Neurobiology of Exceptionality

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Preface

Over the last decade there has been considerable progress in our understanding of the neurobiological basis of many psychologically related phenomena. Significant research endeavors have been mounting in both basic cellular and animal neuroscience. In terms of human behavioural research in neuroscience new and exciting research is now emerging in understanding the causes of the more common psychiatric traits. Certainly drug research in psychiatric disorders has grown exponentially over the last few years. In terms of psychiatry, more often than not, much of this research has focused on the most prevalent psychiatric disorders such as schizophrenia and depression.

As a researcher involved in understanding the neurobiological basis of both psychological and psychiatric traits I am often asked to provide sources of information and references for integrated reviews and expert opinions that focus on the neurobiology of what I might call less frequently studied but important psychological traits and psychiatric disorders. Such traits are often but not exclusively related to childhood behaviours and disorders and invariably involve an understanding of important psychological processes. Unfortunately there is much less research on the neurobiology of constructs such intelligence, personality and creativity and disorders such as ADHD, autism, mental retardation and antisociality. Moreover the research in this field is not easily accessed. Although there are active research groups studying these phenomena, there is not the same sort of resources allocated for research into the large adult disorders such as depression and schizophrenia as understanding human intelligence. This is a shame in many ways, because clearly there is a need for research on the biological basis of important traits such as intelligence and creativity and childhood disorders such as autism. One of the main aims of this book is to provide some coverage of the neurobiology of lesser researched and profiled psychological and psychiatric traits.

Although there are select individual sources of information on some of the topics covered in this book available elsewhere, there is no one single source

that provides up to date accounts, that are easily accessible to researchers, psychologists, teachers, students and parents. Indeed the chapters in this book cover a wide range of research on the neurobiology of fascinating psychological and psychiatric traits and are intended to help readers quickly understand our current knowledge of the biological processes for each of these different areas. In this regard I believe the book will be useful to both researchers, educators and parents.

In this book I have invited leading researchers in different areas to write comprehensive reviews on topics that I believe will be of great interest to researchers, students, educators, parents and psychologists. Indeed I believe that such a book is important for several reasons. First we must continue to attract a new generation of researchers into studying the neurobiological basis of these traits which have traditionally been under-studied. Second, the information contained in this book is long over due for parents who are interested in not just the behavioural information relating to childhood and other disorders but the underlying biological basis of these behaviours in their children. Often, parents make important decisions for their children without the requisite knowledge to make these decisions. This is not a criticism of parents. Up until recently such information was not easily accessible. Perhaps the information contained in the chapters in this book may assist parents in better understanding these disorders. Third, and perhaps most importantly, both psychologists and teachers often have a profound misunderstanding of the biological basis of both key psychological traits such as intelligence, personality and creativity and abnormal psychological traits that are inherent in childhood disorders such as such ADHD. This often stems from a misunderstanding of the difference between nature and nurture. Many teachers and psychologists still confuse genetic influences on our behaviours with the neurobiological processes that underpin our behaviours. Indeed our biology represents both genetic and environmental influences and underpins all of our behaviours, thoughts and actions. Clearly an understanding of only our children's behaviours without an understanding of the underlying biological basis for these behaviours is rather limiting. Probably the other reason that both psychologists and educators commonly do not understand the neurobiology of important psychological and psychiatric constructs is that often neurbiological techniques are highly complicated, confusing and technical. To remediate this latter problem, Aina Puce in Chapter One provides an excellent overview and description for psychologists and educators not involved in neuroscience, explaining the basis of current neurobiology methodologies and techniques. The knowledge expertly outlined in this chapter will greatly facilitate the information contained in the chapters to follow. In Section II, the chapters present current reviews of the neurobiological basis of psychological traits spanning constructs such as intelligence, creativity and personality. In Section III, several chapters are presented that deal with our current understanding of the neurobiology of psychiatric traits,

particularly related to childhood disorders. Although the book is not intended as a comprehensive coverage of all areas in psychiatry and psychology, the book emphasizes areas that are not often covered in both of these areas. Overall the book is concerned with the neurobiology of exceptional psychological traits and psychiatric disorders.

Contents

Part I: An Overview of Neurobiological Methods

1. **Neurobiological Techniques: Overview of Terms, Procedures, and Technologies** 3
   Aina Puce

Part II: Neurobiology of Psychological Traits

2. **The Neurobiology of Impulsive Sensation Seeking: Genetics, Brain Physiology, Biochemistry, and Neurology** 31
   Marvin Zuckerman

3. **Neurobiology of Creativity** 53
   David Camfield

4. **Neurobiology of Intelligence** 73
   Cindy Van Rooy, John Song, and Con Stough

Part III: Neurobiology of Abnormal Traits

5. **Neurobiology of Antisociality** 107
   Lisa J. Cohen

6. **Neurobiology of Autism, Mental Retardation, and Down Syndrome: What Can We Learn about Intelligence?** 125
   Christopher J. Lawrence, Ira Lott, and Richard J. Haier

7. Neurobiology of ADHD 143
Maree Farrow, Florence Levy, and Richard Silberstein

8. Neurobiology of Savant Syndrome 199
Robyn Young

Index 217

I

AN OVERVIEW OF NEUROBIOLOGICAL METHODS

1

Neurobiological Techniques

Overview of Terms, Procedures, and Technologies

Aina Puce

"Whilst part of what we perceive comes through our senses from the object before us, another part always comes out of our own head."

