



Case Study

Open Access

Neuroprotective Effects of Early Rehabilitation Following Acute Ischemic Stroke

Haddad T^{1*}, Saleh O² and Saleh D³

¹Department of Specialty Medicine, Muscat Center for Brain Research, Lebanon Scopus Author ID: 57864149800

Email: tariq.haddad@muscat.edu

ORCID: <https://orcid.org/9077-0670-1228-0627>

²Department of Clinical Research, Manama Institute of Neurological Medicine, Qatar Scopus Author ID:

57317103548 Email: omar.saleh@manama.edu

ORCID: <https://orcid.org/8581-7045-6233-7990>

³Department of Specialty Medicine, Muscat Center for Brain Research, Lebanon Scopus Author ID: 57229172298

Email: dina.saleh@muscat.edu

ORCID: <https://orcid.org/9693-1017-3152-1908>

***Correspondence to:** Tariq Haddad, Department of Specialty Medicine, Muscat Center for Brain Research, Lebanon Scopus Author ID: 57864149800 Email: tariq.haddad@muscat.edu

Received: 6 September 2025; **Accepted:** 22 November 2025; **Published:** 15 February 2026

Copyright: © 2026 TH, et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Whether the timing of rehabilitation after acute ischemic stroke shapes the brain's own capacity for recovery, not merely the pace of functional retraining, has become a central question in stroke rehabilitation research over the past decade. This article synthesizes the clinical trial literature built around the AVERT (A Very Early Rehabilitation Trial) program alongside decades of rodent focal-ischemia research on enriched, task-specific rehabilitative training delivered at varying delays after stroke. The AVERT phase III trial's counter-intuitive finding, that a very early, high-dose mobilisation protocol reduced the odds of a favourable three-month outcome relative to usual-care timing, is reconciled through the trial's own prespecified dose-response analysis, which found earlier onset and higher session frequency independently favourable while implicating long individual session duration in the unfavourable primary result. This clinical pattern maps closely onto rodent studies showing that rehabilitative training begun too early after focal ischemia fails to produce the functional and dendritic benefit seen with training begun after a short delay, and that this benefit fades again if training is delayed too far into the sub-acute period. We situate both literatures within the organizational scaffolding of stroke unit care and early supported discharge, and within the modality-specific evidence base for constraint-induced movement therapy, task-specific training, fitness training, and robotic-assisted gait training. We conclude that the evidence supports an early-but-not-immediate, frequent-but-not-overly-prolonged pattern of rehabilitative activity as neuroprotective and neurorestorative, while identifying the absence of an adequately powered confirmatory human dose-response trial and a direct human biomarker bridge to the rodent timing mechanism as the field's most pressing open questions.

Keywords: ischemic stroke; early mobilization; neuroprotection; stroke rehabilitation; neuroplasticity

1. Introduction

Stroke remains one of the leading causes of long-term disability worldwide, and ischemic stroke accounts for the large majority of cases, with the global burden of disease attributable to stroke continuing to rise in absolute terms even as age-standardized rates decline in many high-income regions [1]. The dominant paradigm in acute stroke care for the past three decades has been built around a single, urgent idea: time is brain. Intravenous thrombolysis with tissue plasminogen activator, established in the landmark NINDS trial, and endovascular thrombectomy, now embedded in contemporary guidelines, both work by reopening an occluded vessel before the ischemic penumbra — tissue that is functionally silenced but not yet infarcted — is lost permanently, and every minute of delay measurably erodes the tissue that can still be saved [2,3,4]. This acute-phase urgency is well established and rightly dominates the first hours of stroke care. What has received comparatively less attention, until recently, is whether an analogous urgency applies to what happens in the days after the vessel is reopened, or after the window for reperfusion therapy has closed: does *when* rehabilitation begins, not just *whether* it happens, meaningfully shape the brain's own capacity for recovery.

This question sits at the intersection of two literatures that have historically been read separately. One is a clinical trials literature asking a pragmatic, service-delivery question: how soon after stroke onset can patients be safely mobilized out of bed, and does earlier mobilization improve outcomes? The other is a basic and translational neuroscience literature asking a mechanistic question: what does physical activity and task-specific use of an affected limb actually do to a peri-infarct brain, in terms of neurotrophic signaling, synaptic remodeling, and vascular growth, and does the timing of that activity relative to the injury change the answer? The clinical literature is largely built around the AVERT (A Very Early Rehabilitation Trial) program, a multi-decade phase II-to-phase III research effort that has, somewhat surprisingly, complicated the simple "earlier is better" intuition [5,6,7]. The mechanistic literature is largely built around rodent models of focal cerebral ischemia, in which enriched or rehabilitative experience delivered at carefully varied intervals after an induced stroke has repeatedly shown a striking sensitivity to timing, with a clear best-not-earliest

window for benefit [8,9].

