CONVENTIONAL AND TOPOGRAPHIC ELECTROENCEPHALOGRAPHY AND SOMATOSENSORY EVOKED POTENTIAL STUDIES IN ISCHAEMIC STROKE

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

by

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ABSTRACT

The purpose of this prospective study was to assess the diagnostic and prognostic value of early electroencephalography (EEG) and somatosensory evoked potential (SEP) studies in cortical and non-cortical ischaemic stroke. Both conventional and topographic/quantitative studies were performed. A parallel study was carried out on healthy volunteers to provide an effective control. Equipment and quantitative EEG (qEEG) variability was also assessed.

Equipment was tested using an external calibration source, from which some amplitudes fell outside the ±4% specified machine limits; a customised software upgrade rectified the problem. Voltage mapping showed that a single colour change could represent a variation of 1% to 25%. Intra- and inter-operator and intersession qEEG studies showed that most variability occurred in Absolute Power, but no significant difference was detected between 3 operators.

Fifty-one unselected acute ischaemic stroke patients were assessed clinically. All underwent non-contrast computerised tomography (CT), 16-channel EEG, 21-channel topographic qEEG, 3-channel SEP and 21-channel topographic SEP studies within 48 hours of the stroke; forty-five underwent all tests 4 to 15 days later. Final stroke classification was based on full clinical assessment, including the later CT. Clinimetric assessment included an early and 3 month Barthel Index (BI). Sixty-five healthy volunteers underwent the above electro-physiological studies after a clinical assessment; fifty-one were studied 5 to 16 days later.

Seventy-three percent of the patients were considered to have had unilateral cortical stroke and logistic regression showed that the tests most discriminating between cortical and non-cortical stroke were qEEG and CT in the first session and qEEG in the second session, at the 0.05 level. Conventional and topographic SEPs were independently associated with BI outcome in the first session, while for the second session this association applied only to conventional SEPs. Models were developed that were predictive of group (cortical/non-cortical) and outcome.

In conclusion, topographic qEEG, reflecting altered brain function after stroke, was useful in distinguishing between cortical and non-cortical ischaemic stroke, while conventional and topographic SEPs proved useful indicators of functional outcome.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

MA HAMILTON-BRUCE
27 March 1998

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ABBREVIATIONS AND SYMBOLS

μ	-	micro
μV	-	microvolt
$\geq$	-	greater than or equal to
$\leq$	-	less than or equal to
$\sigma*$	-	standard deviation of the population
$\mu*$	-	population mean
°C	-	degrees Celsius
3-D	-	three dimensional

ABB	-	Andrew Barham Black
ADL	-	activities of daily living
AED(s)	-	anti-epileptic drug(s)
AEP(s)	-	auditory evoked potential(s)
ANOVA	-	analysis of variance
ASCII	-	American standard code for information interchange
BAEP(s)	-	brainstem auditory evoked potential(s)
BAP	-	bipolar absolute power
BCoh	-	bipolar coherence
BI	-	Barthel Index
BMDP	-	statistical software package originating from biomedical group UCLA
BPA	-	bipolar power asymmetry
BRP	-	bipolar relative power
C	-	carbon
C+	-	central plus frontal and occipital
C2	-	second cervical process
CA	-	Cherie Archer

CA 2	-	coherence all (session) 2
CAST	-	Chinese Acute Stroke Trial
CATS	-	Canadian-American Ticlopidine Study
CCC 2	-	coherence combined central (session) 2
CCT	-	central conduction time
cm	-	centimetre(s)
CME	-	computed mapping of the EEG
CPU	-	central processing unit
cSEP(s)	-	conventional somatosensory evoked potential(s)
CSF	-	cerebrospinal fluid
CT	-	computerised tomography
CVA	-	cerebrovascular accident
CY	-	Con Yiannikas
d-EEG	-	digital EEG
DOS	-	disc operating system
ECASS	-	European Co-operative Acute Stroke Study
ECG	-	electrocardiography/gram
EEG	-	electroencephalography/gram
EMG	-	electromyography/gram
EOG	-	electro-oculography
EP(s)	-	evoked potential(s)
ERP(s)	-	event related potential(s)
FFT	-	fast Fourier transformation
FIM	-	Functional Independence Measure
FN	-	false negative
FO	-	fronto-occipital
FP		false positive

GHP	-	Grant Hartnell Purdie
GVG	-	Vigabatrin
H	-	hydrogen
HMPAO	-	hexamethylpropyleneamine oxime
Hz	-	Herz
I	-	iodine
IBM	-	International Business Machines
ICU	-	intensive care unit
IFCN	-	International Federation of Clinical Neurophysiology
IST	-	International Stroke Trial
k	-	kilo-
LC	-	left central
LF	-	left frontal
ln	-	log e
LP/O	-	left parieto-occipital
LR	-	logistic regression
LT	-	left temporal
m	-	milli-
MAP	-	monopolar absolute power
Mb	-	megabytes
MCNS	-	modified Canadian Neurological Score
MCoh/IMCoh	-	inter-/intra-hemisphere monopolar coherence
MEG	-	magnetoencephalography
MHz	-	mega Herz
mm	-	millimetre
MMF	-	monopolar mean frequency
MPA/IMPA	-	inter-/intra-hemisphere monopolar power asymmetry
MRI	-	magnetic resonance imaging
MRP	-	monopolar relative power

MS-DOS	-	Microsoft Disc Operating System
msec	-	millisecond(s)
NMDA	-	N-methyl-D-aspartate
NPV	-	negative predictive value
O	-	oxygen
OA 2	-	overall all (session) 2
OSET	-	Organisation of Societies for Electrophysiological Technology
P	-	parasagittal
p-EEG	-	paper EEG
Pa	-	parasagittal average
PAA 2	-	interhemisphere power asymmetry all (session) 2
PC	-	personal computer
PCA	-	posterior cerebral artery
PET	-	positron emission tomography
PPV	-	positive predictive value
qEEG	-	quantitative electroencephalography
RAM	-	random access memory
rCBF	-	regional cerebral blood flow
REM	-	rapid eye movement
RIND(s)	-	reversible ischaemic neurological deficit(s)
RL	-	Roy Lee
RPA 2	-	relative power all (session) 2
rt-PA	-	recombinant tissue plasminogen activator
s.e.$(\mu*)$	-	standard error of the population mean
SD	-	standard deviation
SEP(s)	-	somatosensory evoked potential(s)
SG	-	Stacey George
SH	-	Sinead Hanley

SPECT	-	single photon emission computed tomography
SPM	-	significance probability mapping
SPSS	-	Statistical Package for the Social Sciences
T	-	temporal
Ta	-	temporal average
TASS	-	Ticlopidine Aspirin Stroke Study
TIA	-	transient ischaemic attack
TN	-	true negative
TP	-	true positive
tPA	-	tissue plasminogen activator
TQEH	-	The Queen Elizabeth Hospital
tSEP	-	topographic SEP
USA	-	United States of America
V	-	volt(s)
VEP(s)	-	visual evoked potential(s)
VGA	-	video graphics adapter
WHO	-	World Health Organisation

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2. Hamilton-Bruce MA, Black AB, Majedi PM, Dennis S. Quantitative electro-encephalography - intersession variability.

3. Hamilton-Bruce MA, George S, Archer C, Lee R, Luke CG, Black AB. Functional outcome prediction in ischaemic stroke.

4. Hamilton-Bruce MA, Yiannikas C, Black AB. Clinical application of conventional somatosensory evoked potential studies in ischaemic stroke.

Manuscripts in preparation (continued):

5. Hamilton-Bruce MA, Black AB, Yiannikas C, Luke CG. Conventional and topographic electroencephalography and somatosensory evoked potential studies in ischaemic stroke.

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INTRODUCTION

1.0   STROKE EPIDEMIOLOGY

Stroke is a common and devastating disorder. Studies of the population of Rochester, Minnesota, showed a 46% decline in the incidence of ischaemic stroke between 1950-1954 and 1975-1979, which stabilised in the 1970s but then increased again (17%), the latter coincident with the introduction of computerised tomography (Broderick et al. 1989). The annual incidence of stroke is approximately 1 - 2 per 1000 inhabitants, with approximately 5% of the population over 65 being affected (Mas and Zuber 1991), with age and gender specific incidence rates for first stroke rising steeply with age for both genders (Bamford et al. 1988). Projections for England and Wales by Malmgren et al. (1989) estimated that with a 5% increase in population there would be an approximately 30% increase in first-ever-strokes between 1983 and 2023.

In a study to ascertain the true incidence of stroke in the Perth metropolitan area, Anderson et al. (1993) determined a crude annual incidence for first-ever strokes to be 178 per 100,000; a similar incidence being reported by Bonita et al. (1994) for Auckland, New Zealand. Anderson et al. (1993) also estimated that approximately 37,000 people suffer a stroke each year in Australia, about 50% of whom are over 75 years of age, an incidence little different from that of several other Western countries. The economic impact in Australia has been estimated to be between one and two billion dollars annually (Donnan 1992a). As noted by Donnan and Davis (1995), knowledge of the importance of stroke and its effects has resulted in the Federal Department of Human Services and Health identifying stroke as a major priority in its National Goals, Targets and Strategies for Better Health Outcomes into the next century.

More locally, with an increase in population in the Adelaide Health Planning Area (anticipated to be of the order of 11% over the 10 year period from 1991 to 2001) and with the greatest percentage increase anticipated in the over 75 year age group (86% or 5552 people in the Northern Local Government Area, for example), hospital-related stroke activity is expected to increase by 16.6% in South Australia (4447 to 5187 patient separations) by 2001 (1994 base year data, inclusive of interstate visitor-patients). 39.6% of this activity (1285 to 1794 separations) is anticipated to be in the area served by the North Western Adelaide Health Service (Southern, Northern and Western Health Advisory Panels 1996; North Western Adelaide Health Service Strategic Planning and Development Unit 1996).

1.1   STROKE TRIALS

As noted by Norris and Hachinski (1986a): 'Few major illnesses are treated more inconsistently than stroke, ranging from fatalistic resignation to recovery or demise at home to intensive care in specialized units'.

During the last few decades, various salvage therapies for stroke have been trialed. These have included glycerol (Mathew et al. 1972; Larsson et al. 1976; Fawer et al. 1978; Yu et al. 1992), dextran (Spudis et al. 1973; Strand et al. 1984), dexamethasone (Tellez and Bauer 1973; Bauer and Tellez 1973; Mulley et al. 1978; Norris and Hachinski 1986b), aminophylline (Geismar et al. 1976; Britton et al. 1980), ornithine alpha ketoglutarate (Woollard et al. 1978) and naftidrofuryl (Admani 1978). Examples of comparative and combination studies include glycerol versus dexamethasone (Gilsanz et al. 1975), dextran and dexamethasone (Kaste et al. 1976) and glycerol and dexamethasone versus dexamethasone (Albizzati et al. 1979). However, as noted by Santambrogio et al. in 1978, in a comparison of 4 groups of patients (300 in total), one on supportive therapy only, the other three on dexamethasone, mannitol, and a mixture of 3 ergot alkaloids, respectively, none of the treatments proved more useful than conventional supportive therapy in the first ten days after stroke.

Newer potential therapies for acute ischaemic stroke include reperfusion therapies, i.e., non-clot specific thrombolytic drugs (urokinase, streptokinase), relatively clot-specific thrombolytic drugs (prourokinase, tissue plasminogen activator (t-PA) and second-generation thrombolytic agents (t-PA fragments, molecular combinations, thrombus-directed monoclonal antibodies with t-PA). Other treatments include cellular biochemical therapy, i.e., voltage sensitive calcium channel antagonists (nimodipine, nicardipine, isradipine and clentiazem), competitive and non-competitive receptor-mediated calcium-channel antagonists (MK-801, dextromethorphan, CGS-19755 and ifenprodil), free radical scavengers and inhibitors (21-aminosteroids and superoxide dismutase) and miscellaneous agents (inhibitors of inflammatory white blood cells, naloxone and GM-1) (Fisher 1991). Other recent trials have included assessment of monosialogangliosides (Rocca et al. 1992) and N-methyl-D-aspartate (NMDA) receptor antagonists, and are being undertaken in selected centres (Brown 1995).

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Consideration also needs to include recognition of the importance of the time-window. The conclusion drawn by The National Institute of Neurological Disorders and Stroke rt-PA (recombinant tissue plasminogen activator) Stroke Study Group (1995), for example, was that despite the increase in incidence of symptomatic intracerebral haemorrhage, intravenous treatment with t-PA within three hours of ischaemic stroke onset improved clinical outcome at three months. Similarly, the European Cooperative Acute Stroke Study (ECASS) showed that intravenous thrombolysis within six hours of acute stroke was effective in improving some functional measures, as well as neurological outcome (Hacke et al. 1995). However, this was seen in a defined subgroup of stroke patients with moderate to severe neurological deficit and depended on recognition of early major computerised tomography (CT) signs of early infarction. Thus the conclusion drawn was that since treatment of ineligible patients was associated with an unacceptable increase in haemorrhagic complications and death, intravenous thrombolysis could not be recommended for use in an unselected population of acute ischaemic stroke patients.

