ENGINEERING TRIPOS   PART IIA

Monday 26 April 2010   9.00 to 10.30

Module 3G3 Answer: CRIB

INTRODUCTION TO NEUROSCIENCE

*Answer not more than **three** questions.*

All questions carry the same number of marks.

*The **approximate** percentage of marks allocated to each part of a question is indicated in the right margin.*

STATIONERY REQUIREMENTS   SPECIAL REQUIREMENTS
Single-sided script paper

> **You may not start to read the questions printed on the subsequent pages of this question paper until instructed that you may do so by the Invigilator**

Version: Final version

1　(a)　The following questions are about hearing.

(i)　Describe the features of the external ear (also known as the pinna or auricle) that are relevant for sound localisation and the mechanism by which they work.

Answer: The external ear has a complex anisotropic shape which produces peaks and notches in the sound spectrum that depend on the sound location relative to the ear. As such, it is a major contributor to the shape of the head-related transfer function. In particular, the pinna act as a notch filter as it allows multiple paths for sound to reach the ear canal due to a combination of direct and indirect paths due to reflection. High-frequency sounds can be reflected and arrived out of phase leading to destructive interference. This is greatest when the path difference is half a wavelength and leads to an expected notch filter at about 10 kHz. As the pinna is a more effective reflector of sounds from the front there is a pronounced notch for sounds in that location whereas sounds above produce a less marked notch filter. Therefore the shape of the external ear is useful for localisation particularly for monaural localisation and for elevation. This can be shown by filling part of the outer ear with putty which affects sound localisation. In addition, animals such as rabbits can control the orientation of the external ear independent of the head and this can aid localisation of sound.

(ii)　What role does the middle ear play in hearing and why is it necessary?

Answer:　The middle ear is an air-filled pouch containing three bones which transmit vibrations of the eardrum to the inner ear through the oval window. There are two features which make this complex chain of transmission necessary. The first is that the fluid in the cochlea is hard to vibrate with air and therefore if sound waves were to directly strike the oval window they would be reflected. The middle ear performs an impedance matching role with the inner ear taking the weak vibrations over a large area and then acting as a lever system similar to an hydraulic press to produce a more forceful vibration at the oval window which can displace the cochlear fluid. In addition the middle ear performs a gating role with the muscles in the middle ear able to contract in response to loud sounds or in a pre-programmed way in response to one's own speech thereby protecting the inner ear from potentially damaging loud sounds.

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(iii)   Describe the evidence that the inner ear performs active amplification and the mechanism by which it amplifies incoming sound.   [40%]

Answer: Evidence for an amplifier in the inner ear comes from three sources. First performance is too good from passive properties alone as a large portion of energy would be dissipated in the viscosity of the fluid. Second after a click is played into the ear sound is emitted by the ear which has more energy and is, therefore ,not simply echoes. Third, using sensitive microphones, spontaneous acoustic emissions can be heard even in the absence of incoming sound. The amplification process is believed to occur through the action of the outer hair cells which demonstrate electromotilty. As their hair cells are bent by motion of the tectorial membrane this is converted into an electrical signal and causes a change in length of the outer hair cell through a contractile protein in their membrane. Therefore the outer hair cells act as a microphone, amplifier and loudspeaker all in one and can provide around a hundredfold amplification.

(b)   The following questions are about vision.

(i)   Describe the spatial frequency (channel) theory of vision. Provide two pieces of experimental evidence that support the theory.

Answer: The theory proposes that the two-dimensional luminance of an image is represented as a combination of elements such as sinusoidal gratings of different spatial frequencies, amplitudes, phases and orientations. Therefore the neurons are effectively doing a two-dimensional Fourier analysis. Importantly the theory suggests that the different components are processed by separate channels. Evidence for this comes from fatiguing one particular frequency leads to a dominant perception of the other spatial frequencies such as in the spatial frequency aftereffect. In addition the processing of each frequency is independent of others and so if two different frequencies sinusoids are combined the detectability of the stimulus is independent of the phase of the combination. In addition, neurophysiological evidence from the cells in visual cortex show receptive field properties which are wavelet like (sinusoid windowed by a Gaussian) of varying spatial frequencies.