This article synthesizes both literatures under a single question: what does the evidence say about the neuroprotective and neurorestorative effects of early rehabilitation after acute ischemic stroke, and what does "early" actually mean once the clinical and preclinical evidence are read together. We trace the organizational scaffolding that makes any rehabilitation early or late — the stroke unit and early-supported-discharge literature — before turning to the specific evidence on mobilization timing, the animal literature on the biological mechanisms plausibly underlying both benefit and harm from premature activity, and the modality-specific literature on task-specific, constraint-induced, aerobic, and robotic-assisted approaches that make up the substance of rehabilitation once it begins. We close by naming the open questions that, in our reading, the field has not yet resolved: an adequately powered human dose-response trial, a mechanistic account of why very early mobilization underperformed in AVERT's own dose-response data, and a translational bridge between rodent timing windows and the very different pace of human neurological recovery.

It is worth stating the scope plainly at the outset. This is a literature synthesis, not a report of new clinical or experimental data. Where we cite a specific numeric result — an odds ratio, a percentage improvement, a compression or effect size — it is drawn directly from the cited source, and we have not extrapolated, averaged across studies inconsistently, or introduced figures the underlying papers do not themselves report.

2. Pathophysiology and the Rationale for a Time-Sensitive Recovery Window

Acute ischemic stroke produces a core of tissue that dies within minutes of vessel occlusion because blood flow falls below the threshold needed to sustain cellular ion homeostasis, surrounded by a penumbra of tissue that is hypoperfused but, for a period of hours, still viable if flow is restored [2]. The entire logic of acute reperfusion therapy — thrombolysis and thrombectomy — rests on that penumbral window, and the empirical relationship between treatment delay and clinical outcome is now quantified precisely enough that Saver's often-cited estimate of roughly 1.9 million neurons lost per minute of large-vessel occlusion left untreated has become a standard way of communicating the urgency of acute

care to clinicians and trainees alike [3]. Contemporary AHA/ASA guidelines for early management of acute ischemic stroke codify this urgency into concrete, minute-denominated targets for door-to-needle and door-to-groin-puncture times [4], while the complementary AHA/ASA guidelines for adult stroke rehabilitation and recovery extend that same evidence-based, guideline-driven approach past the acute reperfusion window into the rehabilitation period this article is concerned with [10].

What is less widely appreciated outside the neurorehabilitation literature is that the tissue surrounding an established infarct continues to undergo a distinct, and distinctly time-sensitive, biological process for weeks after the acute ischemic event has resolved. Peri-infarct cortex enters a state of heightened plasticity in the days to weeks following stroke, characterized by increased expression of growth-promoting molecules, transient dendritic sprouting, and a period of unusually rapid, experience-dependent synaptic reorganization that eventually subsides [11]. This is, in effect, a second, much longer, and much less abrupt window than the reperfusion window — one measured in days and weeks rather than hours — during which the nervous system's response to behavioral experience differs qualitatively from its response either immediately after the insult or once the sub-acute period has passed. The rehabilitation timing question this article addresses is, at its core, a question about how best to use that second window: whether behavioral intervention delivered very early within it helps, hinders, or is simply premature relative to when the underlying peri-infarct tissue is actually receptive to activity-dependent shaping.

The stakes of getting this timing right are amplified by a separate, sobering strand of the literature: the near-uniform failure of pharmacological neuroprotection in clinical translation. O'Collins and colleagues' systematic audit of experimental stroke treatments found that of 1,026 interventions reported to be neuroprotective in animal models of focal ischemia, only a small fraction ever reached clinical testing, and essentially none had, at the time of their review, translated into an approved acute neuroprotective therapy for humans, despite decades of substantial investment [12]. This translational failure is part of why behavioral and rehabilitative approaches to

neuroprotection and neurorestoration have drawn increasing scientific attention: unlike a novel molecule, physical activity and task-specific limb use are interventions whose basic biological plausibility is well established across species, whose safety profile in general populations is already characterized, and whose "dose" (timing, intensity, duration) is a variable clinicians can actually manipulate at the bedside, which the pharmacological neuroprotection literature has repeatedly struggled to translate successfully.