—William James's 'The General Law of Perception' (1890) in *The Principles of Psychology.*

INTRODUCTION

Intelligence, personality, emotion, creativity are all qualities that all in a sense 'come out of our heads'. The challenge is to study them objectively and scientifically so that we may understand the neurobiology underlying human exceptionality. Humans have always obsessed about their ability or inability to do something relative to others in their peer group or population. The idea that individuals who possess some superior skill or capability, or are different has always encouraged closer scrutiny of that individual's make-up. During the 20th century this took the form of studying the brains of exceptional individuals post-mortem (e.g. Donaldson & Canavan 1928). Indeed, the brain of Albert Einstein was removed and preserved in formalin within 7 hours of his death! It has subsequently been reexamined in terms of its structural idiosyncracies, and found to have differences in the parietal lobes that supposedly differ from the normal population (Witelson, Kigar & Harvey 1999). These findings have been controversial. Firstly, it has been claimed that these structural idiosyncracies are not different from anatomical variants seen in the normal population (Galaburda 1999). Secondly, and more

importantly, these studies cannot address the issue of whether focal brain regions become enlarged through use rather than constitution (Seitz 1999). Hence, the current focus on understanding the differences underlying exceptional individuals and us 'lesser mortals' will probably only be clarified by studying the living, active brain.

During the latter half of the 20th century major advances in digital technology enabled the development of a number of neuroimaging methods effectively providing a 'window onto the brain'. These kinds of techniques have the potential to detect what may be different about the brains of exceptional individuals using *in vivo* studies. In this first chapter of *The Neurobiology of Exceptionality* I present a brief background of procedures and technologies most commonly used to study what 'comes out of our heads'. The purpose of this chapter is not to provide a comprehensive review of all procedures and technologies, but to give the reader:

- a brief explanation of the theoretical basis for some of the more commonly encountered procedures and technologies in studying human cognition;
- an outline of how the procedure and technology are practically applied to study human participants *in vivo*, both from data collection and data analysis points of view;
- the advantages and disadvantages of using the procedure and technology, both from the point of view of sampling and acquiring data, and of risks and discomforts for the participant.

I will attempt, wherever possible, to provide the reader with suggestions for further reading both at a basic and expert level. Technical terms are used sparingly and are accompanied by a definition.

Traditionally, the study of the human brain has been divided along two lines, based on structure versus function. Today, this line is blurred somewhat, as many techniques that assess brain function *in vivo* also use these structural methods as an overlay to display their output.

TECHNIQUES THAT ASSESS BRAIN STRUCTURE

Traditionally, brain structure could only be studied post-mortem e.g. Donaldson & Canavan (1928). An exciting development occurred in the latter part of the 20th century, when brain structure could finally be studied in living individuals. Not only was this important for the study of the normal brain, but it also revolutionised assessment techniques in neurology and neurosurgery. Tumours could be imaged and identified and the regions of permanently damaged brain tissue following stroke could be easily seen with these new techniques, enabling the development of more specific and efficient therapeutic interventions. For readers interested in the history of these developments and their clinical applications a comprehensive

3-part article in *Investigative Radiology* (Hemmy, Zonneveld, Lobregt, & Fukuta 1994, Zonneveld 1994, Zonneveld & Fukuta 1994) gives a concise and clear review of this area. Here, I present two commonly used methods for assessing brain structure *in vivo* that have also been applied to the study of the diseased and healthy brain.

Computerised Tomography

Computerised Tomography (CT), sometimes known as Computer Assisted Tomography (CAT), uses X-radiation to scan the brain or organ of interest. X-rays are produced by chemically unstable substances as a result of a chemical reaction, whereby the substance reaches its chemically stable state. CT scanning allows images of the brain or body to be generated as different tissues will transmit or absorb X-radiation depending on different attenuation coefficients (related to the density) of the various bodily tissues. The patient is placed between an X-ray source and an X-ray detector array. The X-ray tube and detector array trace a circular path around the patient. Multiple samples are taken across a series of orientations around the patient. At each sampled location a profile of different X-ray intensities is obtained. These sampled X-ray profiles are then filter back-projected, or processed using a specific mathematical algorithm, so that a reconstructed image can be produced i.e. a picture which represents the sampled tissue. For detail on the principles behind filtered back projection see Anderson and Gore (1997). CT scanning was introduced by Sir Godfrey Hounsfield in 1972 (Hounsfield 1973), however, it was only about 7 years later that three-dimensional rendering techniques were first used (Herman & Liu 1979) and then pioneered clinically in cranio-facial surgery in Australia (Hemmy 1987; Hemmy et al 1994).