(ii)   In three-dimensional (3D) movies a separate image is provided to each eye to create the perception of depth. What cues to depth are such 3D movies

unable to reproduce?

Answer: There are three cues that such films cannot replicate in depth perception. First, it cannot fool the accommodation system in which the focal length of the lens is adjusted. Second, without tracking the head and adjusting the image it can not replicate motion parallax. Third, it can not replicate the difference in convergence angle between the eyes for different depths.

(iii) Explain what colour constancy is and why it is beneficial. Give an example of a mechanism by which colour constancy might arise.

Answer: The frequency of light emanating from an object depends on two features. First, it depends on the illumination spectral power and second on the reflectance function of the surface. Colour constancy refers to the ability of the visual system to discount the illuminant and extract the reflectance function which is integral feature of the object. One mechanism which has been proposed is based on a double colour opponents cells which would have, for example, centre which is excitatory for green and excitatory for red with a surround that is inhibitory for red and excitatory for green.

[40%]

(c) The following questions are about sensory replacement technology.

(i) Describe the structure and mechanism of action of a cochlear implant.

Answer: A cochlear implant has three main parts. An external part consists of an hearing aid, battery power and decomposes sound into the component frequencies. A radio telemetry link then convey the information as well as power to the implant. The implant itself consists of 20 or so electrodes that sit in the lower chamber of the inner ear and generate electrical impulses to the inner cochlear nerve by an array of electrodes. The mechanism of action is that the microphone picks up the sound and extracts the amplitude envelope for different band pass filtered frequencies. The envelope is then used to modulate the amplitude of a constant rate electrical biphasic pulse train at around 1500 cases per second.

(ii) Why is sensory replacement for the loss of an eye a more difficult problem then sensory replacement for loss of hair cells in the inner ear. Your answer should include a brief comparison of implants in the eye and in the visual cortex.

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[20%]

Answer: Replacement of a loss of an eye is harder than that for loss of the hair cells as the coding is more complex. In the ear there is a very simple linear coding between frequency and location along the cochlear. Therefore, it is relatively simple to decompose sound into the component frequencies and amplitudes. In contrast coding in the visual cortex is complex and there is no simple mapping of features in the visual space onto features in the visual cortex. In contrast by stimulating in the retina there is a simpler topographical mapping and therefore damage to photoreceptors is a more promising avenue.

2   (a)   Write notes on:

(i)   Why the probability of perceiving a sensory stimulus tends to be an increasing sigmoidal (S-shaped) function of stimulus intensity and what the slope of the sigmoidal function can tell you about sensory processing.

Answer: The sigmoidal nature of the curve arises from an input signal which is corrupted by noise. The noise is assumed to be approximately Gaussian in nature. If the signal which is the combination of the input and noise crosse a threshold then it will be percieved. Therefore the probability of perceiving the stimulus is the integral of a Gaussian curve to the right of the threshold. Therefore as the intensity of the input increases the probability of perceiving it is a cumulative integral of a Gaussian curve known as probit function which closely resembles a sigmoid function. The slope allows one to estimate the amount of noise in the processing with a steeper slope meaning less noise.

(ii)   The mechanisms for novelty detection in sensory processing.

Answer: The brain is interested in novelty, particularly sensitive to things that change. Examples of this include spatial changes which are emphasised by lateral inhibition in skin and in the retina. Similarly, visual processing is more sensitive to changing stimuli rather than static stimuli. In addition sensory adaptation (fatigue) reduces responses to constant stimulus is a process calibration and that underlies features such as a spatial after-effect or the colour contrast after-effect.