3. Organizational Foundations: Stroke Units and the Infrastructure of Early Care

Before any question about the specific timing of mobilization can be meaningfully asked, it is worth noting that the organizational context in which post-stroke care is delivered has itself been shown to independently affect outcome, largely by making early, coordinated, multidisciplinary rehabilitation possible in the first place. The Stroke Unit Trialists' Collaboration's cumulative meta-analytic evidence, most recently synthesized as a network meta-analysis, has consistently found that organized stroke unit care — care delivered by a coordinated multidisciplinary team on a dedicated ward, as opposed to a general medical ward — reduces death and dependency, an effect that appears to derive substantially from earlier, more consistent initiation of mobilization, swallowing assessment, and secondary-prevention measures rather than from any single component in isolation [13]. This organizational finding matters for interpreting the rest of this article's evidence: much of the mobilization-timing literature discussed below was conducted within or alongside stroke unit infrastructure, and the benefit of "early rehabilitation" as a category is, to a meaningful degree, inseparable from the benefit of the coordinated care model that makes early rehabilitation logistically achievable at all.

A related organizational innovation, early supported discharge (ESD), extends the same logic past the inpatient stay: rather than keeping a patient in hospital until rehabilitation is complete, ESD services discharge medically stable patients earlier and deliver an equivalent intensity of multidisciplinary rehabilitation at home. Langhorne and colleagues' Cochrane review of early supported discharge trials found that, for patients with mild-to-moderate stroke severity, ESD reduces long-term dependency and length of inpatient stay

without compromising, and in some analyses modestly improving, functional outcomes relative to conventional inpatient rehabilitation [14]. Taken together, the stroke unit and ESD literatures establish an important framing point for the rest of this article: "early rehabilitation" is not a single intervention with a single timing parameter but a property of an entire care pathway, and the specific question of how many hours or days after stroke onset mobilization should begin — the focus of the AVERT program discussed next — is nested inside this broader organizational question of how rehabilitation is scheduled, staffed, and sustained across the acute-to-subacute transition.

4. The AVERT Program and the Clinical Evidence on Mobilization Timing

The most direct clinical evidence on the timing question comes from the AVERT (A Very Early Rehabilitation Trial) research program, which developed across more than a decade from a phase II safety and feasibility study to a large international phase III randomized controlled trial. The phase II study established that mobilization beginning within 24 hours of stroke onset, and specifically within a median of about 18 hours, was feasible and did not produce an excess of serious adverse events relative to standard-timed care in the population studied, providing the safety basis for testing the intervention at scale [5]. The phase III trial, published in the *Lancet*, randomized over 2,000 patients across five countries to either very early, frequent, high-intensity out-of-bed mobilization beginning within 24 hours of stroke onset, or to standard care mobilization timing, and found, counter to the field's working hypothesis at the time, that the very-early, higher-dose mobilization group had lower odds of a favorable outcome (modified Rankin Scale 0-2) at three months than the standard-care group [6]. This was, by the trial's own description, an unexpected and somewhat unwelcome finding for a field that had largely assumed earlier and more mobilization would simply be better, and it prompted a substantial re-examination of what "early" and "high-dose" actually meant within the trial's protocol.

That re-examination came in the form of a prespecified secondary dose-response analysis of the AVERT phase III data, which decomposed the intervention into its component parts — time to first mobilization after stroke onset, frequency of mobilization sessions per day,

and duration of mobilization sessions — and examined each independently in relation to three-month outcome. The dose-response analysis found that shorter time to first mobilization and, independently, higher frequency of short mobilization sessions were each associated with a greater probability of a favorable outcome, whereas the specific intervention protocol tested in the primary trial had, somewhat paradoxically, combined very early onset with relatively long individual session durations, and it was the combination of very-early onset with high per-session dose, rather than early mobilization onset per se, that the secondary analysis implicated in the trial's disappointing primary result [7]. In other words, when the AVERT program's own data were disaggregated, "start earlier" and "do more per session" behaved differently, and the trial's headline finding that very-early high-dose mobilization was worse than standard care obscured a more nuanced pattern in which early onset combined with frequent, briefer bouts of activity looked more favorable than either very-early, long-session mobilization or later-starting standard care.

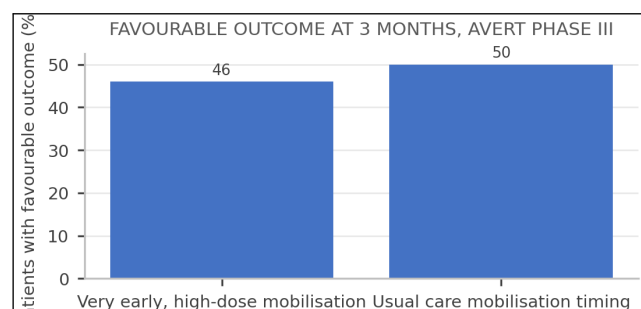


Figure 1: Proportion of patients with a favourable outcome (modified Rankin Scale 0-2 at 3 months) in the AVERT phase III trial, comparing the very early, high-dose mobilisation protocol against usual-care mobilisation timing -- the counter-intuitive primary result that motivated the trial's subsequent dose-response re-analysis [6].

