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Time Is Brain—Quantified

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Background and Purpose—The phrase "time is brain" emphasizes that human nervous tissue is rapidly lost as stroke progresses and emergent evaluation and therapy are required. Recent advances in quantitative neurostereology and stroke neuroimaging permit calculation of just how much brain is lost per unit time in acute ischemic stroke.

Methods—Systematic literature-review identified consensus estimates of number of neurons, synapses, and myelinated fibers in the human forebrain; volume of large vessel, supratentorial ischemic stroke; and interval from onset to completion of large vessel, supratentorial ischemic stroke.

Results—The typical final volume of large vessel, supratentorial ischemic stroke is 54 mL (varied in sensitivity analysis from 19 to 100 mL). The average duration of nonlacunar stroke evolution is 10 hours (range 6 to 18 hours), and the average number of neurons in the human forebrain is 22 billion. In patients experiencing a typical large vessel acute ischemic stroke, 120 million neurons, 830 billion synapses, and 714 km (447 miles) of myelinated fibers are lost each hour. In each minute, 1.9 million neurons, 14 billion synapses, and 12 km (7.5 miles) of myelinated fibers are destroyed. Compared with the normal rate of neuron loss in brain aging, the ischemic brain ages 3.6 years each hour without treatment. Altering single input variables in sensitivity analyses modestly affected the estimated point values but not order of magnitude.

Conclusions—Quantitative estimates of the pace of neural circuitry loss in human ischemic stroke emphasize the time urgency of stroke care. The typical patient loses 1.9 million neurons each minute in which stroke is untreated. **(*Stroke*. 2006;37:263-266.)**

Key Words: brain ischemia ■ imaging techniques ■ neurons ■ physiopathology

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The phrase "time is brain" emphasizes that human nervous tissue is rapidly and irretrievably lost as stroke progresses and that therapeutic interventions should be emergently pursued.[1,2] This general call to action in acute stroke care was adapted from its predecessor in acute coronary care ("time is muscle"),[3] both tracing their lineage to Benjamin Franklin's original aphorism, "time is money."

To date, the proposition "time is brain" has generally been advanced only as a broad, qualitative statement. Just how much brain is lost per unit of time has not been the subject of detailed analysis. Recent advances in stroke neuroimaging and quantitative neurostereology now permit informed estimation of how much brain is lost per unit time in acute cerebral ischemia. Substantive, quantitative statements of the pace of neural circuitry loss in acute ischemic stroke are likely to further enhance the impact of "time is brain" as a rallying cry on patient and health provider behavior.

The Growth Function of an Ischemic Stroke

The appropriate formula for calculating the rate of tissue loss in acute brain ischemia at a particular point in time after onset depends on the shape of the growth function of the typical ischemic stroke. The morphology of the growth function is not well-defined for human stroke and is model-specific in various experimental animal stroke models,[4] with a logarithmic pattern being most common[5,6] but sigmoidal[7] and other patterns also observed. Growth patterns in the geometrically more complex human cerebrum may differ from those in the rodent.[8]

However, to calculate the average rate of growth over the entire period of infarct maturation, the morphology of the growth function does not need to be known. Dividing total growth by total elapsed time yields the average rate of infarct growth over the entire duration of infarct maturation for all possible growth function shapes. Although this simple linear growth function will deviate from the actual rate of growth at particular points in time, it will accord fully with the average rate of growth over the entire duration of ischemia. Linear growth estimates are also directly biologically relevant to most of the period of human brain ischemia if the actual shape of the growth function characterizing human infarcts is the logarithmic pattern seen commonly in animal models. In this pattern, after a brief period of rapid growth soon after onset, most infarct expansion occurs in a relatively linear fashion, followed by a tail of slow, final infarct completion.

With a linear growth function, input values for 3 variables are needed to derive an estimate of how many brain elements are lost per unit time in a typical ischemic stroke: (1) the

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interval from onset to completion of a typical ischemic stroke, (2) the volume of brain tissue compromised in a typical ischemic stroke, and (3) the total number of the neural circuit elements of interest (neurons, synapses, myelinated fibers, etc) in the human brain. From these values, the rate of brain element loss can be calculated by the equation:

$$\text{Brain elements lost per unit time} = [(V_I/V_B) \times T_B]/\text{time}$$

where V_I=infarct volume, V_B=volume of the whole brain (or brain region), not including ventricles, and T_B=total number of the elements (neurons, synapses, etc) in the whole brain (or brain region). Research advances over the last 2 decades allow us to specify reasonable, albeit not definitive, input values for these variables.