CT scanning has been successfully used for demonstrating abnormalities in bone (particularly around the skull base), detecting acute haemorrhages (following a stroke) and highlighting brain tumours (Fig. 1). On the other hand, the main disadvantage with this technique is that the fine structural details of the soft tissues of the brain are not well seen. Another disadvantage is that X-radiation is used, so radiation safety issues become important. A contrast agent may need to be injected into a peripheral blood vessel for some studies where the integrity of the blood-brain barrier is being investigated (e.g. tumours, acute stroke), hence adding an invasive element to the investigation. This method of investigation may sometimes remain the only safe viable option, as the patient may have previously been implanted with a pacemaker, or other metallic device that prevents them from being safely scanned using magnetic resonance imaging (see below).

Magnetic Resonance Imaging (MRI)

Unlike CT, Magnetic Resonance Imaging (MRI) does not use radioactivity. The MRI scanner itself consists of a very large permanent magnet and set of

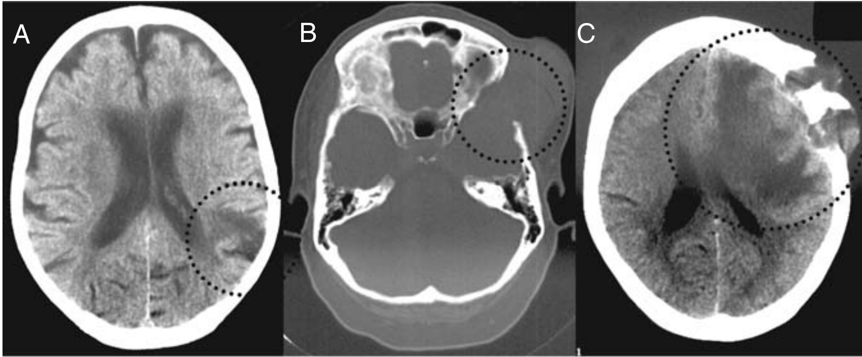

Figure 1. CT scans of the head (in axial orientation) showing regions of abnormality (enclosed by broken circles). **A.** Residual brain injury following a stroke where the blood supply was deprived to the injured region. **B.** An abnormality of bone: erosion of bone has taken place as a result of a tumor. **C.** A tumour has invaded both brain tissue as well as bone. Fluid build-up (oedema) in the surrounding tissue has created some compression of the invaded cerebral hemisphere, as seen by the compressed cerebral ventricle on the affected side. The other cerebral hemisphere has also been compressed across the midline.

cylindrical metallic coils that are capable of modifying the magnetic field experienced in the magnet with a high degree of precision in three dimensions. The broad principles outlining MRI are outlined below. A detailed explanation of the principles underlying MRI can be found in Brown and Semelka (1999).

Every nucleus possesses a spin, or wobble, around an axis. If a body (or tissue) is placed in the permanent magnet of the MRI, overall the spins of the nuclei will align themselves with the magnetic field. The most studied nucleus in MRI is hydrogen, an element that is present in about 90% of our bodies. Each nucleus has a characteristic, so called, magnetic resonance frequency of spin (or wobble). For the hydrogen nucleus, or proton, this frequency is 63.86 MHz in a static magnetic field of 1.5T (or Tesla)[1]. A static field strength of 1.5T is currently the most commonly used field strength in clinical MRI, although recently scanners of 3T and 4T are becoming increasingly used in both research activation as well as clinical studies.

MRI began to be routinely used in clinical practice in the 1980s, quite a considerable time after the phenomenon of nuclear magnetic resonance was first documented (Gabillard 1952). In 1973, Sir Peter Mansfield at Nottingham University in the UK and Paul Lauterbur at SUNY Stonybrook independently created a two dimensional map of nuclear spin densities within a material sample (Lauterbur 1973, Mansfield & Grannell 1973). It was only in the late 1970s that scientists began to apply magnetic resonance techniques to living tissue (Mansfield & Pykett 1978).

During an MRI scan the patient lies in the circular bore, or tunnel, of the magnet while the magnetic field characteristics are changed by rapidly changing magnetic fields in the Radio Frequency (RF) range[2]. The brief RF pulses of energy are briefly absorbed as nuclei change their alignment relative to the static field of the MRI scanner. After a brief period the RF energy is released from the brain or body tissue, as the sampled tissue returns to equilibrium. The special microphone, or receiver, records this RF emission, or MR signal. The receiver is usually just another coil, usually worn around the head or body. MRI images are generated after the released RF energy is sampled by the receiver, which itself is connected to a powerful analog-to-digital converter and signal processing computer. Essentially, the important measurements that need be made on any MR signal are:

(I) its size or magnitude;
(II) its frequency;
(III) its phase, or time difference, relative to the original RF pulse.

These measurements are made rapidly and sampled using specialised analog-digital converters whose output is rapidly sampled and stored on computer.