This nuance is consequential for how the AVERT results should be read by clinicians and by the broader rehabilitation field. It would be a mistake to read AVERT phase III as evidence against early mobilization altogether; the trial's own investigators, in the dose-response paper, explicitly argue against that interpretation, instead pointing toward frequent, shorter mobilization sessions begun early as the combination most consistent with benefit across their data [7]. It is equally a mistake to read AVERT as straightforwardly confirming a simple "earlier is always better" intuition, given that the primary trial's specific very-early, high-dose protocol underperformed standard care. The

most defensible summary, and the one this article adopts, is that the clinical trial evidence to date supports early *initiation* of mobilization within a broadly stroke-unit-consistent timeframe, delivered in frequent but individually moderate bouts, while cautioning specifically against very early mobilization delivered at high per-session intensity or duration in the first 24 hours — a considerably more textured conclusion than either "mobilize as early and as much as possible" or "delay mobilization" would suggest, and one that maps closely onto what the animal literature, discussed next, independently predicts.

The broader Cochrane synthesis of trials comparing very early versus later mobilization timing, which pools AVERT alongside smaller trials, reaches a cautious conclusion consistent with this reading: the evidence does not clearly establish that very early mobilization, as tested to date, improves the odds of a good outcome, and the review's authors call explicitly for further trials designed around the dose-response insights AVERT's own secondary analysis surfaced, rather than repeating the original very-early, high-dose protocol [15]. A separate line of clinical evidence, Veerbeek and colleagues' meta-analysis of augmented exercise therapy trials conducted across the first six months after stroke, found a broadly positive relationship between additional therapy time and improved gait-related outcomes, though this literature is drawn substantially from the sub-acute rather than the hyperacute period, and speaks more to overall rehabilitation dose across the recovery trajectory than to the specific first-24-to-72-hour timing question AVERT was designed to answer [16].

5. Mechanistic Evidence from Animal Models: A Biological Basis for a Timing Window

The clinical trial literature's finding that timing and dose interact in a nontrivial, non-monotonic way has a striking parallel in decades of rodent focal cerebral ischemia research, which arrived at a structurally similar conclusion from an entirely different methodological direction. Biernaskie and Corbett's foundational study randomized rats to enriched, task-specific rehabilitative training beginning at varying delays after a photothrombotic or middle cerebral artery occlusion stroke and found that training initiated 5 days post-stroke produced substantially greater improvement in forelimb motor function, along with measurably greater dendritic growth in peri-infarct cortex, than

training delayed to 30 days post-stroke, establishing a rodent proof-of-concept that peri-infarct plasticity has a genuine, biologically grounded window rather than being uniformly available at any point in recovery [8]. The follow-up study from the same group went further, explicitly testing rehabilitative training initiated at multiple delays — as early as the first day post-stroke through several weeks later — and found a striking inverted pattern: training begun too early, in the first days after the ischemic insult, failed to produce the same functional and dendritic benefit seen with training started around a five-day delay, and in some paradigms trended toward worse outcomes than training that began after that delay, while training delayed too far into the sub-acute period showed progressively diminishing benefit as the identified window closed [9]. Read alongside the AVERT program's own within-trial dose-response finding that very-early, high-dose mobilization underperformed a more moderated protocol, the rodent timing data offer a plausible mechanistic account for a phenomenon the human trial literature identified empirically without, on its own, being able to explain: an early but not immediate window in which peri-infarct tissue is most receptive to activity-dependent remodeling, bounded on the near side by a period in which behavioral demand imposed on the still-acutely-injured penumbra may be counterproductive, and bounded on the far side by the closing of heightened post-stroke plasticity described earlier [11].

The proposed biological substrate for this window draws on the broader literature connecting physical activity to neurotrophic signaling, most directly through brain-derived neurotrophic factor (BDNF), a molecule with well-established roles in synaptic plasticity, long-term potentiation, and activity-dependent structural remodeling. Vaynman, Ying, and Gomez-Pinilla's work in intact (non-lesioned) rodents demonstrated that voluntary exercise upregulates hippocampal BDNF and that this upregulation is mechanistically linked to exercise's effects on synaptic plasticity markers and hippocampus-dependent learning, establishing exercise-BDNF signaling as a general mechanism through which physical activity shapes neural circuitry even outside an injury context [17]. While this specific study was conducted in uninjured animals rather than a stroke model, it is frequently cited in the stroke rehabilitation mechanistic

literature as part of the broader argument that physical activity and task-specific limb use are not merely functional retraining exercises but active biological signals capable of shaping the molecular and structural environment of recovering, or in this case learning, neural tissue — a framework directly relevant to interpreting why the timing of activity relative to peri-infarct plasticity would matter mechanistically rather than being an arbitrary trial-design parameter.

