, associative learning, Visual reproduction), Benton visual retention test, copy cube and Greek cross,	percentage of patients with deficits (n=17) - Verbal logical thinking (7, 41%), visual logical thinking (9, 53%), verbal memory (13, 76%) Visual memory (10, 59%) verbal semantic (10, 59%), visuo-perceptual (14, 82%), voluntary	NR

		statistical difference in age or duration of education).	mean 27.5, range 5-128 days)				drawing clock hands, Luria based tasks.	motor (3, 18%). Any cognitive deficit (15, 88%)	
hokkanen et al. (1997)	follow up of patients referred to Department of Neurology, Helsinki University Central Hospital	3M 1F - Mean age 47.3	Second Review	Second Review	Second Review	Second Review	Second Review	Second Review	NR
Kapur et al. (1994)	NR	HSV encephalitis - 5M 5F mean age 49.3	minimum 6 months (range not clearly reported, indication of 15 years)		WAIS subtests - 1 SD below mean score of 10 derived from distributions scores in normative sample. WMS - dense amnesia described as MQ 50 or less. Naming - impaired if score lower	Premorbid functioning, VIQ, PIQ, Naming, executive function.	NART, WAIS, Picture naming task, WMS-R, RMT,	Verbal & Visual memory (verbal most pronounced), Naming, Problem solving.	NR

					than expected based on reading score and education. Card sorting				
Pewter (2007)	Patients recruited through the encephalitis society.	HSV encephalitis - 3M 1F Mean age 55.8	mean 81 months (18-185)	Group & individual level	>2 SD below normal mean	psychiatric, Premorbid IQ, Current IQ, Memory, Language, Executive function, Visuospatial perception		Memory for new verbal and visual material, object naming, semantic memory, IQ, autobiographical memory, executive function, confrontation naming, working memory, visuo-perceptual.	High levels of depression and anxiety.

Utley et al. (1997)	Patients identified retrospectively from Auckland hospital laboratory records.	6M 16F - Mean age 42.2 (analysis of patients below 16 are not included)	Mean 33 months (4-124months)	Group & Individual	SD>1 below age corrected mean - no deficit, <2 mild deficit, <3 moderate deficit, >3 severe deficit.	Portland adaptability interview, NART, WAIS-R, WMS-R, Rey complex figure, California Verbal Learning Test (CVLT), Warrington word and face Recognition Memory Test, Autobiographical Memory Interview, Otago Remote memory questionnaire, WCST, Controlled Oral Word Association Test, Cognitive estimation test, Short version of Minnesota Test for the differential diagnosis of Aphasia,	Mild impairment - verbal memory (3/22) visual Memory (10/22), Executive functioning (8/22), Remote memory (2/22), non-specific damage (3/22), overall cognitive outcome (13/22). Moderate/Severe impairment - verbal memory (8/22) visual memory (4/22), Remote memory (6/22), Non-specific damage (9/22), Overall cognitive outcome (3/22).	NR