More recently, trials have also been aimed at primary prevention and have included the Stroke Prevention in Atrial Fibrillation (SPAF Investigators 1994), European Atrial Fibrillation Trial (EAFT Study Group 1993), UK-TIA (transient ischaemic attack) aspirin trial (UK-TIA Study Group 1991), Swedish Aspirin Low Dose Aspirin Trial (SALT Collaborative Group 1991), Dutch Transient Ischaemic Attack Trial (Dutch TIA Trial Study Group 1991) and the Canadian-American Ticlopidine Study and Ticlopidine Aspirin Stroke Study (CATS and TASS, respectively), as cited in Brown (1995), the European Stroke Prevention Study 2 (Diener et al. 1996), as well as surgical treatment of asymptomatic carotid stenosis (Warlow 1996).

As well as trials of newer therapies, given the uncertain risk benefit balance for medication such as aspirin and low and medium dose heparin in acute stroke, these have also been reassessed and reported more recently in the International Stroke Trial (IST) (International Stroke Trial Collaborative Group 1997). The findings indicated that neither of the heparin regimes offered any clinical benefit at 6 months, but that aspirin should be started as soon as possible after ischaemic stroke onset (based on IST and the Chinese Acute Stroke Trial (CAST) findings).

Although comparisons of data are difficult, as study designs and data presentation vary, there is a clear need for effective management of people with stroke. It is to be hoped that the outcome of such studies will lead to the practice of more immediate and directed therapy for stroke victims. The heterogeneity, intricacy and complexity of the mechanisms involved in tissue damage resulting from anoxia induced by ischaemia, as well as major differences between animal and human stroke models, differences between stroke subtypes and the lack of consensus on stroke management probably account for the lack of definite evidence of pharmacological effectiveness (Allain et al. 1991; Blecic and Bogousslavsky 1995; Wahlgren 1995).

As summarised in an editorial in Lancet in 1991, stroke therapies require careful, prompt assessment of patients. Thus stroke care needs to be improved to fulfil the potential of new therapies. As the approach to therapeutic strategy may vary with different stroke subgroups, early diagnostic classification has clinical significance (Hacke et al. 1991; Adams et al. 1994; Hacke et al. 1995) and more sensitive, non-invasive electrophysiological methods of assessment of acute stroke could assume major importance.

1.2 NEUROIMAGING OF STROKE

Neuroimaging methods which allow visualisation of cerebral morphology and function include computerised tomography, magnetic resonance imaging (MRI), regional cerebral blood flow (rCBF), single photon emission computerised tomography (SPECT), positron emission tomography (PET), as well as electrophysiological tests such as electroencephalography (EEG), magnetoencephalography (MEG) and evoked potentials. Non-electrophysiological methods are based on measured values and provide structural and metabolic spatial representation, while electrophysiological information is purely functional (Gordon et al. 1986; Maurer and Dierks 1991a).

Detail on the structural and clinimetric methods available for use in this project is provided in Chapter 2 and that for EEG and somatosensory EPs (SEPs) in Chapters 3 and 4, respectively. A brief overview of the history of electrophysiology and brain mapping follows.

1.3   ELECTROPHYSIOLOGY

EEG is the recording of the electrical activity of the brain, and EPs are the electrical responses of the nervous system to stimulation. EEG and evoked potential (EP) brain mapping or topographic studies are procedures where frequency and amplitude patterns are calculated from measurements taken from the electrodes, the external analog signal being converted into a digital equivalent for use in the time, frequency and spatial domains (John et al. 1989; Duffy et al. 1989a; Maurer and Dierks 1991b).

1.3.1   History

Historically, the first EP was recorded on animals by Caton in 1875, who was also the first to discover the EEG (cited in Brazier 1992). The first EEG on humans was recorded by Berger in 1924 (cited in Gloor 1969a). Fourier analysis was first applied to the human EEG by Dietsch in 1932 (cited in Maurer and Dierks 1991c), while an application of the Fourier analysis based on the fast Fourier transformation (FFT) was applied to the EEG by Adey et al. in 1960 - this being the beginning of spectral analysis.

In 'From Graphein to Topos: Past and Future of Brain Mapping', Petsche (1989) mentioned some of the scientists who were brain mapping forerunners. These were: Adrian and Yamagiwa (1935), who confirmed Berger's discovery of the alpha rhythm and claimed that the occipitoparietal alpha focus had a frontal antifocus with the alpha waves undergoing phase shifts along a line of electrodes, seeming to move along the skull; Kornmüller (1937) who published data about characteristic EEG differences recorded from different areas and Motokawa (1942) who was the first to develop and use statistical analysis for EEG quantification and to prepare the first EEG map in 1944 (cited in Petsche 1989).

Subsequent to this, Goldman et al. (1948) designed a model wherein signals from a square array of 16 electrodes mounted on the skull (or heart) could be displayed on cathode ray tubes as a 'map'. In 1950 Lilly developed the Bavatron which consisted of an array of 25 light spots on a screen, while Livanov and Ananiev (1955) developed an 'encephaloscope' based on the same principal, using an array of 5x10 electrodes (cited in Petsche 1989).

A few years earlier Grey Walter and Shipton (1951), using a different design, developed a method to display voltage changes from 24 channels in a spatial co-ordinate system, the equipment consisting of 22 small cathode ray tubes each displaying information from a bipolar recording from the head, while Rémond (1955) and Petsche and Marko (1955) restricted themselves to one dimension, recording from ranges of equidistant electrodes in order to be able to focus on specific questions (cited in Petsche 1989).

At that stage and subsequently, as noted by Petsche (1989), further development was restricted by the complexity of the methods, the status of the technology and the expense of the more sophisticated systems. Gotman et al. (1973) pointed out that the price of a small laboratory computer for spectral analysis and extraction of features from EEGs was US$50,000 in 1973, having been twice that three years previously and anticipated to be halved within a few years, this prediction being echoed by Künkel (1977) in a historical review.

Thus electrophysiological brain mapping developed slowly, due to difficulties with data storage and treatment, until the advent of low-priced digital technology in the late 1970's (Oken and Chiappa 1986). Furthermore, as the time series-oriented pattern recognition of the EEG by electroencephalographers had been considered successful, there was little impetus to change in a tradition-bound discipline (Lehmann 1988).

1.3.2   Technological advances

Further technological advances, particularly in the fields of computing and digital processing of data, resulted in the ready availability of sophisticated software, using a variety of algorithms to quantitate, analyse and map EEG and EP data (Oken and Chiappa 1986). As noted by Nuwer (1989) in 'Uses and abuses of brain mapping', commercial equipment for EEG brain mapping was being offered by approximately 12 vendors in 1989, with an estimated 300 to 500 units being in use in the United States of America (USA) at that time, this previously having been estimated to have changed from zero to 14 between 1984 and 1987 (Duffy 1989a). In 1994, after an informal survey of manufacturers, Duffy et al. suggested an estimated installed database of over 1000 units world-wide, up to 600 of which were in North America. Many were engaged solely in academic research, while some were not used at all. They estimated that approximately 600 were engaged in clinical practice, half of these being in America.

Risk (1993) stated that viewing and interpretation of digital EEG is as quick and accurate as that on paper. Computer methods in routine EEG practice also allow enhancement of the traditional functions of EEG equipment and paper recording by allowing filters, time and amplitude scales to be changed at the time of review, compact record storage, easy creation of record copies, as well as being used for archiving on optical disc, transmission for remote review and telephonic transfer (Lesser et al. 1992; Gotman 1993; Jacobs et al. 1995; Nuwer 1997a).

These techniques herald a new era in electrophysiology, but the application and clinical value are dependent on knowledge of the limitations and value of the results, as well as the ability to integrate the results with the clinical information and other neuroimaging techniques (Oken and Chiappa 1986; Nuwer 1990a; Welch 1992; Majkowski 1994). Warner (1995) commented that qEEG is currently at approximately the same developmental level as EEG was in the 1950's, when there was much disagreement with respect to reliability and validity particularly in relation to clinical application.

1.3.3 Rationale for topography

In 1979, Duffy et al. reported that electrophysiological abnormalities could be demonstrated in patients with functional lesions, but with normal CTs. In 1984, Thickbroom et al. noted that computerised topographical maps of scalp recorded event-related potentials assisted in the interpretation of multiple waveforms, individual components being more readily interpreted and model formulation (of regions of underlying activity from surface distributions) being easier.

When EEG changes are diffuse or questionable, particularly in the delta-theta range, brain mapping is able to demonstrate subtle asymmetries, lateralisation and localisation effects more efficiently than the standard EEG (Rodin 1988; Hooshmand et al. 1989). Graphical representations or maps are more intuitive than laborious numerical expression, the former also having the distinct advantage of providing data ordered in frequency, amplitude and space (Hamburger 1989). The rationale for topography, as succinctly summarised by Wong (1991), is that standard EEG or EP traces contain information not appreciated during visual inspection, as too much is expressed. Some of the applications include the establishment of databanks of patients and healthy control groups, functional diagnoses in Neurology, as well as use in anaesthesia, clinical pharmacology and central nervous system research (Welch 1992; Dimpfel and Schellenberg 1995; Kaminski et al. 1997).

1.3.4 Debate about brain mapping utility

In the syllabus for electroencephalographers, the American Electroencephalographic Society (1994a) note that although the field of computerised EEG is becoming as extensive as that of conventional EEG, there is less consensus about precise utility. Traditionalists have debated the value of mapping, with problem areas such as technique diversity, sampling validity, interpolation, display, artefacts, physiological status and confounding clinical and statistical issues contributing to the reserve shown by some in the field (Duffy 1989b; Pfurtscheller 1989; Nuwer 1990a; American Psychiatric Association Task Force on Quantitative Electrophysiological Assessment 1991; Maurer and Dierks 1991d; Binnie and MacGillivray 1992; Welch 1992).

Although analogue paper EEG (p-EEG) is being superseded by digital EEG (d-EEG), '... this technology is being met with a mixture of admiration, enthusiasm, fear, skepticism, and resistance, not necessarily in that order' (Wirch 1995).

Although hard- and software for brain mapping can be purchased readily, the American Academy of Neurology, Therapeutics and Technology Assessment Subcommittee reported in 1989 that most scientific reports of these techniques had demonstrated research applications, rather than clinical usefulness. Moreover, the false promise of psychiatric diagnosis in the late 1970s and the 1980s, as well as the misuse and abuse of the coloured maps by unqualified personnel in the 1980's, brought disrepute to the field, particularly its clinical application (Welch 1992; Duffy et al. 1994; Warner 1995).

Thus, while current computer technology has simplified previously laborious, complicated calculations, this underlies one of the main difficulties. Petsche (1976) wrote: '... computers, paradoxical as it may sound, frequently decrease the efficiency of work, for nothing is more difficult than to sift the chaff from the wheat considering the huge amount of data put out by the computer. The search for significant results has been becoming increasingly difficult. I even dare to claim that, since the computer has come to dominate electroencephalography, it has become much more difficult to distinguish efficient from foolish problems. I see only one way of escaping this danger: namely to keep in mind the physiological and clinically relevant problems and not to become entangled in problems created by the computer'.

1.4 CLINICAL CONDITIONS ASSESSED USING BRAIN MAPPING

Clinical conditions where quantitative EEG (qEEG) and/or EP brain mapping have been used, include cerebrovascular disease (Hossmann et al. 1980; Nagata et al. 1982, 1984a, 1984b, 1989, 1992; Sainio et al. 1983; Jonkman et al. 1985; Nuwer et al. 1987; Nagata 1989; Brigell et al. 1990; Kappelle et al. 1990; Jonkman et al. 1992a; Yokoyama et al. 1996; Yuya et al. 1996), epilepsy (Duffy et al. 1984a; Hughes and Miller 1989; Miyauchi et al. 1991; Logar 1992; van der Meij et al. 1992; Ebersole 1994; Logar et al. 1994; Rodrigues et al. 1996), migraine (Jonkman et al. 1988; Neufeld et al. 1991), Huntington's disease (Yamada et al. 1991), Creutzfeld-Jakob Disease (Neufeld and Korczyn 1992), brain tumours (Nagata et al. 1985; Dolisi et al. 1990; Poimann et al. 1989), traumatic lesions (Wirsén et al. 1992), sleep apnoea (Walsleben et al. 1993) and surgery (Chiappa et al. 1979; Ahn et al. 1988; Arom et al. 1989; Matsumoto 1990; Suzuki et al. 1990; Nuwer et al. 1992).

These tests (mainly qEEG) have also been used in the evaluation of normal, learning disabled and neurologically 'at-risk' children (John et al. 1981; Tonnquist-Uhlén et al. 1996); psychiatric disorder subtyping and differentiation from other disorders (John et al. 1988a, 1988b; John et al. 1989; John et al. 1992; Prichep and John 1992) and, more specifically, in schizophrenia (Merrin et al. 1990; Kemali et al. 1992; Nagase et al. 1992; Kahn et al. 1993), depression (Pockberger et al. 1985; Carl et al. 1989; Pollock and Schneider 1990; Roemer et al. 1992), Alzheimer's disease and other dementias (Leuchter et al. 1987; Gueguen et al. 1989; Coben et al. 1990; Gallai et al. 1991; Saletu et al. 1991; Martin-Loeches et al. 1991; Maurer and Dierks 1992; Szelies et al. 1992; Neufeld et al. 1994; Besthorn et al. 1995; Signorino et al. 1995; Yuya et al. 1996; Besthorn et al. 1997), in geriatric psychiatry (Sloan and Fenton 1993) and assessing treatment effects (Gerez and Tello 1992; Saito et al. 1992; Sannita 1992), as well as in neurotoxicological studies (Jonkman et al. 1992b).