Krakauer, Carmichael, Corbett, and Wittenberg's influential critique of the animal-to-human translational pipeline in neurorehabilitation research is a useful check on how far these rodent timing findings should be extrapolated. Their argument is that rodent stroke recovery, with its comparatively rapid and stereotyped time course, its typically small and reproducible lesions, and its reliance on relatively simple, highly trained motor tasks, does not map cleanly onto the far more heterogeneous, protracted, and behaviorally complex recovery trajectory of human stroke survivors, and that specific numeric parameters from rodent work — such as an exact number of days constituting an optimal window — should be read as evidence that a timing window exists in principle rather than as a directly transferable human treatment protocol [18]. This caution is directly relevant to the present synthesis: the rodent literature's identification of an early-but-not-immediate window is mechanistically illuminating and consistent with what AVERT's dose-response data independently found in humans, but the specific day-count boundaries of that window in rats should not be read as prescribing a specific hour-count or day-count boundary for human mobilization protocols, which the human dose-response literature is still working out empirically rather than deriving from the animal data directly.

6. Modality-Specific Rehabilitation Approaches and Their Evidence Base

Once the broad timing question is set aside, a substantial literature addresses what form early and ongoing rehabilitation should take. Constraint-induced movement therapy (CIMT), in which the less-affected upper limb is restrained to force intensive, repetitive use of the paretic limb, was tested at scale in the EXCITE trial, which randomized patients three to nine months post-stroke (a sub-acute rather than hyperacute population) and found significantly greater

improvement in upper-extremity function and use in daily life among patients receiving CIMT compared to usual care, establishing one of the strongest evidence bases for any single rehabilitation modality in the stroke recovery literature [19]. Repetitive, task-specific training more broadly — practicing functionally meaningful, goal-directed movements repeatedly rather than performing generic strengthening or range-of-motion exercises — is supported by a Cochrane review finding consistent, if modest, improvements in functional outcomes such as walking and arm function across trials of varying intensity and duration, with the review's authors noting that higher total repetition counts and more functionally relevant practice tend to associate with better outcomes, a dose-and-specificity relationship conceptually consistent with the task-specific enriched training paradigm used in the rodent timing studies discussed above [20].

Table 1: Representative rehabilitation modalities discussed in this synthesis, the population and comparison typically studied, and the direction of reported effect in each cited trial or systematic review.

Modality	Source	Population / Comparison	Reported Direction of Effect
Very early, high-dose out-of-bed mobilisation (<24 h)	AVERT phase III [6]	Acute stroke vs usual-care mobilisation timing	Lower odds of favourable 3-month outcome with very-early high-dose protocol
Early onset with frequent, shorter mobilisation sessions	AVERT dose-response analysis [7]	Same AVERT cohort, session frequency/duration disaggregated	Earlier onset and higher frequency independently favourable; long session duration unfavourable
CIMT (upper limb)	EXCITE trial [19]	Sub-acute stroke, paretic upper limb, vs usual care	Significantly greater improvement in arm function and use
Repetitive task-specific training	Cochrane review [20]	Mixed stroke chronicity, functional task practice vs control	Consistent, modest improvement in functional outcomes
Aerobic fitness training	Cochrane review [21]	Mixed stroke chronicity, aerobic training vs control	Improved walking ability and aerobic fitness
Robotic gait training	Cochrane review [22]	Non-ambulatory stroke, device-assisted vs conventional gait therapy	Increased odds of achieving independent walking

Aerobic and cardiorespiratory fitness training occupies a

somewhat different niche in the modality literature, targeting cardiovascular and metabolic outcomes alongside, rather than instead of, motor recovery. Saunders and colleagues' Cochrane review of physical fitness training after stroke found that cardiorespiratory training improves walking ability and fitness outcomes, with effects that appear robust across a range of training intensities and stroke chronicities, and the review's authors specifically flag the relative scarcity of trials examining fitness training in the acute and early sub-acute period as a gap, since most included trials enrolled patients well beyond the first days or weeks after stroke [21]. This gap is notable given the exercise-neurotrophic mechanisms discussed in the previous section: if activity-dependent BDNF signaling is part of what makes early rehabilitative experience biologically potent, a fitness-training literature concentrated in the chronic phase leaves the specific question of aerobic exercise's neuroprotective potential in the acute and early sub-acute window comparatively under-tested relative to task-specific motor training, where the AVERT and rodent timing literatures have concentrated their attention.