(iii)   The neural basis of the stretch reflex and its use.   [50%]

Answer: The stretch reflex consists of a monosynaptic pathway from the muscle spindle situated in parallel with the muscle sensitive to stretch through a single synapse in the spinal cord to the alpha motor neurone which contracts the same muscle. In addition there are a synaptic pathways which inhibit the antagonist muscle. The stretch reflex is a basic fast response to muscle stretch which can maintain stability in the presence of external perturbations.

(b)   The following questions are about the action potential.

(i)   What mechanisms are responsible for the repolarising phase of the action potential? In particular describe the states of the gates within any

channels you describe.

Answer: The two mechanisms of repolarisation are the opening of potassium channel n gates and the closing of the sodium channel m gates.

(ii) Describe, with the aid of a sketch, the results of a voltage clamp experiment conducted using a typical axon (without application of any drugs). Discuss the significance of each of the important features of the sketch. What are the advantages of using a voltage clamp to study the axon?

Answer:
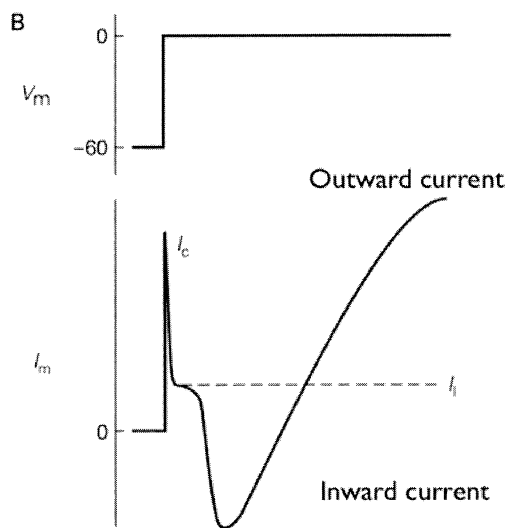
The graph shows an early, transient downward deflection of the tracing, referred to as an "Early Inward Current", that represents an inward-directed Sodium current, and (ii) the prolonged upward deflection of the tracing, referred to as the "Delayed Outward Current", and which represents an outward-directed Potassium current. These two currents reflect the underlying behaviour of voltage-gated channels. The advantage of using voltage clamp technique is that the potential could be clamped at any level to examine the time varying current independent of changes in voltage. This is particularly important as the channels are both time and voltage dependent and therefore by clamping one it is possible to study the time-dependence at a range of fixed potentials.

(iii) What is the role of the myelin sheath in action potential propagation.

　　　　　(TURN OVER for continuation of Question 2

Explain how it works. [50%]

Answer: The spread of an action potential along axons depends on how quickly the voltage settles to a new level away form the action potential site. This depends both on the axial resistance and the capacitance of the membrane. Myelination increases the membrane thickness by about hundredfold and therefore decreases the membrane capacitance. This requires less charge to be deposited for the same change and voltage. Therefore by covering the axon, the action potential can jump between the gaps between the myelin (the nodes). Such white-matter therefore allows for fast propagation and the channels are only present at the nodes

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3   (a)   Describe the experimental procedure for habituating the gill-withdrawal reflex in the Aplysia. In response to stimulating the siphon over the course of habituation, specify for each of the following quantities whether they increase, decrease or do not change

      (i)   activity of the sensory neuron;

      (ii)   amount of transmitter released by the sensory neuron;

      (iii) activity of interneurons;

      (iv)   amount of transmitter released by interneurons;

      (v)   activity of the motor neuron;

      (vi)   amount of transmitter released by the motor neuron.   [20%]

Answer: Habituation can be achieved by repeatedly stimulating the siphon of the animal is with an innocuous stimulus (eg. by touching it with a brush). In response to stimulating the siphon over the course of habituation:

      (i)   activity of sensory neuron: does not change;

      (ii)   amount of transmitter released by sensory neuron: decreases;

      (iii) activity of interneurons: decreases;

      (iv)   amount of transmitter released by interneurons: decreases;

      (v)   activity of motor neuron: decreases;

      (vi)   amount of transmitter released by motor neuron: decreases;

(b)   Describe the experimental procedure for inducing and demonstrating homosynaptic and heterosynaptic long-term depression.   [20%]

Answer: For homosynaptic depression, an excitatory pathway (such as the Schaffer collaterals in the hippocampus, running from CA3 pyramidal cells to CA1 pyramidal cells) needs to be stimulated with low-frequency ($\sim$ 10 Hz) stimulation. The size (or slope) of EPSPs needs to be compared in the postsynaptic cells (eg. CA1 pyramidal cells) in response to stimulating the same pathway, before and after the low-freqquency stimulation.