Many of the conditions previously described are routinely diagnosed on clinical grounds, with or without back-up from tests in other disciplines. However, in cerebrovascular disease, for example, electrophysiological tests can be abnormal when the CT is still normal, i.e., within the first two to three days after the stroke or when the ischaemia is mild enough to result in dysfunction without infarction (American Academy of Neurology, Therapeutics and Technology Assessment Subcommittee 1989). Accurate localisation of the affected region would be expected to increase the understanding of the underlying mechanism of stroke and to direct appropriate medical or surgical management.

Clinical conditions studied with topographic or multichannel SEPs include cerebrovascular insufficiency and stroke (Colon et al. 1985; Tsuji and Murai 1986; Tsuji et al. 1988; Buchner et al. 1992; Franssen et al. 1992; Sonoo et al. 1992; Yuya et al. 1996), central nervous system tumours (Tsuji and Murai 1986; Tsuji et al. 1988; Furlong et al. 1993; Hayashi et al. 1995), epilepsy (Shibasaki et al. 1990 and 1991; Baumgartner et al. 1993), coma and head injuries (Facco et al. 1991; Cusumano et al. 1992; Green et al. 1992; Wirsén et al. 1992; Gütling et al. 1993; Gütling et al. 1994), multiple sclerosis (Colon et al. 1984), Parkinson's disease (Mauguière et al. 1993; Babiloni et al. 1990 and 1994), Huntington's disease (Yamada et al. 1991; Töpper et al. 1993) and Down's syndrome (Kakigi and Shibasaki 1993). They are also used for intraoperative localisation and identification (Urasaki et al. 1990; Nuwer et al. 1992; Suzuki and Yasui 1992).

Since van Buskirk and Webster's description of the prognostic value of sensory impairment in functional outcome of hemiplegic stroke in 1955, there has been evidence that SEPs may be a useful prognostic indicator in stroke (Giblin 1964; Larson et al. 1966; Liberson 1966; Williamson et al. 1970; Kusoffsky et al. 1982, La Joie et al. 1982; Despland and Regli 1985). Using an animal model, Steinberg et al. (1986) demonstrated that SEP disappearance and failure to recover correlated with the degree and extent of histological cerebral ischaemia. When correlated with stroke severity scores or clinical assessment, SEPs have been shown to have prognostic implications (Zeman and Yiannikas 1989; Macdonell et al. 1989; Haupt et al. 1995; Timmerhuis et al. 1996; Djordjevic et al. 1997).

The prognostic significance of conventional SEPs has also been demonstrated in studies other than stroke, eg coma. Rumpl et al. (1983) found that the early appearance of SEPs or early recovery of distorted SEPs and decrease in central conduction time during prolonged coma or recovery, was a favourable prognostic sign and that SEP asymmetry indicated moderate to severe final disability. In a study on 26 patients in a hypoxic coma, Walser et al. (1985) detected a significant difference in mean amplitude ratio in coma patients with a bilaterally recordable scalp response between patients with a good outcome and those with a bad outcome. Cant et al. (1986) reported that median nerve SEPs were superior to BAEPs (brainstem auditory evoked potentials) in detecting brain function abnormalities soon after severe head trauma and that SEPs reliably predicted good and bad outcomes. Ganes and Lundar (1988) found in a study on 76 deeply comatose unresponsive patients with traumatic or non-traumatic cerebral damage that the first parameter to indicate grave prognosis was the disappearance of cortical SEPs bilaterally - this usually occurred hours to a day or two ahead of spontaneous EEG cessation.

It should be noted, however, that prognostic potential for the EEG (including spectral analysis), CT, PET and cerebral blood flow and perfusion has also been reported, as it has for the clinical examination, clinical evolution, neurological scales and erythrocyte sedimentation rate (Heiss et al. 1977; Kayser-Gatchalian and Neundörfer 1980; Valdimarsson et al. 1982; Sainio et al. 1983; Chambers et al. 1987; Kushner et al. 1987; Chester and McLaren 1989; de Weerd et al. 1988; Gott et al. 1990; Cillessen et al. 1994; Chamorro et al. 1995; Fiorelli et al. 1995; Alexandrov et al. 1996; Muir et al. 1996; Toni et al. 1997; Weir et al. 1997). This raises the question of the prognostic value of SEP brain mapping, particularly when compared with the standard SEPs, and, as queried by Kappelle and van Huffelen (1995) the long-term prognostic value of qEEG, individually and with respect to other available tests.

1.5   LABORATORY TEST OBJECTIVES

As the objective of a medical laboratory test is to find an answer to the physician's question emanating from the patient's disease or disorder, tests may be used diagnostically, in the classification of a disease, as well as to determine aetiology and patho-mechanism, to examine the state of the patient and search for risk factors. Tests may also be used prognostically to predict death or cure, course of the disease, future disease and therapy risks, or the assessment of therapeutic measures for selection and control of efficiency of therapeutical measures. (Büttner 1993).

However, the validity of laboratory tests is restricted by 3 levels of uncertainty, namely the technical, biological and nosological levels. At the technical level, errors are due to the analytical technique, with measurements impaired by imprecision and inaccuracy. At the biological level, transverse and longitudinal evaluation needs to be undertaken in order to assess difference from a reference population (inter-individual) and changes that occur with time (intra-individual), respectively. At the nosological level, uncertainties arise from the definition of the clinical state and particularly from the different intensity of the signs and their ambiguity, while inadequate or incorrect pathophysiological explanations or prognostic uncertainties may also lead to errors (Hennekens and Buring 1987; Büttner 1993).

1.5.1   Issues which need to be addressed internationally

Nuwer (1990a and 1992a) highlighted several issues, relating to the evaluation of new EEG techniques, which needed to be addressed internationally. These can be extrapolated to other electrophysiological techniques and laboratory tests, and include the following:

1) The need for well-defined disease definition standards.
2) Criteria for calling the test results abnormal need to be explicitly defined before commencing evaluation.
3) Test interpretation should be performed blinded to the clinical status of the patient.

4) Evaluation should be performed in subjects other than those on whom the original test and control values were established.

5) The subjects evaluated should be from a population similar to that in which the test is to be used, with particular reference to differential diagnosis, disease severity and age.

6) Various validity assessments need to be made.

7) A test to assist in disease diagnosis should have a very low false positive rate, while a test to assist in exclusion of disease diagnosis should have a very low false negative rate.

8) A new test needs to be compared with tests currently available and in clinical use, for example, clinical history, physical examination, conventional EEG and neuroimaging tests.

Winter's earlier call (1989) to test brain mapping equipment by applying a known potential distribution to its input, then checking the map produced for agreement with the known topology, needs to be added to these requirements.

1.5.2   Value of new technology

The clinical use of electrophysiological topographic mapping is in its infancy, and those who introduce new technology bear the burden of proof for demonstrating its cost-effectiveness and usefulness (Nuwer 1990a). For a new technology or application to be of value, it needs to assist in reducing mortality or morbidity by clarifying which intervention is most likely to be effective or by substituting a test with less risk for one with higher risk of complications, contribute to the patient's or family's understanding of the disease to allow the patient's behaviour to improve, and be cost-effective (Nuwer 1990a). This is applicable not only to electrophysiology, but also to CT (Goldstein and Yiannikas 1979) and MRI (Edelman and Warach 1993). As highlighted in the Report of the American Academy of Neurology, Therapeutics and Technology Assessment Subcommittee in 1989, little had been published to that date on how the sophisticated brain mapping tests could affect treatment or diagnosis for individual patients. Cerebrovascular disease was identified as an area in which these tests might fill a specific need.

Warner (1995) noted that the American Board of EEG and Neurophysiology considered it clear that the future of EEG lies in the use of computer analysis, mapping and correlation of the data with pathology and physiology. Thus, as stated earlier by Fisch and Pedley in 1989, 'A constructive first approach would be simply to demonstrate, through appropriate studies, the reliability of computer-based analytic methods in distinguishing between clinically normal and abnormal individuals with definable neurological disorders'.

1.5.3   Need for more studies

For studies to show clinical use, there is a need for many different studies on patients and healthy control subjects, to establish the true clinical usefulness of mapping electrical brain activity (Duffy et al. 1986; Oken and Chiappa 1986; American Electroencephalography Society 1987; American Academy of Neurology, Therapeutics and Technology Assessment Subcommittee 1989; Lopes da Silva 1990; Nuwer 1990a, 1992a; American Psychiatric Association Task Force on Quantitative Electrophysiological Assessment 1991).

The purpose of this study, therefore, is to assess the use of topographic qEEG and topographic SEP in the differentiation of cortical and non-cortical stroke, and as a prognostic tool. This has been undertaken prospectively in a setting simulating intended use and compared with the other medical diagnostic procedures normally conducted when considering the differential diagnosis of stroke.

Thus, in the local setting of a 590 bed teaching hospital (The Queen Elizabeth Hospital (TQEH) Information Bulletin 1993), using equipment and tests available for routine assessment of stroke, the issues considered important were:

1) assessment of new equipment, including determination of some of the accuracy and consistency limits of the hard- and software.

2) determination of qEEG operator and sessional variability.

3) assessment of the diagnostic and prognostic utility of topographic qEEG and topographic SEP, compared with the more conventional tests, i.e., CT, EEG and conventional SEPs in ischaemic stroke, both cortical and non-cortical.

1.6   PURPOSE OF THE THESIS

It is the purpose of this thesis, therefore, to address some of the issues considered crucial internationally to the interpretation of EEG and SEP brain mapping in stroke, in a routine clinical laboratory under standard monitoring conditions.

This has been undertaken by an overview of the methods of stroke assessment, particularly those available locally, assessment of brain mapping equipment (calibration and consistency as well as operator and sessional qEEG variability), before a clinical investigation on stroke subjects. The latter study has included assessment of the diagnostic and prognostic utility of brain mapping compared with other tests used for these purposes, and it is concluded by placing these results in clinical perspective.

CHAPTER 2

NON-NEUROPHYSIOLOGICAL METHODS OF ASSESSMENT IN STROKE

2.0   INTRODUCTION

A World Health Organisation (WHO) collaborative study definition of stroke is that of 'rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin' (Aho et al. 1980). Thus stroke is a clinical diagnosis, although consideration of its differential diagnosis and refinement in the diagnosis of the stroke itself are often checked by CT and MRI. Pathophysiological mechanisms include primary abnormalities of cerebral circulation, i.e., thrombosis, embolism, haemorrhage, compression, vasospasm and dissection of arterial wall, as well as abnormalities of the general circulation, i.e., hypotension, hypertension and alterations in blood biochemistry and metabolic demands (Ad Hoc Committee on Cerebrovascular Disease 1975).

2.1   IMAGING

Until the 1970s, 'brain imaging' of cerebrovascular disease consisted of cerebral angiography, with structural change in brain tissue being deduced from displacement or occlusion of the blood vessel(s) (Donnan 1992b). With the development of CT in 1973 (Spencer 1985), brain structure could be imaged directly, and there have been numerous technical developments in areas such as ultrasound and MRI, as well as non-invasive studies of metabolism and cerebral perfusion (Donnan 1992b).

2.1.1   Necessity for brain imaging in stroke

As the treatment for ischaemic and haemorrhagic stroke is different and clinical features are not always readily distinguishable, brain imaging is considered essential (Tatemichi 1995). Thus, as part of the diagnostic work-up for stroke, evaluation to differentiate between ischaemic and haemorrhagic stroke may be by means of CT or MRI (Sandercock et al. 1985; Sacco 1995), although Barer and Mitchell (1989) noted that stroke patients seen in the general and geriatric medical units of most British hospitals are unlikely to have scans. Other techniques, for example MEG, SPECT and PET, may be used but availability and expense are limiting factors. Information about the site, size and severity of the stroke is also important in estimating the prognosis, defining the baseline for comparison of future development, clarifying some aetiology-specific syndromes and assisting in selecting or stratifying patients for clinical therapeutic trials or outcome determination (Giubilei et al. 1990; Baird and Donnan 1993; Hanson et al. 1993; Tatemichi 1995).

Assessment may also include investigations to attempt to determine the patho-physiological mechanisms. For example, if a focal abnormality of the blood supply is determined, corrective measures may be undertaken (Ad Hoc Committee on Cerebrovascular Disease 1975), as in the study by Chen et al. (1992), where brainstem compression from the mass effect of brain oedema in cerebellar infarction was treated by decompressive suboccipital craniotomy - clinical opinion being that these patients would have died without surgical intervention.

Assessments of therapeutic effect, be they of survival, neurological or functional recovery or measuring infarction size with neuroimaging, all have limitations. As discussed in Chapter 1, different therapies are required for different types of stroke, the correct selection being dependent on clinical criteria for stroke diagnosis, as well as imaging (CT, MRI, arteriography, Doppler) for type, area, extension of cerebral damage and cerebrovascular mechanism. Orgogozo and Dartigues (1991), when considering stroke incidence and the number of drugs tested for more than thirty years, stated that the lack of proof of efficacy indicated that there was no standard acute stroke therapy. However Donnan and Davis (1995) point out: 'giving the right agent to the right patient at the right time may be the future of stroke management'.

Brain imaging may assist in this determination, as it has the potential to clarify much that is still elusive and nebulous in stroke.