How are MR signals sampled and processed to produce the kinds of pictures that we are used to seeing the brain's anatomy in fine detail? First, different tissues have different relaxation times i.e. times of emitting the absorbed RF energy pulse, which form the basis of contrast in the MR image. For example, fat has a shorter relaxation time than does tissue or water. Pulse sequences are a series of RF pulses and gradients applied in a precise reproducible manner which are varied to emphasize different tissue types relative to their respective relaxation times (Fig. 2). So-called T1-weighted images emphasize grey-white brain tissue

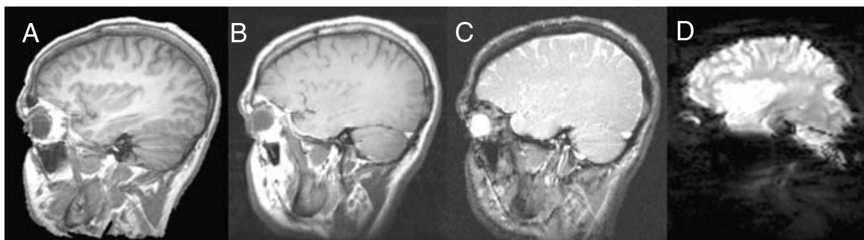

Figure 2. MRI scans (sagittal view) of the brain at around the level of the eye produced with different sequences to emphasize different tissue type and detail. **A.** High-resolution T1-weighted image shows excellent differentiation between grey and white matter. **B.** Low resolution T1-weighted image shows less of the detail. **C.** Magnetic Resonance Angiography (MRA) image shows major blood vessels and spaces with cerebrospinal fluid. **D.** Gradient echo echoplanar image acquired within a single shot and high speed in a functional MRI study. Note the difference in resolution between the structural MRI scans (**A–C**) and the functional MRI image (**D**).

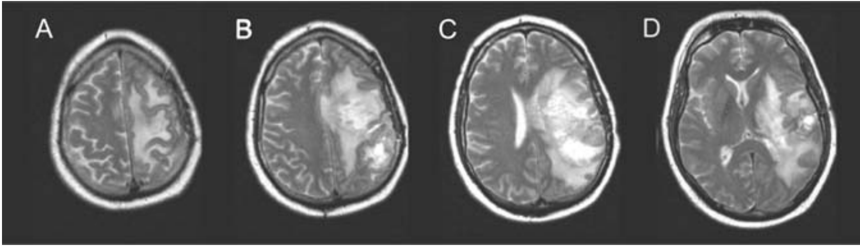

Figure 3. A structural MRI scan (axial MRI T2-weighted) of the brain (top to bottom presented from left to right) showing a malignant high-grade tumour with associated oedema which has invaded most of the left cerebral hemisphere (shown as a large bright region on the right side of the image) in scans taken from different levels through the brain.

differences (Fig. 2A and 2B). Fat appears white and water appears black. So-called T2-weighted images emphasize fluids such as water, and blood which appear white (Fig. 3 and Fig. 2D) and deemphasize fat and bone which appear dark in the image. Magnetic resonance angiography (Fig. 2C) also has this emphasis and is designed to specifically image blood vessels. The RF pulses and other static magnetic field gradients are used so that each point in 3D space can be coded uniquely. Sometimes a contrast agent (gadolinium-DTPA) is injected into the bloodstream when information about the integrity of the blood-brain barrier is sought. The MRI scanner can therefore detect a large variety of suspected abnormalities, some examples of which are shown in Figure 3.

The advantages of MRI over CT scanning are clear. MRI has better tissue resolution and uses non-ionizing radiation—attractive from a radiation safety point of view. However, MRI scanning comes with its own potential safety hazards. Any person entering the MRI scanner room must be screened for any metallic objects either on their person, or within the body itself. Some metals have magnetic properties (e.g. recall a school science experiment with iron filings and a bar magnet) and may be strongly attracted to the very strong magnetic field in the MRI scanner. They will be propelled towards the center of the MRI scanner at breakneck speeds and could injure anyone in the vicinity of the magnet's bore. Similarly, any devices that have been surgically implanted in the body, or accidentally embedded e.g. schrapnel, that are themselves magnetic may begin to move within the body and cause internal injury. Additionally, there is the problem of the strong magnetic field erasing credit cards, stopping watches, and reprogramming implanted pacemakers that has to be watched for. Hence, all facilities housing MRI scanners will have a thorough screening procedure, including a safety questionnaire, which is completed before a patient enters the magnet. Despite these hazards, being in the presence of the strong magnetic field itself is not known to be associated with any health risks.

TECHNIQUES THAT ASSESS BRAIN FUNCTION

Direct Measures of Neuronal Output

The following methods give us the most direct assessment of brain function by providing direct measures of neuronal output, usually by sampling the electrical activity of the brain produced in the course of neurons at work.

Electroencephalography (EEG)

Our brains possess, on average, about 10^{10} nerve cells, or neurons (Shepherd 1998). The neurons (pyramidal cells) are arranged in the cerebral cortex in very organised manner. They usually align their bodies and longitudinal axes perpendicular to the brain's (cortical) surface. The summed electrical activity from millions of our neurons is continually spontaneously generated regardless of whether we are at work, play or asleep. This electrical activity can be non-invasively recorded from recording electrodes placed on the scalp, as well as from invasive recordings made from inside the brain itself, or on its surface. This technique is called Electroencephalography, or (EEG), and was first performed on human subjects by Hans Berger in Germany in 1929. Many years earlier, Richard Caton had already demonstrated that this was feasible in recordings made directly from the brain's surface in rabbits as early as 1875 in England. A fascinating history of the developments in this field and in neuroscience in general is given by Stanley Finger in his *Origins of Neuroscience* (1994).