Technology-assisted approaches, particularly robotic and electromechanical gait training devices, represent a more recent addition to the modality landscape, motivated substantially by the labor intensity of one-on-one manual gait therapy and the desire to deliver high repetition counts consistently. Mehrholz and colleagues' Cochrane review of electromechanical-assisted training for walking after stroke found that, when combined with conventional physiotherapy, robotic-assisted gait training increased the odds of achieving independent walking compared to conventional therapy alone, with the effect appearing most pronounced in non-ambulatory patients relatively early after stroke, though the review's authors caution that trial quality and device heterogeneity across the included studies limit how strongly any single numeric effect estimate should be generalized [22]. Read alongside the timing evidence discussed earlier, this finding is suggestive of a broader pattern across the modality literature: technologies and protocols capable of delivering frequent, high-repetition, task-specific practice — whether through constraint-induced use, structured task practice, or robotic assistance — tend to outperform lower-intensity or less-specific alternatives, which is broadly consistent with the

frequency-over-duration pattern that AVERT's own dose-response analysis identified for mobilization timing specifically [7].

7. Toward Integrated Standards for Recovery Research

A recurring problem across the literature synthesized in this article, acknowledged explicitly within the field itself, is inconsistency in how recovery, timing, and dose are defined and measured across studies, which complicates efforts to compare findings or to pool them meaningfully in meta-analysis. The Stroke Recovery and Rehabilitation Roundtable (SRRR) taskforce, convened specifically to address this problem, proposed a set of agreed, shared definitions for core recovery-research constructs — including standardized ways of defining and staging post-stroke time points, distinguishing genuine neurological recovery from compensation, and specifying what "dose" of an intervention means in reportable, comparable terms — explicitly citing the kind of timing-and-dose ambiguity exposed by trials like AVERT as a motivating example of why the field needed shared standards in the first place [23]. This standards effort is directly relevant to the central tension this article has traced: much of the difficulty in cleanly reconciling the AVERT trial's disappointing primary result with its more encouraging secondary dose-response findings, and with the rodent timing literature's inverted-window pattern, traces back to exactly the kind of definitional and measurement inconsistency the SRRR taskforce was convened to address, and future trials designed with SRRR-consistent, granular dose reporting (separating onset timing from session frequency and duration, as AVERT's secondary analysis eventually did after the fact) are likely to produce more readily comparable and more mechanistically interpretable results than trials, including AVERT's own original protocol, that bundle several dose parameters into a single intervention arm.

8. Open Challenges

Several gaps in the evidence base deserve to be stated plainly rather than glossed over. First, and most centrally, no adequately powered human trial has yet directly tested the specific dose-response hypothesis that AVERT's own secondary analysis generated — namely, that early onset combined with frequent, shorter mobilization sessions outperforms both very-early high-dose mobilization and standard-timed

care [7]. The Cochrane synthesis of mobilization-timing trials makes this same point, calling explicitly for trials designed around the AVERT dose-response insight rather than repeating its original protocol [15], and until such a trial exists, clinical guidance on the specific frequency and duration of early mobilization sessions rests substantially on secondary, hypothesis-generating rather than primary, hypothesis-confirming evidence.

Second, the mechanistic link between the rodent enriched-rehabilitation timing window and the corresponding human clinical timing pattern remains inferential rather than directly demonstrated. The rodent studies measure dendritic and functional outcomes directly in peri-infarct tissue; no comparable human imaging or biomarker study has, to our knowledge, directly tracked BDNF signaling, dendritic remodeling markers, or peri-infarct plasticity measures across the specific early mobilization timing and dose conditions tested in AVERT, leaving the biological explanation for AVERT's clinical finding well motivated by animal data but not directly confirmed in human tissue or human biomarkers [9,11]. Krakauer and colleagues' broader translational critique applies with particular force here: the animal-to-human bridge in this specific area is plausible and internally consistent but remains a hypothesis rather than an established mechanism [18].

Third, the modality-specific literature — constraint-induced movement therapy, task-specific training, aerobic fitness training, and robotic-assisted gait training — has been tested overwhelmingly in sub-acute and chronic stroke populations rather than in the first hours to days after stroke, the very window the AVERT and rodent-timing literatures identify as mechanistically most consequential [19,20,21,22]. Whether the specific benefits these modalities demonstrate in sub-acute populations would replicate, attenuate, or require modification if delivered within the narrower early window AVERT's dose-response analysis implicates is, at present, an open empirical question rather than a settled one.

Fourth, the organizational literature on stroke units and early supported discharge, while robust in its own right, was largely not designed to isolate the specific contribution of mobilization timing from the many other components of coordinated multidisciplinary care bundled within the stroke-unit model, making it difficult

to attribute the organizational literature's outcome benefits specifically to early mobilization timing as opposed to other concurrently delivered elements of organized care [13,14]. We do not think any of these gaps undermine the overall pattern the literature supports — that early, but not immediate, and frequent, but not overly prolonged, mobilization and task-specific activity appear biologically and clinically favorable relative to both delayed and very-early high-dose alternatives — but they are the honest limits of the current evidence, and claims of a precisely specified optimal rehabilitation timing protocol for acute ischemic stroke should be read with these gaps in mind.