2.1.2 Radiography

2.1.2.1 Computerised Tomography

While medical imaging extends back to the discovery of the X-ray by Röntgen in 1895, development of CT in the early seventies was based on a classic treatise by Radon in 1915 which described a mathematical inversion formula for reconstructing an object from its projections (Robb 1995a; Robb 1995b). The first CT units were produced in Britain in 1973, by EMI Medical Ltd., having been designed by GN Hounsfield (Spencer 1985).

CT is an x-ray technique, resulting in the production of cross-sectional representation of tissue structure. A beam of x-rays from a single source passes through the head to an array of detectors. The source rotates around the head to allow measurement of x-ray attenuation in cross-sectional slices, each requiring a few seconds. The slices are divided into compartments or picture elements (pixels). The computer assigns a number to each pixel from approximately 800,000 measurements and, using a grey scale, an image is produced on a monitor and/or film. (Chan et al. 1995.)

The CT allows differentiation between white and grey matter and cerebrospinal fluid (CSF), it shows the thalamus and the main divisions of the basal ganglia, and, after intravenous administration of iodinated water-soluble contrast agents, depicts major arteries. A major limitation is imaging the posterior fossa, where, due to attenuation of the x-ray beam by the thick osseous structure at the base of the skull, lucent linear artefacts may project across the brainstem and obscure underlying lesions (Chan et al. 1995).

2.1.2.2 Magnetic Resonance Imaging

This technique does not rely on ionising radiation or intravenous contrast agents, as it exploits the inherent biophysical characteristics of tissue to provide superior contrast. It is based on the interaction between radio-waves and nuclei of interest (usually hydrogen) in the tissues of the body, within a strong magnetic field, the latter making the tissues susceptible to excitation by the radiofrequency pulse. Most clinical MRI uses proton resonance, as the concentration of proton-rich lipids and water is particularly high in the brain. (DeWitt 1986; Mohr and Prohovnik 1995.)

After excitation, the return of protons to the original energy state results in the emission of radio-waves characteristic of particular tissues, the time taken (relaxation time) following an exponential pattern. In diagnostic imaging, two simultaneous relaxation times are of interest, i.e., T1 - the spin-lattice relaxation time, which describes the time taken for nuclei to shed the energy obtained from the radiofrequency pulse into the lattice, and T2 - the spin-spin relaxation time, caused by coherence or interactions between the nuclei. The differences in T1 and T2 relaxation values allow muscle, fat, bone marrow and grey or white matter to be distinguished. The image intensity results from the proton distribution density modified by relaxation times. The extent to which all three (proton, T1 and T2 relaxation times) contribute is varied by the use of different imaging methods, MRI imaging being dependent on physical and chemical characteristics of tissues. A new dimension is added to the application of MRI to medicine by the use of functional MRI, allowing the non-invasive spatial evaluation of various biophysical and biochemical processes in living systems. For example, water motion can be measured in vascular and capillary flow, diffusion and exchange, and metabolite concentration can be determined for assessment of regional metabolism regulation. (Manning 1985; DeWitt 1986; Moonen et al. 1990; Chan et al. 1995; Mohr and Prohovnik 1995.)

A practical disadvantage of the MRI, however, is the need for patient co-operation, as most individual MRI sequences require several minutes. Approximately 5% of subjects exhibit claustrophobia inside the unit and, although subjects can be sedated, this results in the need for closer monitoring. In some cases, the investigations may not be performed. Absolute contraindications to MRI assessment include some metallic implants, particularly cardiac pacemakers, cochlear implants, old aneurysm clips, metallic foreign bodies in the eye and implanted neurostimulators. (Chan et al. 1995.)

2.1.2.3 Computerised Tomography and Magnetic Resonance Imaging in stroke

In 1977, Constant et al. reported that CT scans did not change within the first hours - the development of the hypodensity being greatest during the second week when oedema was linked with increased liquefaction necrosis. They found that only 27/105 (26%) CTs were enhanced by the administration of a contrast agent to the patient, peaking at the end of the second week and concluded that oedema peaked in the second week, disappearing after the twentieth day, while necrosis onset was variable, with cavitation evolving subsequently. Initial and permanent neuronal damage was considered to be related to the extent of the infarct and, if the patient survived, medium-term prognosis could be established beyond the twentieth day. With TIAs, they found that 2/16 (13%) CTs were abnormal between day 1 and the end of year 2 - these abnormalities being low density lesions unrelated to the cerebrovascular accident under investigation.

Masdeu et al. (1977) showed that 20% (4/20) of infarctions could not be detected with CT in the first 2 weeks after ictus, while Janati et al. (1987) found that 8% (4/50) of CTs performed after intravenous administration of diatrizoate meglumine were negative within this time. While MRI is more sensitive than CT in the early detection of cerebral infarction, for example 82% versus 51% sensitivity in the first week, respectively (Kertesz et al. 1987), it is also non-specific, as most pathological processes in the brain produce oedema.

As some of the acute changes occur at a biochemical rather than a morphological level, Kucharczyk and Brant-Zawadzki (1987) considered that proton MRI alone was probably insufficient to explore the numerous variables. MRI could also be positive in normal volunteers, although in a study of patients with clinical stroke syndromes and normal volunteers by DeWitt et al. (1984), the 10 normal volunteers did not demonstrate any cerebral lesions (one study showed a small piece of ferromagnetic material embedded in the scalp).

2.1.2.4 Other methods of stroke assessment

Other methods, such as SPECT and PET, are still limited to research at this stage, but have potential for clinical application (D'Alton et al. 1983; Donnan 1992b; Hanson et al. 1993; Robb 1995c).

SPECT relies on the gamma-emitting properties of radioligands, for example $^{99}Tc^m$-hexamethylpropyleneamine oxime (HMPAO) and ^{123}I-iodoamphetamine, to generate computer reconstructions of regional cerebral perfusion. Thus, in acute ischaemic stroke, SPECT scanning may assist in predicting affected vascular territory, in diagnosis of acute stroke and in prognosis. (Ell et al. 1985; Yeh et al. 1986; Giubilei et al. 1990; Baird et al. 1991; Donnan 1992b; Robb 1995c.)

In PET, cyclotron-generated radioligands, for example $^{15}O_2$, $C^{15}O_2$ and $C^{15}O$ are used in the creation of quantitative images of cerebral perfusion, oxygen extraction fraction and cerebral blood volume. Due to the very short half-lives (two minutes) of the radioligands and the expense and lack of cyclotron/PET cameras near acute stroke units, although PET has assisted in increasing understanding of event sequences subsequent to acute vessel occlusion, in its present form it is not expected to contribute to routine management. (Wise et al. 1983; Baron 1991; Donnan 1992b; Robb 1995c.)

Further imaging development during the last 2 decades has been that of multimodality imaging (Graf von Keyserlingk et al. 1989; Yang et al. 1993; Buchner et al. 1994; Gevins et al. 1994; Maclin et al. 1994; Renault et al. 1995; Robb 1995c; Warach et al. 1996; Zifko et al. 1996; Fuchs et al. 1997;

Kristeva-Feige 1997; Soufflet et al. 1997; Towle 1997; Wagner at al. 1997; Wong 1997; Yoo et al. 1997). With the current availability of advanced computers and software, clinical application lies in tissue pathology quantification, as well as surgery simulation, anatomical education and radiotherapy planning. Examples of applications include three dimensional (3-D) MRI with EEG projection for planning neurosurgery in epilepsy, craniofacial bone graft pre-surgical planning, orthognathic surgery, dose distribution with radiation treatment, tumour localisation and illustration of tumour status (advancing, static, regressing). (Robb 1995d; Towle 1997; Wong 1997). Further blurring of the boundaries between the disciplines is seen in studies such as that of Baudewig et al. (1997), where electrical stimulation of the median nerve was used in localisation of the central sulcus by means of functional MRI.

2.1.3 Method of choice

Technically, MRI would be the neuroimaging method of choice for intracranial lesions, other than where contra-indicated, although access may be limited and the cost prohibitive. The advantages of MRI include display of the information in three dimensions, demonstration of blood/CSF flow, better visualisation of the posterior fossa and intraspinal contents and there is no ionising radiation (Chan et al. 1995). However, Hommel (1995) noted that although there is no true 'gold standard' for in vivo imaging of cerebral infarction or ischaemia, CT is considered the standard against which any new technique must be measured. It is less sensitive than MRI in showing non-haemorrhagic infarction during the 24 hours immediately following ictus. Infarcts within the brainstem and cerebellum and focal lesions responsible for reversible TIA are also seen less frequently on CT than on MRI. However, CT is commonly used for screening in the acute evaluation of stroke, because of ready availability, speed and comparative inexpense, being particularly useful for patients who are medically or neurologically unstable, unco-operative, claustrophobic or with absolute contra-indications for MRI. (Chan et al. 1995.)

2.2   CLINIMETRICS

The goal of treatment in stroke is to improve clinical outcome and stroke assessment scales may be used in patient care to predict outcome and to guide decision-making in management, as well as for clinical monitoring. In research they may be used as a diagnostic guide, in the study of the natural history of acute stroke and in the evaluation of therapeutic modalities (Côté et al. 1988).

2.2.1   Definition of Clinimetrics

Clinimetric methods of assessment to quantitate and follow progress include impairment and disability scales. Feinstein (1987) stated: 'Clinimetrics can be defined as the domain concerned with indexes, rating scales, and other expressions that are used to describe or measure symptoms, physical signs, and other distinctly clinical phenomena in clinical medicine'. Selecting the appropriate measures of outcome for a clinical study of stroke subjects is an exercise in realism (Wood-Dauphinee et al. 1990).

One impairment and two disability scales are used at TQEH, thus these will be discussed.

2.2.2   Impairment Scale

Impairment is considered to be any loss of psychological, physiological or anatomical structure or functions, in the health context (de Kleijn-de Vrankrijker 1995), and the scale used in our Neurology Department is the modified Canadian Neurological Score (MCNS).

The Canadian Stroke Scale was designed by Côté et al. (1986), based on a literature review and their clinical experience, with validity and reliability of a slightly modified version reported in 1989 (Côté et al. 1989). The modified scale assesses level of consciousness, orientation, speech, motor function of the face, arm and leg (distal and proximal), with different tests for patients with and without comprehension deficits. Selection of items was based on clinical importance and prognostic value, but, with the need for assessibility by medical and non-medical staff, some modalities such as visual field and gaze were excluded, despite their importance (Côté et al. 1986).

Validity was confirmed by Wade and Hewer (1987), but the scale was criticised by Brass and Kernan (1989) with respect to consistency, criterion and content validity, construct validation, and 'trying to be all scales to all strokes'. Hantson and de Keyser (1994) noted that inter-rater reliability and internal consistency were considered acceptable, with kappa ranging from 0.535 to 1 (-1 reflecting total disagreement, +1 reflecting total agreement) and Cronbach's alpha coefficient being 0.792 (0 reflecting more than one construction underlying the scale, 1 reflecting perfect consistency). The scale also has considerable predictive value for six months' outcome, good discriminant validity (giving better quantification of neurological condition than the Glasgow Coma Scale) and a good negative predictive value (the chance of missing change in the neurological condition of the patient is small). The scale is easy to use, taking approximately 10 minutes to complete, however, sensitivity is low (2-4 scores per item) and patients with comprehension deficits are not tested for distal and proximal limb parts separately.

2.2.3 Disability Scales

A disability is any restriction or lack of ability (resulting from an impairment) to perform an activity in the manner or within the range considered normal for a human being, in the health context (de Kleijn-de Vrankrijker 1995).

Activities of daily living (ADL) scales consist of a battery of tasks providing an index of performance ability with respect to self-sustaining activities for meeting personal requirements in daily life (Ad Hoc Committee on Cerebrovascular Disease 1975). ADL scales need to be measured from the time of the stroke onset and at generally recommended time intervals thereafter. The Task Forces on stroke impairment, stroke disability and stroke handicap (1990) recommended measurement at onset, 3, 6 and 12 months. However, for specific intervention studies, a more intensive assessment protocol may be warranted.

The scales that staff at The Queen Elizabeth Hospital have used are the Barthel Index and Functional Independence Measure.

2.2.3.1 Barthel Index

The Barthel Index (BI), used in Maryland's chronic disease hospitals and otherwise known as the Maryland Disability Index (Wylie and White 1964), was developed by Mahoney and Barthel (1965) to measure functional status and improvement in patients. It was used as a standardised measure of the patient's disability severity, where the disease interfered with independent movement. Wade and Collin (1988) considered it to be as good as any other single simple index and recommended that it be adopted as the standard against which future indices were compared.

The BI is a 10-item, 5-scale index assessing personal hygiene, bathing, feeding, going to the toilet, stair-climbing, dressing, bowel and bladder control, ambulation (or wheelchair use) and chair/bed transfers. A total score of 100 indicates no assistance is needed, 91 to 99 - slight dependence, 61 to 90 - moderate dependence, 21 to 60 - severe dependence and 0 to 20 - total dependence (Shah et al. 1989).

Collin et al. (1987), regarded it as a reliable and repeatable index of the activities of daily living in both skilled and unskilled hands (Kendall's Coefficient W=0.93, p<0.001), although Ranhoff and Laake (1993) reported that BI scores by the physician from patient interview were different to those of the reference method.