The EEG is biased to record mainly the activity of neurons that are located in the smooth surface, or gyri, of the cerebral cortex. The EEG, as recorded from the scalp, is measured using specialised amplifiers as it is of the order of around one tenthousandth of a volt (100μ Volts). Unfortunately, the neuronal activity that is picked up in the form of electrical signals on the scalp is attenuated, distorted and 'smeared' by the fluid bathing the brain (the cerebrospinal fluid, or CSF), the skull and the scalp, so that the exact source of activity can be difficult to determine (Allison, Wood & McCarthy 1986). Recordings made direct from the surface of the brain are usually of the order of around one thousandth of a volt and are used only in specialised neurosurgical applications, most typically epilepsy surgery.

We can study the changes in EEG with a great degree of accuracy in time – in the order of thousandths of seconds (milliseconds). The EEG itself is composed of a range of activity spanning frequencies of around 1–40 Hz, and can be sorted and classified into activity in various frequency bands known as delta (1–3.5 Hz), theta (3.5 Hz–7.5 Hz), alpha (7.5–12.5 Hz) and beta (12.5–40 Hz). Activity in the alpha band characteristically occurs at the back of the head, over the visual areas of brain, and can be seen most clearly on eye closure (Fig. 4).

In clinical laboratories the EEG is recorded from a standardised set of recording electrodes, based on lines of electrodes proportionally spaced in 10% and 20%

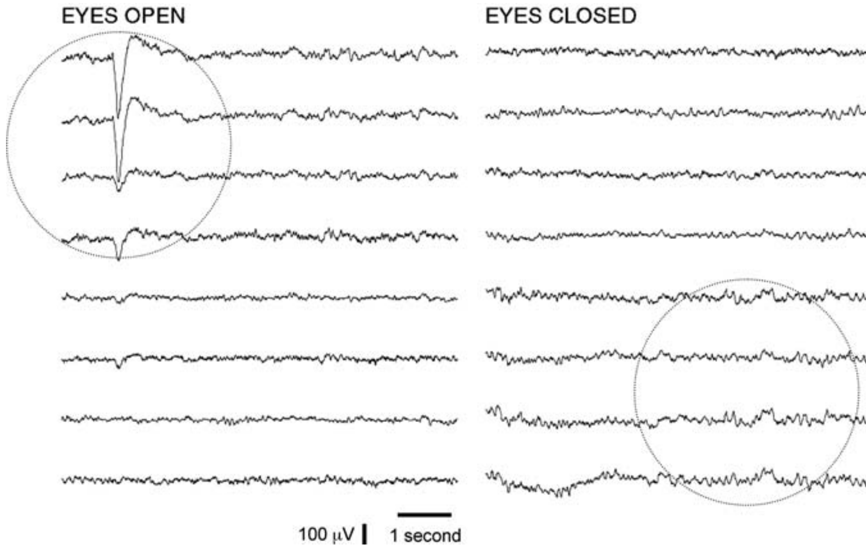

Figure 4. EEG rhythms recorded during EYES OPEN (left) and EYES CLOSED (right). Recordings have been made using an array of electrodes beginning at the front of the head (top) and ending at the back of the head (bottom). In the EYES CLOSED condition alpha activity is seen usually at the back of the head (enclosed by broken circle), and is absent in the EYES OPEN condition. The large deflection in the EYES OPEN condition (enclosed by the broken circle) at the front of the head is an eyeblink, illustrating that other electrical signals from the body can occur as unwanted signals, or artifacts, in the EEG.

increments of distances from the front-to-back, and side-to-side of the head (using the so-called International 10–20 system). All together there are around 30 or so electrodes. In research laboratories, it is common to use more dense arrays of electrodes, with 64 and 128 electrodes, for example. The electrode positions in these instances can be either related to 10–20 system sites, or can be placed in an array in which all electrodes have the same distance to their nearest neighbour (geodesic placement).

Power Spectral Analysis of the EEG. The frequency content of the EEG can be charted using Power Spectral Analysis. Here the EEG is essentially displayed in an alternative format: instead of looking at the EEG waveforms in time (Fig. 4), the same data can be displayed in terms of frequency (Fig. 5). Sometimes, the display of EEG data in the frequency domain can highlight rhythmic features in the EEG that are not as clearly seen when it is displayed in the time domain (Fig. 5).

Spectral EEG analysis relies on the mathematically based technique of Fourier transformation, based on a branch of mathematics made famous by Jean Fourier in

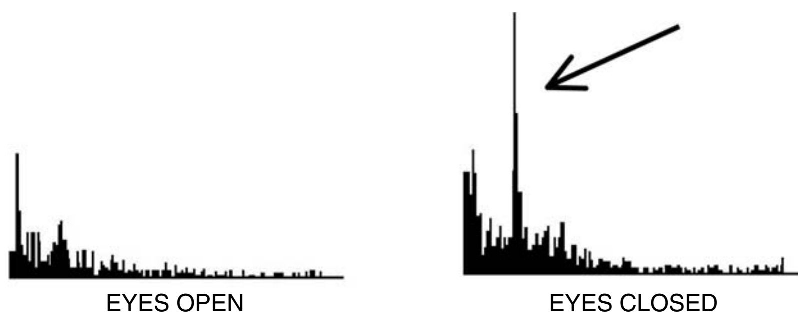

Figure 5. Power spectra of the EEG activity seen from the bottom trace of Figure 4 for the eyes open (left) and eyes closed (right) conditions. Alpha activity appears as the most prominent peak in the trace (right, arrow). The y-axis displays power and the x-axis displays frequency ranging from 0 to 60 Hz.