For heterosynaptic depression, an excitatory pathway (such as the Schaffer collaterals in the hippocampus, running from CA3 pyramidal cells to CA1 pyramidal cells) needs to be stimulated such that LTP is induced, eg. with high-frequency ($\sim$ 100 Hz)

stimulation. The size (or slope) of EPSPs needs to be compared in the postsynaptic cells (eg. CA1 pyramidal cells) in response to stimulating another pathway leading to the same postsynaptic cells (eg. the commissural pathway), before and after inducing LTP in the first pathway.

In both cases LTD occurred if the size (or slope) of EPSPs after the inducing protocol is smaller than before.

(c)   In a classical conditioning experiment, two different CSs, CS_1 (a light), and CS_2 (a tone) are used to signal the same US (delivery of food). Before training, none of the CSs evoke a response. During training, three kinds of trials are intermixed:

- CS_1, US
- CS_2, US
- $(CS_1 + CS_2)$, no US

where X, Y stands for sequential presentation of stimuli X followed by Y, and (X+Y) means simultaneous presentation of stimuli within a trial. After training, the following are observed in response to the CSs (where the response is salivation):

- $CS_1 \longrightarrow$ response
- $CS_2 \longrightarrow$ response
- $(CS_1 + CS_2) \longrightarrow$ no response

(i)   Explain with reasons whether the Rescorla-Wagner rule can account for these results.

Answer: These results cannot be accounted for by the Rescorla-Wagner (RW) rule, because there the strength of response for a combination of stimuli is always the sum of the response strengths for the individual stimuli. Therefore, the rule either predicts that the two stimuli individually cause a response, and together they also lead to a (greater) response, or it predicts that neither the two stimuli individually nor their combination elicits a response.

(ii)   Someone proposes a new theory to describe animal learning in this experiment. The new theory starts from assuming that an animal's response to a combination of CSs reflects how much it predicts the occurrence of a US. In the case of two CSs this prediction, r, is given by the following equation:

$$r = w_1 s_1 + w_2 s_2 + w_3 s_1 s_2$$

where s_1 and s_2 indicate the presence (1) or absence (0) of CS_1 and CS_2,

respectively, and w_1, w_2, and w_3 are prediction strength parameters. Just like the Rescorla-Wagner theory, the new theory also assumes that during learning the prediction strength parameters are gradually changed over trials such that the average squared prediction error $E = (u - r)^2$ is minimised, where u indicates the presence (1) or absence (0) of the US in a trial.

A. Write down the equations describing how each of the prediction strength parameters will change in a trial, based on u, s_1, s_2, and r, according to this new theory.

Answer: To minimise squared error, the change in a prediction strength parameter, w, should be negatively proportional to the (partial) derivative of the squared error, E, with respect to that parameter:

$$\frac{dw}{dt} \propto -\frac{\partial E}{\partial w}$$

This results in the following update rules for the three parameters:

$$w_1 \rightarrow w_1 + \varepsilon (u - r) s_1, \quad w_2 \rightarrow w_2 + \varepsilon (u - r) s_2, \quad w_3 \rightarrow w_3 + \varepsilon (u - r) s_1 s_2$$

B. Explain with reasons if this new theory can account for the experimental results described above. [60%]

Answer: This new theory can account for the experimental results by setting w_1 and w_2 to have large positive values, while setting w_3 to have a large negative value ($w_3 = -(w_1 + w_2)$).

