

Neurobiology and Human Behaviour
Matthew Belmonte
solutions to Lent term problems

An amphipathic molecule has both hydrophilic and hydrophobic groups. Such a structure aids penetration of the aqueous/membrane boundaries that constitute the blood-brain barrier.

An allosteric ligand binds at a site distinct from the active site, and operates by changing the molecule's conformation. Whereas GABA binds its receptor on the beta subunit, the benzodiazepines bind the same receptors on the alpha subunit, and also depend on steric interaction with the gamma subunit for their full effect.

The therapeutic index is the ratio between the effective dose and the harmful dose of a drug, commonly computed as LD₅₀/ED₅₀ (*i.e.*, the dose that is lethal in 50% of test animals versus the dose that is effective in 50%). A high therapeutic index indicates a relatively safe drug.

Valproate blocks GABA catabolism by competitively inhibiting the second-stage catabolic enzyme succinate semialdehyde dehydrogenase.

Dopamine won't pass the blood-brain barrier; L-DOPA will.

Excitotoxicity is a phenomenon in which over-active neurons die. Its putative mechanism relates both to epilepsy and to ischaemia. In the case of epilepsy, chronic depolarisation leads to a large calcium influx. The resulting high concentration of calcium activates proteases that normally are involved in local modifications to the cytoskeleton during exocytosis and synaptic plasticity. When chronically activated, though, these proteases digest the cell, producing a degree of damage that induces apoptosis (programmed suicide of severely damaged cells). In the case of ischaemia, a decrease in glucose lowers cellular metabolism, producing a decrease in the concentration of ATP and a consequent reduction in the activity of the sodium-potassium ATPase. The result is an increase in intracellular sodium, leading to chronic depolarisation. The remainder of the pathway is as in the case of epilepsy.

Here are some techniques that you could mention:
fMRI – millimetres, seconds

PET – centimetres, minutes (but good for binding assays – can use radioligands)
EEG, MEG – centimetres, milliseconds
intracranial recording – microns, milliseconds
lesions – as precise as the surgical technique or nature of the accidental injury
allows, no time resolution

Horizontally distinct layers (six in neocortex) and vertically connected columns
and minicolumns.

Blindsight is the above-chance detection of optical stimuli by patients who
have no conscious visual awareness. The two main proposed explanations
are the propagation of visual information via a subcortical pathway (*e.g.* the
retinotectal projection) or the processing of visual information in small islets
of cortex that have been spared from the lesion.

Although most cases of neglect follow lesions of the right parietal lobe, neglect
can also be a symptom of lesions in dorsolateral prefrontal cortex, frontal eye
fields, superior colliculus, and the pulvinar nucleus of the thalamus.

Many simple tests of neglect are available – *e.g.* line bisection, clock-face
drawing, visual extinction.

Amnesia can be a symptom of lesions in the medial temporal lobe (hippocampal
complex and adjacent cortices), dorsolateral prefrontal cortex, or diencephalon.
In addition, loss of skills or loss of particular sensory aspects of memory
can result from lesions in a wide array of locations subserving the relevant
processing – *e.g.* temporo-parietal junction, cerebellum.

The two main subtypes are declarative memory (knowing that) and procedural
memory (knowing how). Declarative memory can be subdivided into episodic
memory (events) and semantic memory (facts). Finer taxonomies of memory
are possible – *e.g.* subdivisions by particular sensory modality or skill.

The patient likely has suffered bilateral damage to the hippocampus. The
lack of severity of the patient's mnemonic deficit reflects the probability that the
adjacent cortices which make up the rest of the hippocampal formation have
likely been completely spared. The hippocampus is particularly vulnerable to
ischaemic damage, probably because of its high density of NMDA receptors.
(See question on excitotoxicity above.)

Because the hippocampus is enfolded by the adjacent entorhinal, perirhinal, and parahippocampal cortices, a surgical approach to the hippocampus inevitably damages these adjacent cortical regions. Although it was initially believed that the hippocampus was absolutely critical, it turns out that lesions of adjacent cortex produce greater behavioural impairment than selective lesions of the hippocampus itself.

The diagnosis is agnosia, and the patient has likely suffered a lesion in the temporal lobe.

Entorhinal cortex, perforant path, dentate gyrus, mossy fibres, CA3, Schaffer collaterals, CA1, subiculum.

Entorhinal cortex and the subiculum project directly to neocortex.

CA3 and the subiculum project subcortically via the fornix and fimbria.

Single-unit recordings from the hippocampus reveal correlations between cells' firing rates and the animal's presence in a particular location ('place cells'). Rats with hippocampal lesions are impaired at learning the location of the submerged platform in the Morris water maze. In humans, structural MRI reveals enlargement of the hippocampus in London taxi drivers, a population in whom demands on spatial memory are high. fMRI reveals hippocampal activation during tasks of spatial memory. However, the apparent spatial function of the hippocampus may simply be the most obvious aspect of a general role in binding together the separate sensory elements of experiences to form memories.

Supervised learning uses an externally supplied error signal to correct inappropriate outputs. In unsupervised learning there is no error feedback; rather, correlations in the inputs are detected in order to minimise some intrinsic measure of error. An example of a supervised learning process is cerebellar learning, where the error signal seems to be supplied by climbing fibres. Hippocampal learning, in contrast, seems unsupervised.

Firstly there is the circumstantial evidence: the voltage-dependent magnesium blockade of the ion channel is exactly the sort of neurochemical mechanism that could implement a logic gate, that is, could selectively detect an excitatory input to a neuron that has already received one such input. Also there is the observation that AP5, an antagonist selective for NMDA receptors, mimics

the effect of a hippocampal lesion on maze learning.

Broca's aphasia: non-fluent, semantics intact, comprehension spared.

Wernicke's aphasia: fluent, no semantics, no comprehension.

Conduction aphasia: paraphasic substitutions, and impaired repetition.

Transcortical motor aphasia: resembles Broca's, but repetition is spared.

Transcortical sensory aphasia: resembles Wernicke's, but repetition is spared.

anomia: selective impairment in naming – could be classified as a memory deficit as much as a language deficit.

This patient's symptoms of transcortical motor aphasia and impairment in complex motor sequences suggest a frontal lesion.

While parietal cortex seems more directly involved in implementing the shift of visual attention (or programming the eye movement), the activity of frontal cortex is more correlated with the task of remembering the location towards which the eye movement is to be targeted. Lesion studies and functional imaging can provide further information when combined with behavioural tasks that separate the two factors of spatial memory and eye movements – for example, subjects could be asked to remember a location, and then to move their eyes to that location only if a particular signal is given.

Orbitofrontal cortex is particularly susceptible to injury from rapid acceleration (or deceleration) since it abuts the rough inner surface of the skull, directly above the sinus. (Under conditions of rapid acceleration, skull can go through brain like a cheese-grater.)