the 19th century. It allows any signal that changes in time to be expressed as a function of frequency by expressing the signal as a series of Fourier coefficients, which effectively describe the amount of signal that is present at particular frequencies. The Fourier Transform of a signal, therefore consists of a theoretically infinite series of summed Fourier coefficients. The computer algorithm which calculates the Fourier transform uses some mathematical short-cuts and is often called the Fast Fourier Transform, or FFT.

The behaviour of the EEG can be concisely and accurately plotted using spectral analysis and changes may be monitored over time and specified as either changes in the overall power (or energy) of the EEG signal, or in terms of the relative power in the various EEG frequency bands.

EEG Coherence. Another common way of analysing the EEG signal is known as Coherence Analysis (Nunez, Srinivasan, Westdorp, Wijesinghe et al., 1997, Nunez, Silberstein, Shi, Carpenter et al., 1999). Here the degree to which various brain regions generate synchronous EEG signals i.e. are coherent can be calculated. The coherence between individual electrodes sites on the scalp, or between regions of brain can be calculated. For accurate measures of coherence to be calculated, usually a large number of recording electrodes in the scalp are used—typically 128 or greater.

Evoked (and Event-Related) Potentials (ERPs)

It has been known for some time that the EEG could change predictably and reproducibly in response to sensory stimulation (e.g. Berger's work in the 1930s). However, considerable time passed before an approach was developed in which these changes in the EEG could be reliably seen. In 1949 Dawson working at Cambridge University was able to use a cathode ray oscilloscope (the first type

of TV tube) to store multiple traces of nerve action potentials in the periphery, Erb's point and the scalp EEG in response to peripheral electrical stimulation of the median nerve of the hand (Dawson & Scott 1949). The final display indicated that there were reliable changes in the EEG that were time-locked, or occurred at fixed times, to the brief electrical stimulus. These time-locked changes in the EEG are known as Evoked Potentials, or EPs.

Today, EPs are recorded routinely by digitally sampling and storing the EEG. The EEG is basically cut into brief segments known as epochs that begin at the time that the stimulus is delivered. Then the epochs are all summed together, or averaged. The resulting signal average is a display consisting a serious of voltage 'bumps' that change over time (Fig. 6). Averaging can be performed by a special device

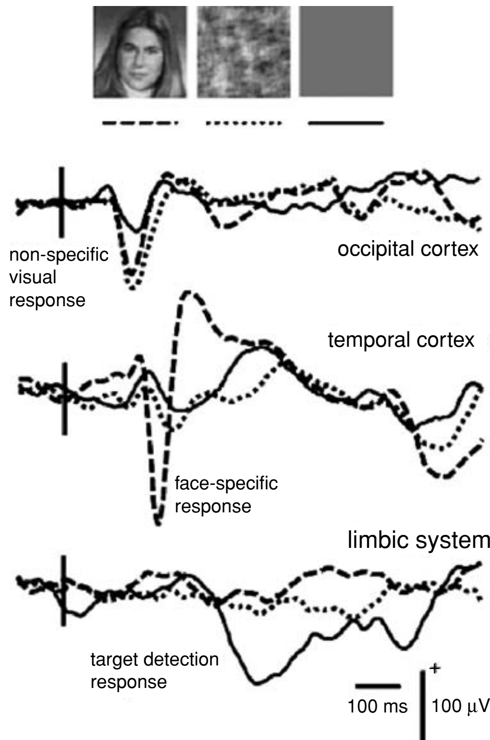

Figure 6. Averaged ERP waveforms recorded from within the brain itself using special brain surface and depth electrodes. Note the large size of the ERPs, which are about an order of magnitude greater than those usually recorded from the scalp. Here data from a target detection task (subjects made a button press to grey squares) are shown. Early ERP activity is seen to all stimulus categories (top) in occipital cortex. Later category-specific ERP activity occurs to only one stimulus category i.e. task irrelevant faces (middle) in visually sensitive temporal cortex. Late ERP activity in response to the target is seen in the limbic system (bottom).

such as an EP Averaging System which is routinely used in clinical applications. In the research environment it is more common to digitally store the EEG for subsequent analysis. The EEG data can then be averaged and analysed using additional methods that are not available on a clinical EP system. Typically, in research studies we are interested in examining EPs to various stimulus types in a single experiment, and it is not usually possible to separate responses to different stimulus types on most clinical EP systems.