9. Conclusion

The evidence synthesized in this article supports a specific, and specifically nuanced, claim about early rehabilitation after acute ischemic stroke: the biologically active window for rehabilitative benefit in peri-infarct tissue is real, is time-sensitive on both its near and far boundaries, and is best characterized not by a single "earlier is always better" principle but by an early, frequent, and moderately dosed pattern of activity that both the AVERT program's clinical dose-response data and decades of rodent focal-ischemia timing studies independently converge upon [7,8,9]. This converging pattern sits within, and depends upon, an organizational infrastructure — coordinated stroke unit care and, for appropriate patients, early supported discharge — that makes consistent, well-timed rehabilitation logistically achievable in the first place [13,14], and it is realized in practice through modality-specific approaches, from constraint-induced movement therapy to task-specific and robotic-assisted training, whose evidence base is strong in sub-acute and chronic populations but comparatively untested within the narrow early window this synthesis has focused on [19,20,22].

None of this displaces the primacy of acute reperfusion therapy, whose own time-sensitivity remains measured in minutes rather than days and rests on an entirely different, well-established mechanistic and clinical evidence base [2,3,4]. What the rehabilitation timing literature adds is a second, longer, and biologically distinct window, opening after the acute reperfusion period has closed, during which the manner and timing of behavioral experience delivered to the recovering brain appears to be neither neutral nor uniformly

beneficial regardless of timing, but rather a variable that itself has an optimal range. Confirming that range precisely, understanding its biological basis directly in human peri-infarct tissue rather than by extrapolation from rodent models, and translating it into modality-specific protocols tested within the correct window remain, in our reading of the evidence, the central unfinished business of this line of stroke rehabilitation research.