2.2.3.2 Functional Independence Measure

The Functional Independence Measure (FIM) is an 18-item, 7-scale index for the assessment of disability. It was developed from the BI, as a more sensitive scale was needed. It allows assessment of personal care (eating, grooming, dressing upper and lower body, going to the toilet and bathing), continence (bowel and bladder function), transfers (bed, chair, toilet, tub and shower) and locomotion (walking, wheelchair transportation and stair-climbing). In addition, it allows social and cognitive assessment, i.e., comprehension, expression, social interaction, memory and problem solving. It was developed to provide an appropriate, quickly and uniformly administered, valid and reliable measure, that is discipline-free and acceptable to clinicians in the field. Thus assessment can be undertaken by a variety of appropriate professionals, several of whom (for example, clinician, nurse, speech pathologist) may partly assess one subject. (Task Force for development of a uniform data system for medical rehabilitation 1987.)

It can be used for a variety of purposes, i.e., as a description of the patient's need for assistance with daily activities, the level of dependence, to predict the burden of care or length of stay in hospital and to measure rehabilitation outcome (Grimby 1994). Pilot trials performed since 1984 have tested validity and reliability, both of which were confirmed (Task Force for development of a uniform data system for medical rehabilitation 1987). Further validation by Dodds et al. (1993) showed internal consistency (Cronbach's α=0.93 and 0.95 for overall admission and discharge, respectively), temporal responsiveness (significant improvement between admission and discharge, p<0.0005) and construct validity (discriminating capacity), while Heinemann et al. (1993) reported that FIM demonstrated adequate clinical precision.

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2.3   SUMMARY

In summary, while there are limitations to the radiographic modalities (CT and MRI) and clinimetric scales (BI, FIM and MCNS) used in this thesis for assistance in diagnosis and as outcome measures, respectively, they are in widespread use and are well-documented. They were all available in-house, with the exception of MRI where limited access at another public hospital was available. These, therefore, were the tests and scales used in this study.

CHAPTER 3

ELECTROENCEPHALOGRAPHY (EEG) -

BACKGROUND AND USE IN STROKE

3.0 INTRODUCTION

No standard name has yet been agreed for quantitative or computer-based EEG or EEG brain mapping, and these do not all describe the same thing. EEG brain mapping refers specifically to the topographic representation of scalp electrical activity. EEG frequency analysis applies specifically to calculations of EEG frequency band content, and quantitative neurophysiology is the terminology used by some when evoked potential tests are included. (Nuwer 1992b.)

Gotman stated at the XIIIth International Congress of Electroencephalography and Clinical Neurophysiology in 1993 that there had been a trend to develop computer-assisted methods, where the user interacts with the analytical program or verifies the results of the program, rather than full automation. Where the latter has been developed, for example the system of Matousek and Göthe (1993), it has been used mainly for research.

3.0.1 Issues

In the conventional bipolar EEG, each channel produces a two dimensional representation of potential difference between two electrodes as a function of time; the interpreter then mentally integrates the information across the channels to visualise the topography. The characteristic features of conventional EEG (and EP) recordings are the visual determinations of waveform and amplitude maxima and minima, as temporally oriented measures.

With the increasing availability and relative inexpense of digital systems, it has become practical to record the EEG on magnetic or optical storage media, rather than on paper. Advantages include the ability to review using montages, filters and scaling different to those of the original recording, further digital processing and reduced storage requirements. (Binnie and MacGillivray 1992; American Electroencephalographic Society 1994b.)

This field is still very much in its infancy as can be seen by reading the guidelines developed by the American Electroencephalographic Society (1994b) with recommendations on electronic patient identification and EEG storage, calibration, recording parameters and media, as well as display (video, paper or both). The Organisation of Societies for Electrophysiological Technology (OSET) guidelines for digital EEG are still being developed (Gregory n.d.).

The American Electroencephalographic Society guidelines (1994a, 1994b) for computerised EEG are somewhat more limited and less explicit than those for digital EEG. However, the recommendations are that clinical neurophysiologists have some familiarity with computerised EEG frequency analysis (artefacts, normal variability, development and ageing, dementia, focal lesions, epilepsy and statistics), display techniques (compressed spectral array, topographic mapping and others (for example, density spectral array and chronotopogram)) and monitoring in the intensive care unit (ICU) and the operating room (auditory and somatosensory evoked potentials, EEG and the effect of anaesthetics) is required by anyone involved in such monitoring.

'Brain mapping' consists of quantitation of a set of multiple EEG signals, i.e., feature extraction for shaded or colour contour plotting representing cerebral activity. The features are: a direct variable such as amplitude, a transformed variable such as absolute power and the result of a statistical procedure, for example probability. Thus reports may be in the form of 'raw' maps or based on z-scores, z-differences, significance probability mapping (SPM) and T-Score Analysis. (Duffy et al. 1981; John et al. 1989; Lopes da Silva 1990; Nagata et al. 1992.)

Such spatial resolution of ongoing activity or events and topographic patterns of peaks and troughs allows resolution mostly in two dimensions, although three dimensional representation can be made. Thus brain mapping transforms the multi-lead data from the frequency and time domain to the spatial domain, and statistical measures can then be used to evaluate abnormalities. (Maurer and Dierks 1991e; Medina et al. 1994.)

Thus mapping can be undertaken in the time domain as amplitude mapping, i.e., no FFT - only voltage parameters and the topography thereof, or in the frequency domain with presentation of frequency parameters and topography after FFT. Examples of use in the time domain include amplitude of the EEG waves (delta, theta, alpha and beta) and patterns (sharp waves, spike/wave complexes, K complexes and sigma spindles), while in the frequency domain examples include spectra of EEG activity presented as power (μV^2) or the square root thereof, relative activity (percentage) or coherence, or as statistical parameters. (Maurer and Dierks 1991e, 1991f.) Various methods of interpolation are used, for example three or four point linear, inverse distance to the power n and polynomial approximation (Duffy and Maurer 1989). The surface spline interpolation allows interpolation of data from electrodes spaced irregularly, resulting in a continuous surface with better estimation of peripheral locations (Perrin et al. 1987). In a study assessing interpolation methods, Fletcher et al. (1996) reported that among the best interpolation methods, adequate electrode density was more important than the method of interpolation. Interpolation error, they concluded, could be controlled locally by making the interelectrode distance inversely proportional to the expected potential gradient.

For diagnostic work, primary issues are those of baselines, references, data reduction and evaluation, as well as standardisation of procedures and knowledge of normative data and deviation due to disease. As the main task in analysing maps is to describe and compare spatial patterns, these need to be addressed on the basis of expediency and efficiency, in order to best show the direction of deviation in disease from the norm (Lehmann 1988; Duffy and Maurer 1989; Nuwer 1990a). EEG brain maps produced on-line have been considered to enhance EEG information provided to the clinician (Persson and Hjorth 1983). Quantitation of the EEG can be used to provide numerical taxonomy to identify different profiles of brain functions within groups of behaviourally similar people (John et al. 1977) and, using the Neurometric database as supplied by Cadwell Laboratories, to assist in the diagnosis and treatment of a wide variety of patient disorders (Noland 1990).

In answer to the question of whether a brain map adds value to a table of quantitative data, Lopes da Silva (1990) offers the following. It is more attractive to look at a brain map and extract a characteristic pattern than to interpret numbers in a table. A brain map also provides information that can be used for a more extended interpretation in conjunction with imaging techniques such as EEG, MEG, MRI and PET.

3.0.2 Pitfalls in brain mapping

While the information from brain mapping may be more understandable, simple clinical application could be misleading, due to technical and clinical problems. Critically important is the recognition of the limitations and pitfalls of this technology, including artefact, both traditional and new, the loss of transients included in the analysis, the effect of normal variants, the subject's physiological and clinical status, as well as a variety of statistical and other issues. (Goff et al. 1977; John et al. 1977; Hossmann et al. 1980; Walter et al. 1984; Oken and Chiappa 1986, 1988; Nuwer and Jordan 1987; Coburn and Moreno 1988; Kahn et al. 1988; Nuwer 1988a, 1990a, 1996; American Academy of Neurology, Therapeutics and Technology Assessment Subcommittee 1989; Bickford 1989; Pfurtscheller 1989; Winter 1989; Gonzalez Andino et al. 1990; Myslobodsky et al. 1990; Perrin et al. 1990; Rodin 1990; Tomberg et al. 1990; American Psychiatric Association Task Force on Quantitative Electrophysiological Assessment 1991; Anderer et al. 1992; Binnie and MacGillivray 1992; Welch 1992; Klotz 1993; Logar et al. 1993; Pivik et al. 1993; Duffy et al. 1994; Epstein 1994; Nuwer et al. 1994a; Nuwer and Hauser 1994; Adams et al. 1995; Klass 1995; Battistini et al. 1996; Blum 1998.)

However, caution is required when interpreting the warnings issued by many of the above. For example, Adams et al. (1995) noted that software, rather than being faulty, may not have been appropriately implemented (Edmonds and Singer 1996; Gugino et al. 1996).

Artefacts may be due to the automated analyses and unfamiliar methods of display, particularly if the sensitivity of the analysis techniques is not appreciated. They include electro-oculographic (EOG), electromyographic (EMG), electrocardiographic (ECG) and photomyoclonic activity, as well as tremor, volume conducted cortical activity and 50 or 60 Herz (Hz) interference (Coburn and Moreno 1988).

Oken (1986) noted that the main problem with electromyographic artefact is that it includes activity with some of the same frequencies as the EEG signal from which it cannot be differentiated or separated routinely. To ensure that subtle artefacts do not distort computerised EEG analyses, dedicated channels are needed to monitor artefact. The data then needs to be analysed in parallel with that of the signal channels, and all the results need to be displayed. As a minimum, the mapped data should also be displayed in the traditional format (Coburn and Moreno 1988). To allow identification of certain types of artefact, maps may also be constructed of artefact, as, for example by Lee and Buchsbaum (1987) and Coburn and Moreno (1988), who illustrated maps contaminated with artefact caused by gritting teeth, eye movement, blinking, tremor and ECG.

Algorithms to detect head and body movements, eye movement and large muscle potentials were developed by Gevins et al. (1977). Their system correctly identified 65% of the events identified as artefact by a consensus of expert scorers. This was not considered to be statistically different from the average of the individual scorers as compared with the consensus. False positives were mainly high amplitude, intermittent events of cortical origin, which were not evident during the calibration period. Barlow and Rémond (1981) described a multichannel nulling technique for eliminating or minimising vertical and/or horizontal eye movement artefact, including blinks, in EEGs. While simple to design and easy to implement, limitations included decreased effectiveness with anterior small EOG and high amplitude EEG spikes and sharp or slow wave signals in the EOG leads, with the inadvertent introduction of these in the more posterior derivations. Jervis et al. (1985) assessed both computerised correlation and analogue techniques for removal of eye movement artefact and found that the computerised correlation technique was superior, with the analogue technique proving to be time-consuming and possibly erroneous.

In 1991 Larsen and Prinz proposed a method to identify the ECG as outlying data, using an algorithm which they considered could be applied universally to all EEG recordings. MacCrimmon et al. (1993) concluded from their study of computerised pattern recognition of EEG artefact that very low levels of artefact contamination would result if their current classifier were used, and they anticipated that improved data collection technologies and a broadened feature set would increase accuracy. More recently, Vigário (1997) described an approach using a statistical technique of independent component analysis, where pure eye activity could be isolated in the EEG recording, resulting in a reduction in the amount of brain activity extracted with the EOG signals.

Computerisation of the EEG has also introduced artefacts such as aliasing, which are not found in the standard EEG. Aliasing occurs when a signal containing high frequencies is sampled at a rate that is too low, resulting in the generation of spurious low frequency signals. However, if using sophisticated techniques such as the discrete Fourier transform, aliasing can be avoided by sampling at least twice the highest frequency of the input signal (the Nyquist frequency). (Lopes da Silva 1987; Coburn and Moreno 1988; Nilsson et al. 1993.)

Other issues include some of the methodological concerns which relate to sampling validity, mathematical manipulation and the use of colour (Burgess 1990). As he noted in 'The Scientific Basis of Computed Neurophysiologic Topography', in CT and MRI the intensity of every pixel is based on a measurement. However, in brain mapping, where, for example, only 16 points may be measured, the balance is obtained by interpolation, thereby creating an illusion of a higher resolution than that which exists.

Furthermore, changes in data that are quite similar could appear very different when displayed in colour. Photorealism (by means of graphic enhancement) may be gained at the cost of diagnostic accuracy; the 'gold standard' for displaying a medical image should be human performance with respect to a medically relevant task (Kundel 1990). The medical imaging truism 'what is subjectively most pleasing, or technically most sophisticated or glitzy, is not necessarily the optimal way to display an image in terms of visual perception and clinical diagnosis' is often ignored (Klymenko and Coggins 1990).

3.1   EEG MAPPING IN DIFFERENT STATES

In this brief overview, EEG activity is shown to be partly dependent on the mental state and activity of the subject, resulting in some of the variability that can make quantitation difficult.

3.1.1   Resting and activated states

EEG mapping can be performed with the subject in the resting or activated state (eyes open or closed), as well as during sleep or anaesthesia. EEG mapping in the activated state (dynamic cartography) includes reading and studying during the 'eyes-open' state, and listening and calculating during the 'eyes-closed' state, for example (Maurer and Dierks 1991f).