In an experiment using multiple stimulus types we are often interested in studying not only the perception of the stimulus, but also cognition. The perceptual EP components are often called exogenous potentials, as their structure or morphology, and timing is predictable, pretty invariant and can be attributable to various structures in primary cortical or subcortical sensory structures in the central nervous system. EP components, which typically occur after the activity in sensory structures has occurred, and are related more to cognition are known as endogenous potentials. They are called endogenous as they are internally generated mental events that may occur even in cases of stimulus omission (Ruchkin, Sutton, Stega 1980)! Hence, it is common to speak of Event-Related Potentials, or ERPs, in this type of context. An ERP experiment will generate potentials that are both exogenous and endogenous, and typically uses an experimental design where multiple stimulus types are presented in random order. ERP experiments can often clearly differentiate responses to different stimulus categories as shown in Figure 6.

Topographical Mapping Techniques

Any aspect of the EEG (power, coherence) or ERP (peak voltage at a certain time point) can be displayed across the recording electrode space, in a topographic map which shows how the displayed parameter behaves across the head. Similarly, current source density maps, calculated from the first mathematical derivative of the EEG voltage are also a common form of displaying the EEG or ERP activity. Additionally, the results of statistical tests may also be displayed in the way, where the results of contrasting 2 test conditions may be displayed to show the variation in activity across the head. These types of mapping technique can also be applied not only to scalp EEG and ERP data, but to data recorded directly from the brain's surface itself (Fig. 7).

Additionally, the scalp EEG and ERP data may be plotted out in terms of what the voltages would look like on the surface of the brain. Here, a mathematical algorithm takes into account the attenuation and smearing effects of the scalp, skull and CSF and generates a plot of the theoretically calculated profile of voltages on the brain's surface. These techniques are known as Laplacians (Nunez, Silberstein, Cadusch, Wijesinghe et al., 1994), named after a branch of mathematical transformation credited to the French mathematician Pierre-Simon Laplace in the late 19th century.

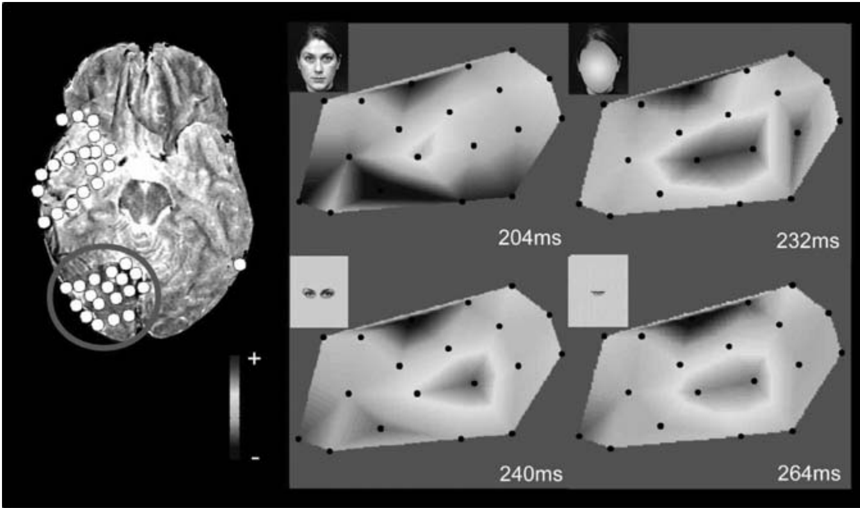

Figure 7. Example of a voltage topography map created from a grid of intracranial electrodes sited on the surface of the brain, seen here from its underside in an MRI based reconstruction (left). The voltage distributions elicited in response to faces and face parts over the occipitotemporal cortex show both positive and negative voltages at key time points following stimulus onset. The gray scale displays voltages from $\pm 200\ \mu V$.

Steady-State Probe Topography (SSPT)

Like conventional ERP techniques, SSPT also relies on demonstrating changes in the EEG that occur as a function of stimulus presentation, however, the approach is conceptually quite different. The SSPT technique uses a ‘probe’ stimulus which consists of a continuously presented sinusoidally flickering light stimulus, which is essentially presented as a ‘background’ stimulus while the subject watches a stimulus display and performs a cognitive task or participates in an experiment with a pharmacological manipulation. The sinusoidal flicker stimulus is delivered through a set of goggles with a semi-transparent mirror, and the subject watches the stimulus display that is associated with the task on a computer screen. By examining changes in the amplitude (size) and phase difference (expressed as a change in latency) of the so-called steady-state visual evoked potential (SSVEP), it is possible to infer dynamic changes in brain activity and processing mode associated with a cognitive task.

The SSVEP was originally recorded from depth electrodes implanted in visual cortex (Kamp, Sem-Jacobsen & Van Leeuwen 1960), and subsequently from the scalp (Van der Tweel & Verduyn Lunel 1965) in recordings made from small sets of electrodes. In these studies the sinusoidal flicker was the sole stimulus and the response properties of the SSVEP were examined. Today, SSVEP recordings are

typically made using large sets of electrodes using the flicker stimulus as a probe (Silberstein, Schier, Pipingas, Ciorciari et al., 1990), and the data are displayed as topographic maps of SSVEP amplitude and latency changes across conditions (Fig. 8A and 8B). The approach used was based on probe evoked potential studies where a well-defined, repetitive stimulus was used to indirectly study perception and cognition (Papanicolaou & Johnstone 1984). The amplitude of the SSVEP to a 13 Hz flicker stimulus changes similarly to alpha EEG activity (10–13 Hz) in that decreases in conditions of increased visual vigilance (Silberstein et al., 1990, Nield, Silberstein, Pipingas, Simpson, Burkitt 1998). SSVEP latency changes are interpreted as highlighting changes in neural information processing speed in the neural generators of the SSVEP, which in turn index regional variations in excitatory and inhibitory tone (Silberstein, Farrow, Levy, et al., 1998). Additionally, the statistical reliability of these effects may be evaluated using statistical measures that takes