Duration of Infarct Growth

The interval from ischemic stroke onset to completion varies widely from patient to patient, reflecting interindividual differences in site of vessel occlusion, degree of ischemic preconditioning, richness and patency of collaterals, systemic blood pressure, blood volume, serum glucose, and many other factors.[9] Two broad categories of studies provide evidence regarding the average duration of infarct growth in humans: neuroimaging studies that delineate the ischemic penumbra at different timepoints after onset and therapeutic studies that characterize the time interval in which efficacious therapies are of benefit.

Although modest sample sizes and infrequent repeated measures limit the time resolution of studies, MRI diffusion-perfusion mismatch and PET [18F]fluoromisonidazole and misery perfusion investigations suggest that the timepoint at which half of patients with large vessel ischemic stroke show evidence of persisting penumbra is between 8 to 12 hours.[10,11,12] Similarly, randomized clinical trials of intravenous and intra-arterial thrombolytic therapy and cohort studies of transcranial Doppler monitoring of the time course of thrombolytic-related recanalization have suggested that the time window in which reperfusion is beneficial extends to at least 6 hours.[13,14,15] This estimate is a lower bound because these trials used agents that achieve effective recanalization in only a proportion of patients and harm others by producing intracerebral hemorrhage. An agent that achieved instant, 100% recanalization without any adverse effects would undoubtedly have a longer time window in which it would be beneficial. A reasonable estimate for the interval from onset to completion of the average large vessel human ischemic stroke is 10 hours, varying this value in sensitivity analysis from 6 to 18 hours.

Infarct Volume

Many clinical trial and large cohort studies have characterized the final volume of ischemic stroke, with findings ranging widely, from 19 to 138 mL.[7,16] Differences in measured stroke volumes between series reflect several factors, including timing of final imaging, scanner type, acquisition sequences used, selection bias, and ascertainment bias.

The timepoint at which imaging of final infarct is obtained has a substantial impact, as cytotoxic edema causes infarcted tissues to swell to larger than their prestroke volume over the first 3 to 8 days, and organization and retraction causes them to shrink to less than their prestroke volume by 2 weeks to 3 months.

Computed tomography (CT) scans tend to underestimate infarct size because of less contrast between tissue compartments, less spatial resolution, and the "fogging" effect causing isodense appearance of some infarcted tissue during the first 2 weeks to 3 months poststroke. Unless fluid-attenuated inversion recovery (FLAIR) is used to suppress CSF background, magnetic resonance T2-weighted images may overestimate lesion size because of partial volume averaging. Also, both T2-weighted and FLAIR sequences are vulnerable to the fogging effect, though much less so than CT.[17]

Selection bias is an especially difficult problem in the literature. Most clinical trials exclude lacunar, very mild, and very severe stroke patients from study entry. In general, more mild and lacunar than severe patients are excluded. As a result, the typical median entry National Institutes of Health Stroke Scale (NIHSS) severity of clinical trial populations is in the 8 to 18 range, whereas the median presenting NIHSS severity of unselected patients is 5 to 6.[18,19] Ascertainment bias also afflicts stroke volume studies because patients with large volume strokes differentially tend to die or become too unstable to travel to a scanner in the interval from study entry to outcome scan.

The best estimate of the final volume of the average supratentorial infarct would be provided by a study enrolling consecutively encountered ischemic stroke patients, with broad entry criteria, no effective infarct-volume–reducing treatment applied, MRI (rather than CT) measurement of stroke volume, outcome scan acquisition at a uniform timepoint in all patients, outcome scan completion in all enrolled patients, and registration of entry brain anatomy and final infarct volume scans, permitting warping of the final infarct to correct for tissue swelling or shrinkage. No such study is available. For supratentorial ischemic strokes, the report of Warach and colleagues comes closest (broad entry criteria, final uniform timepoint outcome scans in all patients, utilization of MR).[19] Averaging the day 7 (57.6 mL, SE 9.3) and the 3-month (50.8 mL, SE 9.6) infarct volumes in the placebo group from this study yields 54 mL as a reasonable estimate of the average final volume of a supratentorial ischemic stroke, which may be varied in sensitivity analysis from 19 to 100 mL. Because the volume of the human forebrain with CSF spaces excluded is 1020 mL [coefficient of variation (CV)=0.14], the typical 54 mL supratentorial infarct destroys 5.29% of the human forebrain tissue.[20]