4   (a)   Sketch the postsynaptic current as a function of the postsynaptic membrane potential for an AMPA, and an NMDA receptor under the following four conditions:

(i)   when glutamate is available in the synaptic cleft;

(ii)   when glutamate and AP5 are available in the synaptic cleft;

(iii)   when AP5 is available in the synaptic cleft;

(iv)   when NMDA is available in the synaptic cleft.   [40%]

Answer: The postsynaptic currents will look like:
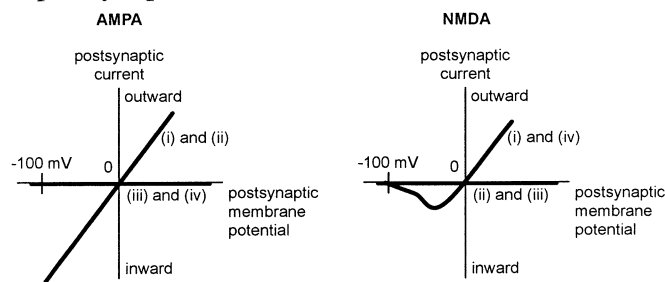
When the AMPA receptor opens due to ligand binding, the current is a linear function of voltage (increasing outward current for increasing voltage, reversal potential around ~ 0 mV), because the conductance does not depend on voltage. When the NMDA receptor opens, its current is a linear function of voltage for high enough voltages (above ~ 0 mV), as for the AMPA receptor, but decreases back to zero for lower voltages (below ~ -50 mV) because its conductance is decreased due to the Mg^{2+} block. These receptors open and close in the four conditions as follows:

(i)   When glutamate is available in the synaptic cleft: both recpetors are glutamate receptors, so both will be open.

(ii)   When glutamate and AP5 is available in the synaptic cleft: AP5 is a selective NMDA antagonist, so only the AMPA receptor is open.

(iii)   When AP5 is available in the synaptic cleft: neither receptor opens.

(iv)   When NMDA is available in the synaptic cleft: NMDA is a selective NMDA agonist, so only the NMDA receptor is open.

(b)   Describe how the Morris water maze and its variants are used in learning experiments. Include the following in your answer:

•   What are the physical properties of the apparatus?

•   What is the animal's task?

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- What aspects of behavioural performance are measured to quantify learning?

- What variants of the Morris water maze can be used to show that a treatment specifically impairs spatial learning as opposed to other factors required for the task?   [40%]

Answer:

- The Morris water maze is a circular tank of diameter ~ 1 m filled with opaque (eg. milky) water used to measure spatial learning.

- On each trial, the animal (usually a rat) is started from some position close to the wall of the tank and has to swim to find a platform hidden under the surface of water. (There is a natural motivation for performing this task, because rats don't like being in water.) On consecutive trials, the rat is started from different (random) positions, but the platform remains in the same place (relative to some external reference frame, eg. the experimental room), so the rat needs to remember the location of the platform to be able to improve its performance over trials.

- Performance measures include escape time (time from start until the rat fins the platform), path length (overall distance taken until finding the platform), time spent in target quadrant or near the location of the platform (on catch trials, when the platform is not in its usual place).

- Starting a rat from the same position across trials will allow procedural learning to be effective (learning the sequence of actions needed to reach the platform). Making the water non-opaque will allow the rat to see where the platform is, thereby also (partially) reducing the need for spatial memory for solving the task. If a treatment impairs performance in the original Morris water maze but not in these modified tasks, then it specifically affects spatial learning.

(c)   Explain the difference between retrograde and anterograde amnesia. Which kind of amnesia did H.M. suffer from?   [20%]

Answer: Retrograde amnesia means that one is not able to recall memories from the past, ie. memories that had been stored before some impairment (eg. a lesion) was inflicted. Anterograde amnesia means that new memories can not be stored after the impairment is inflicted. H.M. suffered from both kinds of amnesia, although his

retrograde amnesia was milder and graded (earlier memories were more spared).

END OF PAPER