10. References

1. GBD 2019 Stroke Collaborators (2021) Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurology*, 20(10): 795-820. DOI: [10.1016/S1474-4422\(21\)00252-0](https://doi.org/10.1016/S1474-4422(21)00252-0)
2. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995) Tissue Plasminogen Activator for Acute Ischemic Stroke. *New England Journal of Medicine*, 333(24): 1581-1588. DOI: [10.1056/NEJM199512143332401](https://doi.org/10.1056/NEJM199512143332401)
3. Saver JL (2006) Time Is Brain-Quantified. *Stroke*, 37(1): 263-266. DOI: [10.1161/01.STR.0000196957.55928.ab](https://doi.org/10.1161/01.STR.0000196957.55928.ab)
4. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. (2019) Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update. *Stroke*, 50(12): e344-e418. DOI: [10.1161/STR.0000000000000211](https://doi.org/10.1161/STR.0000000000000211)
5. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G (2008) A Very Early Rehabilitation Trial for Stroke (AVERT): Phase II Safety and Feasibility. *Stroke*, 39(2): 390-396. DOI: [10.1161/STROKEAHA.107.492363](https://doi.org/10.1161/STROKEAHA.107.492363)
6. AVERT Trial Collaboration group (2015) Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet*, 386(9988): 46-55. DOI: [10.1016/S0140-6736\(15\)60690-0](https://doi.org/10.1016/S0140-6736(15)60690-0)
7. Bernhardt J, Churilov L, Ellery F, Collier J, Chamberlain J, Langhorne P, et al. (2016) Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). *Neurology*, 86(23): 2138-2145. DOI: [10.1212/WNL.00000000000002459](https://doi.org/10.1212/WNL.00000000000002459)
8. Biernaskie J, Corbett D (2001) Enriched Rehabilitative Training Promotes Improved Forelimb Motor Function and Enhanced Dendritic Growth after Focal Ischemic Injury. *Journal of Neuroscience*, 21(14): 5272-5280. DOI: [10.1523/JNEUROSCI.21-14-05272.2001](https://doi.org/10.1523/JNEUROSCI.21-14-05272.2001)
9. Biernaskie J, Chernenko G, Corbett D (2004) Efficacy of Rehabilitative Experience Declines with Time after Focal Ischemic Brain Injury. *Journal of Neuroscience*, 24(5): 1245-1254. DOI: [10.1523/JNEUROSCI.3834-03.2004](https://doi.org/10.1523/JNEUROSCI.3834-03.2004)
10. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. (2016) Guidelines for Adult Stroke Rehabilitation and Recovery. *Stroke*, 47(6): e98-e169. DOI: [10.1161/STR.0000000000000098](https://doi.org/10.1161/STR.0000000000000098)
11. Murphy TH, Corbett D (2009) Plasticity during stroke recovery: from synapse to behaviour. *Nature Reviews Neuroscience*, 10(12): 861-872. DOI: [10.1038/nrn2735](https://doi.org/10.1038/nrn2735)
12. O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW (2006) 1,026 Experimental treatments in acute stroke. *Annals of Neurology*, 59(3): 467-477. DOI: [10.1002/ana.20741](https://doi.org/10.1002/ana.20741)
13. Stroke Unit Trialists' Collaboration (2020) Organised inpatient (stroke unit) care for stroke: network meta-analysis. *Cochrane Database of Systematic Reviews*, 2020(4): CD000197. DOI: [10.1002/14651858.CD000197.pub4](https://doi.org/10.1002/14651858.CD000197.pub4)
14. Langhorne P, Baylan S, Early Supported Discharge Trialists (2017) Early supported discharge services for people with acute stroke. *Cochrane Database of Systematic Reviews*, 2017(7): CD000443. DOI: [10.1002/14651858.CD000443.pub4](https://doi.org/10.1002/14651858.CD000443.pub4)
15. Langhorne P, Collier JM, Bate PJ, Thuy MNT, Bernhardt J (2018) Very early versus delayed mobilisation after stroke. *Cochrane Database of Systematic Reviews*, 2018(10): CD006187. DOI: [10.1002/14651858.CD006187.pub3](https://doi.org/10.1002/14651858.CD006187.pub3)
16. Veerbeek JM, Koolstra M, Ket JCF, van Wegen EEH, Kwakkel G (2011) Effects of Augmented Exercise Therapy on Outcome of Gait and Gait-Related Activities in the First 6 Months After Stroke: A Meta-Analysis. *Stroke*, 42(11): 3311-3315. DOI: [10.1161/STROKEAHA.111.623819](https://doi.org/10.1161/STROKEAHA.111.623819)
17. Vaynman S, Ying Z, Gomez-Pinilla F (2004) Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *European Journal of Neuroscience*, 20(10): 2580-2590. DOI: [10.1111/j.1460-9568.2004.03720.x](https://doi.org/10.1111/j.1460-9568.2004.03720.x)
18. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF (2012) Getting Neurorehabilitation Right: What Can Be Learned From Animal Models? *Neurorehabilitation and Neural Repair*, 26(8): 923-931. DOI: [10.1177/1545968312440745](https://doi.org/10.1177/1545968312440745)
19. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al. (2006) Effect of Constraint-Induced Movement Therapy on Upper Extremity Function 3 to 9 Months After Stroke: The EXCITE Randomized Clinical Trial. *JAMA*, 296(17): 2095-2104. DOI: [10.1001/jama.296.17.2095](https://doi.org/10.1001/jama.296.17.2095)
20. French B, Thomas LH, Coupe J, McMahon NE, Connell L, Harrison J, et al. (2016) Repetitive task training for improving functional ability after stroke. *Cochrane Database of Systematic Reviews*, 2016(11): CD006073. DOI: [10.1002/14651858.CD006073.pub3](https://doi.org/10.1002/14651858.CD006073.pub3)

21. Saunders DH, Sanderson M, Hayes S, Johnson L, Kramer S, Carter DD, et al. (2020) Physical fitness training for stroke patients. *Cochrane Database of Systematic Reviews*, 2020(3): CD003316. DOI: [10.1002/14651858.CD003316.pub7](https://doi.org/10.1002/14651858.CD003316.pub7)
22. Mehrholz J, Thomas S, Werner C, Kugler J, Pohl M, Elsner B (2017) Electromechanical-assisted training for walking after stroke. *Cochrane Database of Systematic Reviews*, 2017(5): CD006185. DOI: [10.1002/14651858.CD006185.pub4](https://doi.org/10.1002/14651858.CD006185.pub4)
23. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. (2017) Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. *International Journal of Stroke*, 12(5): 444-450. DOI: [10.1177/1747493017711816](https://doi.org/10.1177/1747493017711816)

11. Declarations

Funding

This literature synthesis received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare that they have no competing interests relevant to this article.

Data Availability Statement

This is a literature synthesis and no new clinical or experimental data were generated. All findings discussed derive from the cited publications, which should be consulted directly for their own data and code availability statements.

Ethical Approval

Not applicable. This article synthesizes previously published literature and did not involve new human participants, animal subjects, or primary data collection by the authors.

Citation: Haddad T, Saleh O, Saleh D. "Neuroprotective Effects of Early Rehabilitation Following Acute Ischemic Stroke." *J Neurol Brain Res* (2026): 001-010 doi: [10.5281/zenodo.22849451](https://doi.org/10.5281/zenodo.22849451)