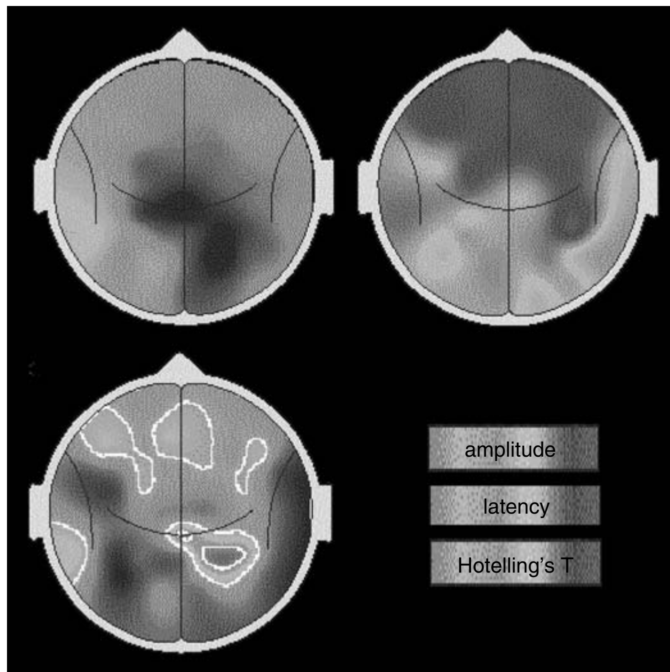

Figure 8. Topographic maps of SSVEP changes during nicotine administration relative to a placebo condition. **A.** Normalised amplitude difference (in μV) with cool colors representing increased SSVEP amplitudes in the nicotine condition relative to placebo. **B.** SSVEP latency differences (in msec) with warm colors representing latency decreases for the nicotine condition, relative to placebo. **C.** Hotelling's T statistic showing significant differences between nicotine and placebo conditions for both SSVEP amplitude and latency. (Modified from Thompson, Tzambazis, Stough, Nagata, Silberstein, 2000.)

into account *both* the SSPT magnitude and phase changes, the Hotellings-T test (Fig. 8C and see Silberstein, Ciorciari & Pipingas 1995), to display significantly activated brain regions. Alternatively, the SSPT magnitude and latency differences between conditions can be tested separately using regular t-tests or other statistics.

Magnetoencephalography (MEG)

Like EEG and ERP studies, magnetoencephalography detects rapid changes in brain activity over time. Rather than measuring voltages from recording electrodes placed on the scalp, MEG uses electromagnetic sensors to sample the changes in the magnetic field that are emitted from the brain as a function of time (George, Aine, Mosher, Schmidt et al., 1995, Lounasmaa, Hamalainen, Hari & Salmelin et al., 1996). It was first described by Cohen in the late 1960s-early 1970s (Cohen 1968, 1972). This method uses principles similar to those described in the MRI section: the sensors themselves consist of wires that detect small currents that are induced in them as a function of the changing magnetic fields that the brain produces. These tiny currents are difficult to detect, and the MEG sensor array is also cooled by liquid helium and nitrogen, just as an MRI scanner's magnet. This ensures that extremely small currents can be detected, however, it makes the system susceptible to noise (unwanted magnetic fields that are not generated by the subject's brain). For this reason MEG recordings are usually performed in a shielded room, i.e. a purpose built room that has been specially designed to screen out stray magnetic fields from outside. In addition, no electrical equipment or other sources unwanted magnetic fields are in the room itself. The internal structures of the room are usually made of wood and other non-metallic materials, and the participants themselves remove all items of metal on their person[3].

MEG has the advantage over EEG techniques, in that the magnetic fields emitted from the brain are not distorted or smeared by the cerebrospinal fluid, skull and scalp (Cuffin & Cohen 1972). On the other hand, as the MEG sensors themselves are coils of wire that sit parallel to the scalp's surface, they will be biased to sample activity that comes mainly from neurons that are oriented perpendicular to them[4]. Hence, EEG and MEG techniques sampled potentially complimentary brain activity, with the EEG biased to recording activity from the flat surfaces or gyri of the brain, and MEG recording activity of neurons in the folds or sulci. The detected MEG activity comes mainly from so-called radial sources[5], and the EEG activity comes mainly from tangential sources.

The collected MEG data can then be mapped as a series of sources and sinks of current emanating from the head (Fig. 9B). Given that the positions of the sensors are known exactly (Fig. 9A), the neuronal populations within the brain that produce this activity can be identified: sources and sinks located close together usually indicate that the origin of the neural activity lies close to the cortical surface near the detector. On contrast, large separation distances between sources and sinks usually indicate a deep-seated neuronal generator.