Gundel and Wilson (1992), found that high task difficulty resulted in a decrease of occipital and parietal alpha (due to visual scanning) and an increase in theta in the left frontal electrodes, possibly associated with the amount of general mental processing. Inouye et al. (1993) suggested that calculation processing was activated in the left temporo-centro-parietal region and spread frontally with active mental arithmetic. Fernández et al. (1995) demonstrated an increase in delta in all leads and a concomitant decrease of alpha during mental calculation. It should be noted, however, that changes in alpha activity during calculation and problem solving were reported by Berger in 1937 (cited in Gloor 1969b).

3.1.2 Drowsiness and sleep

Santamaria and Chiappa (1987) reported a great deal of variability between different subjects in the conventional EEG of drowsiness, but considered it possible to classify most EEG drowsiness patterns. Broughton et al. (1994) pointed out that the 'eyes-closed' resting state was generally considered to produce parieto-occipital alpha activity which, if the subject became drowsy, appeared slow and spread anteriorly. They considered this 'anterior slow alpha of drowsiness' to be distinct from the alpha rhythm, as it was dependent on a different state (drowsiness versus wakefulness), and had a different reactivity and separate equivalent source dipole, i.e., near the thalamus versus the mesial occipital lobes.

Buchsbaum et al. (1982) assessed topographic cortical mapping of qEEG in normal subjects napping during the day, showing delta activity to be relatively uniform and of low amplitude in awake, eyes-closed subjects and in rapid eye movement (REM) sleep. Delta increased in the vertex in stage one, and with progressing non-REM sleep stages, increased further in power and spread radially. Alpha frequency activity occurred frontally in slow wave sleep, while low amplitude beta which was maximal parietally, decreased and became more uniform in stage one and REM sleep. During night time sleep in healthy volunteers, Zeitlhofer et al. (1993) also used topographic mapping to show an increase in delta power from stage one to four, a decrease in theta in stage two and a decrease in alpha particularly parieto-occipitally, as well as alpha slowing.

3.2   DATABASES

Assessment of control subjects and the development of a normative database is a necessary but time-consuming process. Bickford (1989) and John et al. (1989) emphasised that databases provided with the equipment may include not only healthy control subjects, but neurological patients who have do not have head related problems (normative) or those with specific disorders (abnormative). Furthermore, recording conditions in research laboratories and busy clinical laboratories were not likely to be the same.

From the results of a multicentre study on equipment reliability, Battistini et al. (1996) suggested that reliability within and between different systems needed to be verified prior to developing data analysis, collaborative projects and networks between laboratories. Thus validation needs to be performed in the laboratory concerned to determine the correctness of classification.

3.2.1 Gender differences

Gender-linked differences have been reported in the literature. For example, Giaquinto and Nolfe (1986) showed a gender-linked difference in a group of 16 normal subjects, 40 to 60 years old, with women having less delta and more beta. Veldhuizen et al. (1993), Jonkman (1994) and Brenner et al. (1995) recommended the construction of gender-based data-banks and control for variance related to gender. The regression equations used in Neurometric evaluation, however, describe the development of electrical activity of the normal human brain independent of gender factors (John et al. 1980).

3.2.2 Age-related differences

Issues such as EEG variability due to change over time are important considerations in the development of a database. John et al. (1980 and 1983) reported that for Neurometric evaluation, after appropriate initial transformation to achieve Gaussian distributions of the extracted EEG features, linear regression equations were computed as a function of age for mean EEG values of the healthy population. Duffy et al. (1984b) also reported age-related change in a cross-sectional study of 63 healthy men aged 30 to 80 years, in all frequencies. They noted that slow activity was reduced, fast activity was augmented, alpha frequency was slightly reduced, alpha blocking was correlated with age (decreasing reactivity) and the EEG data demonstrated age-related changes in the temporal lobes. In contrast, Breslau et al. (1989) showed significantly greater mid-parietal and left mid-temporal delta and theta in older normals, with relatively less occipital but greater mid-parietal alpha and beta.

After a study of electrophysiological changes in the optimally healthy extremely old (22 subjects aged 85 years and older), Oken and Kaye (1991) reported that their subjects demonstrated significant changes in neurophysiological function and that it was important to be aware of such changes when attempting to interpret the EEG results. Wu (1993) reported slowing of background frequency in the EEG and lower power in 11 healthy centenarians when compared with younger adults. Duffy et al. (1993) examined EEG spectral analysis in 202 healthy subjects aged 30 to 80 years and concluded that age-related change was not a simple linear process, but differed for different absolute and relative spectral measures and bands, as well as for gender, with none of the age-related changes demonstrating an increased prevalence of slow activity with age. Karnaze et al. (1993) have also noted significant normal variation in the EEG of the elderly, for example common intermittent theta not necessarily localised to temporal areas, in their study of 25 elderly normals (age: 55 to 84 years, mean 68 years), which, they considered, could confound interpretation, while Shigeta et al. (1995) reported an intermittent slowing in a longitudinal study of 13 aged healthy controls (age: 76 to 83 years, mean 77.6 years) - regarding this as non-specific and clinically silent. Polich (1997) found, in general, that increasing age produced a reduction of delta, theta and alpha band spectral power, while the EEG mean frequency remained constant (generally) for all bands.

Duffy et al. (1996) have speculated that the age-related decrease in interhemispheric coherence may partly account for age-related EEG desynchrony and that it stems from an age-related reduction in cortical connectivity; they also reported that females demonstrated higher interhemispheric connectivity than males.

Thus ageing in humans is seen to be associated with electrophysiological changes, with effects being multifactorial.

3.2.3   Inclusion/exclusion criteria

Initial inclusion and exclusion criteria are determined by the researcher. Use of very strict criteria can result in a 'super-normal' database with many false positive test results.

Once a subject has been screened and accepted, the results of this subject should not be excluded (Salinsky et al. 1992), although Jonkman (1994) recommends excluding the EEG results where the trace shows the subject becoming less vigilant during the study, when there are unexpected obvious pathological findings (for example, slow wave complexes) or physiological slow or fast variants, as these will increase the variance.

3.3   NEUROMETRICS

In 1977 John et al. proposed that statistical analysis of standardised quantitative electrophysiological features could assist in differential diagnosis of various subtle brain dysfunctions. Neurometrics is such an analysis, being considered to be '... a method which estimates the probability that the quantitative features extracted from brain electrical activity reflect dysfunction'. The developmental equations used have been reported as providing reliable descriptors of brain electrical activity. (John et al. 1980; John et al. 1983; Prichep and John 1986; John et al. 1988b.)

Neurometrics uses a unique database derived from EEGs recorded from normal and abnormal subjects. The normative database, collected at 6 acquisition sites, was derived from more than 750 subjects between 6 and 90 years of age, using standardised methods and criteria. Evaluation of candidates for the normative database included an extensive psychiatric and neurophysiological test battery, a neurological and psychiatric examination, achievement tests and determination of hand, foot and eye dominance. Further evaluation consisted of psychosocial and medical histories, pre- and peri-natal data, as well as assessment of current and post-school or work records. Subjects with significant abnormal findings or events in their history were excluded, as were any using prescription drugs or with a history of head injury or loss of consciousness, previous neurological examination or EEG and febrile convulsions. (John et al. 1989.)

The goals of a Neurometric analysis approach were considered to be:

- acquisition of accurate reliable data relating to both brain function and dysfunction
- quantification and extraction of the features providing accurate and reliable indices of the brain status, by means of computer analysis
- use of statistically defined profiles to classify patients for diagnostic purposes.

As detailed by Cadwell, anticipated applications were:

- as a screening procedure for the assessment of brain dysfunction or damage, providing an image of the functional state of the brain, thereby allowing more accurate diagnosis
- as a screening tool for those at risk of brain disease or damage, for example, individuals demonstrating peripheral signs of atherosclerosis but who are otherwise asymptomatic
- as a screening tool for patients with neurological disorders, allowing early detection of disorders, for immediate treatment and improved prognosis
- intraoperative monitoring.

3.3.1 Data gathering

Sixty seconds of artefact-free EEG samples were gathered, with both 'eyes-open' and 'eyes-closed', however, the recommendation for analysis was that forty-eight 2.5-second epochs of artefact-free EEG should be recorded. A patented on-line artefact detection system allowed automatic rejection of data contaminated by artefact, for example that arising from muscle, eye-movement, environmental noise or any other activity. Each 2.5-second epoch of analogue EEG was digitised into 512 individual binary points, so that the waveforms were represented by a series of numbers, with multiple epoch values being averaged. The fast Fourier transform was applied to provide a frequency composition divided into the four traditional frequency bands, namely delta (1.5 - 3.5 Hz), theta (3.5 - 7.5 Hz), alpha (7.5 to 12.5 Hz) and beta (12.5 - 25 Hz).

3.3.2 Spectral analysis

3.3.2.1 Univariate features

The spectral analysis results in the following four basic categories of univariate features.

Absolute Power: the average amount of power, in microvolts squared (picowatts), from each of 21 electrodes of the International 10/20 System (Fp1,z,2, F7,3,z,8,4, T,5,7,4,8, C3,z,4, P3,z,4, O1,z,2) in each frequency band, as well as in the total frequency spectrum.

Relative Power: the percentage of the total power for each of the 21 electrodes, in each frequency band.

Power Asymmetry: the ratio of levels of activity between homologous electrodes or brain regions, in each frequency band.

Coherence: the phase relationship or amount of synchronisation of electrical activity in homologous regions of the brain, in each frequency band, as well as in the total frequency spectrum.

Quantitative features are extracted from the 21 electrodes and additional features are computed from the 8 bipolar derivations (C3/z, C4/z, T3/5, T4/6, P3/O1, P4/O2, F7/T3, F8/T4); the construction is made from the monopolar recordings by means of a patented algorithm. Each of these univariate measures provides quantitative information about the EEG at one derivation.

Subsequently, the data is log transformed to obtain a Gaussian distribution and age-regressed to describe the distribution of each feature as a function of age. Developmental equations in the Neurometrics database were derived allowing prediction of the average value and the standard deviation for each feature in a group of healthy people of the same age as the subject, thereby providing the basis for evaluation of the patient's features.

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The difference between the value of each of the patient's features and the appropriate age average value predicted by the developmental equation is divided by the predicted standard deviation of the distribution of the feature in an age matched normal population to provide the z-score:

$$z = \frac{\text{subject value - mean value of sample}}{\text{standard deviation of the sample}}$$

This deviation from the mean in standard deviation units defines the probability that the value observed in the subject in question may or may not be found in a normal healthy person.

3.3.2.2 Multivariate analysis

Neurometrics also provides a multivariate analysis, by means of patented techniques, to combine different univariate features from a single region, or single univariate features across different regions, into new multivariate features. The pattern of relationships characteristically found among any set of univariate features in the normative database can be described by a covariance matrix. Once specified, the Mahalanobis distance, i.e., the extent to which the corresponding set of features deviates from the normal pattern, can be calculated. This calculation improves the ability to discriminate between normal and abnormal scores.

Measures are provided for Relative Power, Power Asymmetry and Coherence for regions and hemispheres, with overall measures providing estimations of abnormality. The significance of multivariate measures lies in the provision of an index of global activity reflecting a general pattern of cortical activity.

3.3.2.3 Results

The results can be displayed numerically in a series of statistical tables, presenting the information calculated from the EEG recorded by the electrodes, or as functional maps of EEG activity, constructed using a four-point linear interpolation program. Interpretation of the results therefore requires appreciation of z-scores, correlation and regression analyses and multivariate statistical procedures. Evaluation of the maps needs to include correlation with the colour scale and the statistical data provided with the analysis, as variations can only be defined as statistically significant, if the statistical data indicate this.

John et al. (1988a, 1988b) reported that patients with different disorders could be reliably discriminated from each other. They considered that there was sufficient evidence to use 'Neurometrics' as an objective diagnostic clinical tool, reporting marked electrophysiological differences between normal subjects and patients with a variety of psychiatric disorders (John et al. 1989).

(John et al. 1980; John et al. 1983; Shuttlesworth 1987; Cadwell n.d.(a).)

3.4 ELECTROENCEPHALOGRAPHY AND BRAIN MAPPING IN STROKE

In 1989, the American Academy of Neurology, Therapeutics and Technology Assessment Subcommittee reported that little had been published on how EEG brain mapping could affect the diagnosis or treatment of individual patients, but that cerebrovascular disease was one area where such tests may fill occasional specific needs. They considered that as several quantified EEG parameters were highly correlated with regional blood flow, with respect to ischaemia-related cerebral impairment, sensitivity and specificity were high, and that these tests could be abnormal when the CT was still normal, as in the first few days after stroke or when the degree of ischaemia was mild enough to cause dysfunction without infarction.

3.4.1 Pre-CT

Many EEG abnormalities were reported in cerebrovascular and related diseases in the pre-CT era. Jones and Bagchi (1951) considered that the degree of focal activity paralleled clinical symptom severity, findings confirmed by Hass and Goldensohn (1959) in 35 cases of verified carotid artery occlusion, where the frequency of EEG abnormalities was 83%.