Total Counts for Neurons, Synapses, and Myelinated Fiber Length

Investigations of brain morphometry and the total number of neurons, synapses, and myelinated fibers in the human brain span >50 years. Early estimates of neuron number ranged widely (10 to 500 to 1000 billion), reflecting lack of rigor in tissue sampling methodology and imprecision of early 2-dimensional counting methods. Refinements in quantitative neurostereology have recently yielded more precise projections. Modern quantitiative neurostereology allows unbiased estimation of the total number of neurons, glia, synapses,

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Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km/4470 miles	36 y
Per Hour	120 million	830 billion	714 km/447 miles	3.6 y
Per Minute	1.9 million	14 billion	12 km/7.5 miles	3.1 wk
Per Second	32 000	230 million	200 meters/218 yards	8.7 h

and myelinated fibers by using a disector probe that samples isolated particles with a uniform probability in 3-dimensional space regardless of their size, shape, or orientation in tissue.[20]

The total number of neurons in the average human brain is ≈130 billion. However, cerebellar granular cells contribute disproportionately to this sum. There are 21.5 billion (CV 0.19) neurons in the typical human neocortex and no less than 109 billion (CV 0.17) granule cell neurons in the typical cerebellum.[20,21] Given the divergent cellular architectures of the forebrain and the hindbrain and the fact that the great preponderance of ischemic strokes are supratentorial, it is most sensible to estimate neuronal circuitry in a typical ischemic stroke based on events occurring in the forebrain. Volumetrically, human forebrain gray matter is on average comprised of the neocortex (86%), the archi/paleocortex (7%), and the central gray (7%).[20] The total number of neurons comprising the neocortex are well-delineated.[20] The total number of neurons in the archi/paleocortex and the central gray are not well-described but can be roughly imputed from studies of neuronal density in select compartments.[22,23] The resulting estimated total number of neurons in the average human forebrain is 22 billion. Stereological methods have also demonstrated that there are an average of 150 trillion (CV 0.15) synapses in the average human neocortex.[24] Applying the same imputations to synapses as to neurons yields an estimated 157 trillion synapses in the average human forebrain.

Several studies have used neurostereological techniques to estimate the total length of myelin fibers in human hemispheric white matter. Among estimates ranging from 118 000 to 180 000,[20,25] the figure of 135 000 km (84 500 miles) is a reasonable figure to use as the total length of myelinated fibers in the average human forebrain.[26] Stereological measurement of brains from across the human lifespan has demonstrated that the neocortex loses ≈31 million neurons per year in normal aging.[20]

Time Is Brain Quantified

The Table shows the values for the pace of brain circuitry loss in a typical large vessel supratentorial ischemic stroke derived from the above inputs.

Every minute in which a large vessel ischemic stroke is untreated, the average patient loses 1.9 million neurons, 13.8 billion synapses, and 12 km (7 miles) of axonal fibers. Each hour in which treatment fails to occur, the brain loses as many neuron as it does in almost 3.6 years of normal aging.

These estimates are robust across the range of values interrogated in sensitivity analysis. Varying single inputs to their maximum or minimum alters the estimates up or down only 3-fold. (For example, inputting into the neurons lost per unit time formula a low value of 6 hours and a high value of 18 hours for the duration of evolution of stroke, rather than the best estimate value of 10 hours, yields, respectively, rates of neuronal loss estimates of 3.2 and 1.1 million neurons per minute, rather than the best estimate of 1.9 million.) These estimates apply only to large vessel, supratentorial ischemic strokes, the most common ischemic stroke subtype. Lacunar and infratentorial ischemic strokes likely have different values, which are less reliably estimated from the current literature.

A Call to Action

Densely packed, intricately patterned, substrate of mind and awareness, the human brain is a wonder of nature. In an acute ischemic stroke, vast numbers of neurons, synapses, and nerve fibers are irretrievably lost every moment in which treatment does not occur. The figures stagger and motivate. Ischemic stroke is a highly treatable neuroemergency. For patients experiencing acute ischemic stroke, and for the physicians and allied health personnel treating them, every second counts.

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