Roseman (1958) reported on serial EEGs in patients with cerebrovascular disease, concluding that the EEG (delta activity and dynamic changes thereof) could definitely lateralise an intracranial aneurysm or haematoma, although in the weeks subsequent to rupture, an initial EEG appeared inconclusive for this purpose. In 10 cases of internal carotid occlusion, Markovic (1958) found massive long lasting focal EEG abnormalities. Tucker (1958) reported 4 cases of brainstem vascular disease showing EEG abnormalities, while Friedlander (1959) reported abnormal EEGs in 9 of 31 patients with definite brainstem vascular lesions.

In 1959, Birchfield et al. investigated 94 patients with cerebral infarction or thrombosis caused by arteriosclerosis. Forty-eight were diagnosed with unilateral infarction of the cerebral hemisphere, 30 of whom had definite EEG abnormalities (7 of these having bilateral changes). After a study of 138 patients with cerebral vascular disease, Paddison and Ferriss (1961), concluded that EEG was useful in localisation of the area of the brain involved, thereby aiding in localisation and determining the relative adequacy of cerebral blood flow.

3.4.2   CT era, and beyond

As noted by Sananman in 1983, the EEG provides a range of information separate from the CT and if combined with the CT, increased information may be yielded. In a study of 100 consecutive cases of acute forebrain infarction using CT and EEG, Macdonell et al. (1988) predicted ipsilateral cortical infarction, using lateralised theta and/or delta activity, with a sensitivity of 76% and specificity of 82%, while cerebral hemisphere lacunae produced similar EEG abnormalities in only 9% of cases. They concluded that EEG was particularly useful if the initial CT following stroke excluded haemorrhage, but did not detect infarction. Thus, together with the clinical details, the EEG could be used to detect the likelihood of cortical involvement.

In a study of 12 patients with CT confirmed lacunar infarcts, Kappelle et al. (1990) found that visual EEG assessment alone led to correct diagnosis and correct side of lesion in 8 patients, while assessment of both visual and quantitative EEG increased this to 10 patients. These studies, they concluded, were in contrast to previous studies, as they showed subtle EEG abnormalities in CT confirmed lacunar infarct. However they emphasised that further studies were needed to establish the value of the EEG in patients with lacunar stroke and a normal CT. Petty et al. (1995) conducted a single-blinded EEG study on 55 patients with acute lacunar infarction and concluded that EEGs showing major lateralised abnormalities were useful in excluding lacunar or brainstem infarction within the first 48 hours, when CT often fails to show abnormalities.

Hossmann et al. (1980) quantified EEG abnormalities in 18 patients with acute ischaemic stroke and concluded that computerised frequency analysis improved the correlation between anatomico-clinical and neurophysiological localisation, but contributed little to evaluation of the pathological process temporally.

In an examination of 20 patients with aphasia due to cerebral infarction, using computed mapping of the EEG (CME) Nagata et al. (1982) reported that 12 patients showed high-voltage foci and 6 showed asymmetrical alpha activity. These findings correlated well with the lesions on CT and/or rCBF. Notably, CME demonstrated the abnormality in advance of the appearance of a low density area on CT. They thus considered CME to be a useful objective measure in the diagnosis of functional lesions, despite the source of the data being the same as that of the conventional EEG. In a subsequent report, Nagata et al. (1984b) reported unilateral CME abnormalities in 68% of their 25 TIA patients, after they had recovered completely from their neurological deficits. They considered that association of clinical symptoms with CME findings could be reflective of residual cerebral dysfunction caused by the TIA. Van Huffelen et al. (1984) considered the most sensitive and specific parameters in TIA to be alpha and mu asymmetry and alpha reactivity, showing a similar abnormality in 72% of patients with TIA, compared with 10% for CT. They concluded that qEEG was superior to conventional EEG and CT, and that qEEG might prove to be the only objective non-invasive method to confirm the diagnosis of transient ischaemia.

Sainio et al. (1983), in an assessment of serial EEGs in 15 subjects with cerebral infarction, recorded the EEG within 48 hours of the first symptoms and weekly for 4 weeks subsequent to this. They found that 87% of the patients had an abnormal EEG by visual analysis and that spectral parameters correlated well with visual findings, particularly the delta and alpha bands. Spectral analysis was found to be superior to visual analysis with respect to lateralisation, identifying the correct side of the lesion in 87% of the cases, as opposed to 54% in the latter. Köpruner and Pfurtscheller (1984), using a multiparametric asymmetry score, showed a distinction between normal and ischaemic brains, with 92% of their 32 patients and 94% of their 50 normal subjects being correctly classified.

Using Neurometrics in stroke, Jonkman et al. (1985) found a significant overall asymmetry in 82% of their 94 patients (54 with permanent neurological deficit and 40 with reversible or transient neurological symptoms) versus 2% of a reference group of 64 normal volunteers. Ninety percent of all patients had an abnormal Neurometrics result (with 3% false positive). The qEEG showed an abnormality not detected by visual assessment in 34% of patients, while only 1.9% of the patient EEGs revealed abnormality on visual but not qEEG assessment. In the group of EEGs considered normal when assessed visually, Neurometrics yielded abnormalities in 84%. In assessing lateralisation, using delta activity asymmetry in the midtemporal region (the parameter they considered optimal in indicating the pathological side), there were no false positives (100% specificity), however, the number of true positives, i.e., where the more diseased side was indicated, was only 53% in the 54 stroke subjects with permanent neurological deficit (completed and partial non-progressive stroke).

Schaul et al. (1986) concluded that the EEG provided lateralising rather than localising information, after assessing the field, amplitude, frequency, persistence and reactivity of focal or lateralised slow-wave activity in a study of 54 patients with acute cerebral infarct or haemorrhage documented by CT. Nuwer et al. (1987), in a study evaluating frequency analysis and topographic mapping in stroke showed an increase in delta and a decrease in alpha in 17 of 20 mild stroke patients, but not in 20 normal subjects. They noted that theta was unreliable by itself, but concluded that the computerised EEG, albeit with simple techniques, was abnormal significantly more frequently than conventional EEG (30% sensitivity) - findings they considered in keeping with previous studies undertaken with more complex EEG analyses. In a study of 19 cases of acute stroke involving the cerebral hemispheres, Jackel et al. (1987) considered that computed EEG topography could prove useful in the early diagnosis of stroke, having found EEG and computed EEG topography to be similar in 11 cases, with the latter test being better than EEG in 8 cases.

In a study of the clinical utility of topographic EEG brain mapping on 100 patients referred for EEG and neuroimaging, Jerrett and Corsak (1988) reported topographic map abnormalities in 78% of the 46 patients with stroke. 30% of the patients with abnormal EEGs had sole or better localisation using mapping as opposed to conventional EEG or neuroimaging procedures, with no false localisation using EEG mapping. They concluded that topographic mapping appeared to detect low amplitude slow activity that was not readily discerned on conventional EEG, and that, at times, it distinguished abnormalities not immediately obvious on CT or MRI, thus proving a useful adjunct to the conventional EEG.

In a model of transient ischaemia in young human subjects, Kraaier et al. (1988) reported an increase in relative and absolute power slow activity and a decrease in alpha and beta in qEEGs during reversible hyperventilation-induced ischaemic hypoxia, with no significant differences when the study was repeated a week later.

After a review of topographic EEG in brain ischaemia, Nagata (1988) concluded that delta and theta activity increased, while alpha and beta activity decreased as cerebral blood flow and oxygen metabolism decreased, but that this correlation could decrease or disappear depending on the stage of cerebral infarction. EEG slowing, he considered, could be reflective of decreased cortical blood flow in the acute stage of cerebral infarction, decreased oxygen metabolism in the subacute stage and both in the chronic stage. The qEEG may therefore provide useful information when interpreted in the clinical context.

In a study of topographic EEG mapping in cerebrovascular disease, Nagata (1989) and Nagata et al. (1992) reported that delta and theta activity from power spectral analysis correlated negatively with cerebral blood flow and cerebral oxygen metabolism, while alpha correlated positively. He concluded that z-score maps were a useful tool in the topographic extraction of the features of the EEG power data. When Nagata et al. (1989) assessed electroencephalographic correlation of blood flow and oxygen metabolism as provided by PET in patients with cerebral infarction, they found no significant difference in the quantitative EEG data between a group of patients with cortical infarcts and a group with small subcortical infarcts, despite hemispheric mean cerebral blood flow and oxygen metabolism being significantly lower in the cortical group.

Oken et al. (1989) found that 2 patients (1 with a tumour and 1 with cerebral infarction) of 20 (12 with cerebral infarction, 3 with brain tumours, 2 with intracranial bleeding, 2 with porencephalic cyst and one with post-traumatic encephalomalacia) with CT or MRI documented focal lesions and focally abnormal conventional EEG had normal computerised EEG frequency analysis. They cautioned that this could be related to the presence of:

- episodic EEG slowing which could be indiscernible in computerised EEG averaged over a relatively long time period
- bilateral slowing which would diminish the utility of the asymmetry measures
- EEG epochs containing some drowsiness in patients and controls.

If obvious focal lesions could produce abnormal results, more subtle disturbances may not be detected. They therefore considered that the clinical utility of the method still needed to be proven. It should be noted, however, that in their illustrated case of cerebral infarction (a subject with multiple previous cerebral infarctions), the qEEG cut-off used on an EEG with continuous predominantly lateralised abnormal activity was 3 standard deviations, versus the 2 standard deviations used in the case with the tumour, where EEG slowing was somewhat episodic. In contrast to their findings, Johnson (1990) reported 2 cases of stroke where the CT and MRI were all normal and the FFT brain maps clarified the situation, resulting in altered therapy in both cases.

Psatta et al. (1990) considered EEG mapping able to indicate the affected zone in TIA. Logar and Boswell (1991) assessed the value of EEG-mapping in focal cerebral lesions (43 subjects with completed stroke and 43 with TIA) and reported focal changes in 86% of (37) patients with completed strokes using EEG mapping, versus 65% (28 patients) with conventional EEG. Similarly, focal changes were seen in 63% of patients with transient ischaemic attacks using brain mapping, versus 26% in conventional EEG.

Where focal abnormalities were seen on CT, corresponding focal abnormalities were seen using EEG mapping in 90% (27 patients) of completed strokes and 77% (10 patients) with TIAs, as compared with 57% (17 patients) with completed strokes and 31% (4 patients) with TIAs using conventional EEG. They considered that EEG mapping allowed additional lateralisation, particularly in patients with TIA, and therefore provided additional useful information. (Logar and Boswell 1991.) It should be noted, however, in a subsequent study on volunteers with no clinical signs of cerebrovascular or neuropsychiatric disease, that they reported focal changes in 22 subjects (30%) in EEG mapping, but only 12 (16%) in the conventional EEG (Logar et al. 1993).

In a further report by Jonkman et al. in 1992(a), using the Neurometrics measure Overall All Frequencies, sensitivities of 90%, 61% and 17% were obtained in stroke subjects with severe (n=33), moderate (n=18) and reversible (n=12) deficits respectively. Follow-up studies showed that almost all qEEG improvement occurred in the first three months after the stroke.

3.5 ONGOING CONTROVERSY

Thus, while many studies have shown a positive difference between visual and computerised or brain mapped EEGs, its application has remained controversial. In an assessment of the 'cons' of the role of quantitative topographic mapping or 'Neurometrics' in the diagnosis of psychiatric and neurological disorders, Fisch and Pedley (1989) considered that most of the controversy with respect to the routine clinical use of qEEG and EPs resulted from the failure of some clinicians to recognise:

a) the methodological limitations of quantitative techniques
b) the absence of:
   - controlled experiments, using blinded data analysis
   - independent controlled corroborating studies
c) the lack of verification of abnormal qEEG results obtained in some disorders, where the conventional EEGs were unaltered.

They considered that the specificity needed in the contribution of qEEG to diagnosis and patient care was lacking; furthermore, where normative databases were provided, use of these could encourage misdiagnosis by the clinician. Their recommendation for a constructive first approach was the demonstration of the reliability of computer-based analytical methods in distinguishing between clinically normal and abnormal subjects with definable neurological disorders, through appropriate studies. They also endorsed the statement of the American Electroencephalographic Society (1987) that these tests should be used as an extension of the conventional EEG.

Duffy noted in 'Controversies in Neurology' in 1989(c) that a metamorphosis was taking place in clinical neurophysiology as a result of the increasing power of microcomputers for decreasing cost, the outcome of which could be colourful evanescence or legitimate lasting advancement. To maximise the increased reliability, sensitivity and objectivity anticipated from topographic EEG and EP analyses, the users of this technology needed to increase their knowledge and care, with full awareness of the strengths and limitations (Duffy et al. 1989c). Resolution of the scientific and clinical issues would increase the productive contribution of the field, and, as Hachinski (1989) noted, while advances should be welcomed, '... the burden of proof of the clinical usefulness of brain mapping remains with those who would make diagnosis more elaborate, complex or costly'.

SOMATOSENSORY EVOKED POTENTIALS (SEPs) -

BACKGROUND AND USE IN STROKE

4.1 INTRODUCTION

Somatosensory evoked potentials are electrical potentials generated mainly by the large fibre sensory pathways in peripheral and central parts of the nervous system, with short and some middle latency responses occurring within the first 50 milliseconds (msec) of brief stimulation, allowing quantification of data for localisation of lesions. (Chiappa and Young 1985; Chiappa 1990a; Nuwer et al. 1994b.)

Cortical SEPs arising from peripheral nerve stimulation were first demonstrated in humans by Dawson in 1947. He showed that in a patient with myoclonic seizures, after sensory stimulation, latencies were similar to those of healthy subjects, but amplitudes were increased 5 and 10 times. Techniques such as superimposition and summation of responses were necessary to allow the small potentials to be identified from the larger amplitude ongoing EEG and EMG activity. (Dawson 1947a, b; Dawson 1951; Dawson 1954.)

Initially the focus was on the larger middle (30 - 75 msec) to late (>75 msec) latency evoked potentials, but as these potentials are not always well-defined or consistent in healthy control subjects, their utility in clinical studies is considered more limited. However, the development of field-effect transistors allowing increased amplification of the bioelectric signals and improvement in computer averaging techniques with improved signal-to-noise ratios allowed rapid reliable resolution of the small short-latency SEPs. (Chiappa 1990a.)

Topographic maps of EPs are even more complex than those of EEGs, as they are compounded by a multiplicity of time points in a map movie. Quantitative descriptors capable of decomposing the EP into standard constituents analogous to broadband frequencies, as for EEGs, should simplify objective interpretation, factor analysis z-scores being an example of these statistical neurometric descriptions. (Lehmann 1986; John et al. 1989.) Although the use of many channels raises data management problems, the animated time history of bit-mapped SEP fields may be displayed by freezing the maps at predetermined intervals, allowing in-depth assessment of the SEPs, as noted by Desmedt and Bourguet (1985). Thus, for example, they considered that suspected phase reversals in the SEP could be assessed to identify coherence and spatial features. Furthermore, in a bit-mapped colour imaging SEP study, Desmedt et al. (1987) concluded that this form of analysis allowed separation of the evolving spatial features of the various waveforms.

However, Chiappa (1990b) considered that EP mapping contributed little clinically, as the contribution of mapping to human generator source determination was difficult to determine. He noted, however, that they were a good topic for academic discussion.

4.2   SEP TRANSMISSION AND GENERATION

4.2.1   Pathways

The largest myelinated fibres in the peripheral nerve are excited by the stimulus intensity used for the SEPs; these fibres include cutaneous and subcutaneous somaesthetic and proprioceptive fibres and alpha motor neurons. This is substantiated by the detection of SEP abnormalities in cases of clinical abnormality in light touch, stereognosis, joint position and vibration sense, while SEPs are usually normal in patients with clinical abnormality of pain and temperature. (Halliday and Wakefield 1963; Giblin 1964; Williamson et al. 1970; Mastaglia et al. 1978; Anziska and Cracco 1980; Crespi et al. 1982; Mauguière et al. 1983; Despland and Regli 1985; Karnaze et al. 1987; Chiappa 1990c.)

As summarised by Chiappa and Ropper (1982a), the Erb's Point waveform is generated by the large myelinated sensory and motor fibres in the brachial plexus. Large fibre sensory system cell bodies lie in the dorsal root ganglia, their central process travelling rostrally in the ipsilateral posterior columns of the spinal cord before synapsing in the dorsal-column nuclei at the cervico-medullary junction. Second order fibres cross to the opposite side soon after leaving their origin and travel to the thalamus through the medial lemniscus, while third order fibres continue from the thalamus to the fronto-parietal sensorimotor cortex.

4.2.2 Generators

In a review of short latency SEP generation in the cerebral cortex in 1991, Allison et al. concluded that there was no evidence that short-latency SEPs were generated in cortex other than the primary somatosensory cortex. Later waves (P45, N60 and P100) were probably generated mainly by the contralateral area 1 of the somatosensory cortex (Allison et al. 1992). However, cephalic generator-identification is not absolute, and debate is ongoing, with early and more recent findings indicating complexities which do not permit easy rapid resolution of the generator issues.

For example, Yamada et al. (1984, 1985) noted that the relationships between the type of SEP abnormality and the location of cerebral lesions were complex and postulated the presence of multiple partially independent thalamocortical projections mediating regionally specific somatosensory inputs. Mauguière et al. (1987) favoured a hypothesis of parallel independent thalamo-parietal and thalamo-frontal SEP projections, that could be damaged selectively in thalamo-cortical radiation lesions. Gandevia and Burke (1990) showed that the cortical projection contained a focal negativity over the contralateral parietal cortex and a focal positivity over the frontal cortex, which they considered likely to be reflective of activation within primary somatosensory and motor cortex, respectively.

In a study of somatosensory evoked potentials and magnetic fields which addressed the separation of multiple source activities, Scherg and Buchner (1993) found evidence for a minimum of 4 sources in or close to the contralateral hand projection areas, having activities substantially overlapping in time. They concluded that additional overlap originated from subcortical sources not recognised previously, with the proximity of the activated cortical areas further confounding the issue. However, they felt that simultaneous measurement and analysis of multichannel MEG and EEG held potential for resolving these issues. Another complicating dimension is added by the implications of Szczepaniak and Møller's (1993) finding of interaction between the auditory and somatosensory systems in the inferior colliculus in an animal study of EPs (median nerve stimulation modified the auditory response by increasing the amplitude of the first 2 peaks and decreasing that of 2 later peaks).

In 1994 the International Federation of Clinical Neurophysiology (IFCN) Committee report (Nuwer et al. 1994b) on recommended standards for short latency SEPs documented SEP generators for standard upper limb studies as follows.

N9, the Erb's Point response, probably arising from the distal brachial plexus.

N11, probably arising from the cervical cord at approximately the fifth cervical level, where the median nerve roots enter, branch and synapse.

N13, the spinal response, generated within the rostral cervical spinal cord, possibly from the dorsal horn or branches from the dorsal column.

P14, a positive peak broadly distributed across the scalp, probably arising above the cervico-medullary junction, from the medial lemniscus or its collateral brainstem branches.

N18, a negative peak broadly distributed over the scalp, probably a far-field potential originating at the thalamus or collateral branches in the rostral brainstem.

N20, a negative peak localised to the central scalp region, thought to be generated from the primary somatosensory cortex in the posterior lip of the central sulcus.

P25, the main prominent positive peak subsequent to the N18-N20 complex, appearing earlier at approximately 22 msec with the use of a 30 Hz filter.

Additional cortical peaks were not considered to be used generally for routine clinical purposes.

As the absolute latencies were considered to be affected by peripheral differences such as arm length and temperature, it was customary to focus on the more proximal areas of interest by means of interpeak latencies. These were:

N9 - N13: plexus - cord time, representing conduction through the proximal plexus, roots and cervical cord

N13 - N20: cord - cortex time, representing central conduction time

N9 - N20: plexus - cortex time.

Hsieh et al. (1995) have suggested that interaction occurs in several structures along the sensory pathway in the central nervous system, including the cuneate nucleus, the sensory thalamic nucleus and the sensory and motor cortices, the largest interactions being in the cerebral cortices and the weakest in the brainstem.

Recent studies have also focussed on mathematical algorithms for generator identification, with Namiki et al. (1996), for example, employing second-order differentiation in the temporal dimension to identify short latency SEP neural generators. They concluded that the dipoles generating the N20/P20 and P25 were located in the posterior wall of the central sulcus (area 3b) and the crown (areas 1 and 2) of the post-central gyrus, respectively. Okada et al. (1996) applied a neural network to estimate the N20-P20 dipole SEP potentials from the scalp. They estimated the rotation effect of the dipole moment, and considered that this could possibly provide pre-operative information on the relationship of a tumour to the central sulcus.

With respect to late SEP components, in a study of the scalp topography of these in 7 patients with unilateral supra-tentorial lesions, Yuya et al. (1996) noted that the amplitude of the responses from the frontopolar, frontal, anterior-temporal and/or occipital electrodes was smaller on the affected side at 240 msec and 360 msec, whether a sensory deficit was present or not. They concluded that late SEP components were not associated with primary somatosensory function, but possibly with other cortical pathways.

Finally, in 1997, using 19 scalp electrodes for recording SEPs on a patient with a right frontal astrocytoma, Valeriani et al. proposed that the radial dipolar source of the P22 was independent of the N20 and N30 generators, being located in area 3a or 4. They considered that their report illustrated the usefulness of multichannel recordings in diagnosis of sensorimotor cortex dysfunction. Kany and Treede (1997) considered that SEP scalp topography studies yielded 'a relatively clear concept' with respect to the areas generating early cortical components. The parietal N20 and P30 were considered to be generated by a tangential dipole in area 3b (of the primary somatosensory cortex), with other components in this latency range possibly due to radial dipoles in areas 1 and 2 or in the pre-central sulcus cortex, conclusions supported by subdural recordings, MEG investigation and dipole source modelling (Deiber et al. 1986; Desmedt et al. 1987; Allison et al. 1989; Allison et al. 1991; Baumgartner et al. 1991; Buchner et al. 1995a).

Puce (1995) noted that the clinical importance of localisation was due to the need for accurate assessment of sensorimotor cortex location in pre-surgical investigation and planning for patients with lesions impinging on this area.

4.3   METHOD

Chiappa (1990d) observed: 'unfortunately, there are almost as many different techniques used in the registration of SEPs as there are investigators studying them'. In the following brief description, the method described is from the IFCN Committee report on recommended standards for short latency SEPs (Nuwer et al. 1994b), with some additions, as annotated.

4.3.1   Stimulation

SEPs can be elicited by superficial stimulation of peripheral nerves. In the case of the median nerve, for example, for distal stimulation the anode is positioned on the wrist crease and cathode is positioned 2 centimetres (cm) proximal to the wrist crease.

Electrical stimulation is usually performed at 3 to 8 Hz, most frequently at 5 Hz and responses to several hundred to thousands of stimuli are usually averaged and recorded within the first 100 msec. Stimulation, using a 200μsec square-wave pulse, can be by means of constant current or voltage, and is provided by a conventional surface stimulating electrode adjusted to produce a barely visible twitch of the thumb (1 to 2 cm thumb movement). (Nuwer et al. 1994b.)

However, García-Larrea et al. (1992) considered that there was no 'optimal' stimulus rate for SEP recording, but that use of a combination of different frequencies should improve diagnostic utility. McLaughlin and Kelly reviewed the literature in 1993, noting that SEPs underwent systematic and often marked changes when stimulated repetitively. They thought such findings were in keeping with a then recently proposed neurophysiological model of short-term plasticity in the somatosensory cortex.

In 1994, Fujii et al. reported more amplitude attenuation at the frontal P22 and N30 than at the parietal N20 and P26 peaks when the stimulus rate was increased from 1.1 Hz to 5.7 Hz. This they ascribed in part to interference from 'secondary' afferent inputs, although the possibility of frontal suppression by cortico-cortical pathway connections from the primary sensory cortex to the frontal cortex could not be excluded. Huttunen (1994) reported that increasing the stimulation rate from 1 to 5 Hz diminished the frontal P20, while the parietal N20 remained unaltered. This change in stimulation rate also reduced the central P22 and attenuated the frontal N30 and parietal P27. These findings supported his view that a change in stimulus rate could functionally dissociate frontal and parietal activity around 20 msec, which he considered indicated that several partially independent neural populations contributed to the frontal P20. Amplitude attenuation has also been noted in lower limb studies with Tinazzi et al. (1996) reporting attenuation of both the P37 and P60 at 7.5 Hz stimulation compared with 2 Hz, while latencies and topographies remained unchanged.

Thus stimulation rates should be included in all reports, as recommended in the American EEG Society guidelines for writing clinical EP reports (Aminoff et al. 1991).

4.3.2 Recording positions

The electrode placed at Erb's Point is located in the angle formed by the clavicle and the posterior border of the clavicular head of the sternocleidomastoid muscle, 2 to 3 cm above the clavicle. The spinal electrode should be located over the fifth cervical process. The central scalp electrodes should be located 2 cm posterior to the C3 (C3') and C4 (C4') positions of the 10 - 20 international system of EEG electrode placement, the positions being designated Cc and Ci to whichever is contralateral or ipsilateral, respectively. (Nuwer et al. 1994b.)

Optimal inter-electrode spacing for SEP cerebral topographic mapping, as recommended by Spitzer et al. (1989), is less than 3 cm, a distance significantly smaller than the 7 cm spacing of the 10-20 international system of EEG electrode placement. SEP recordings using the latter system, therefore, may have significant errors, with respect to accurate recording of the small components of the SEP in the region of the sensory strip.

4.3.3 Reference choice

The debate about a choice of reference is also still ongoing, highlighted by difficulties in the search for generators. The standard 3 electrode montage using Fz as a reference is that of Fz to contralateral cortex, second cervical spine and Erb's Point (Chiappa 1990e). However, dependent on the number of channels available, he suggests that additional derivations could be used to assist in the interpretation of the responses from the standard channels. Thus, for example, additional derivations can include referencing to the hand, knee, wrist or toe.

With respect to SEP mapping, Tsuji and Murai (1986) found no substantial differences in SEP morphology using scalp-A1A2, scalp-A1, scalp-A2 or scalp-shoulder derivations (12 recording electrodes, with 4 additional electrodes in selected cases) and selected the scalp-A1A2 for their study of scalp topography and cortical SEP distribution to median nerve stimulation.

Earlobe reference recording was also considered best by Desmedt et al. (1987), allowing easier discrimination of the positive and negative cortical SEP fields, while non-cephalic reference recording was considered necessary to depict subcortical generators producing widespread farfield responses at the scalp. Tomberg et al. (1990) considered the average reference inadequate for topographic mapping of focal enhancements of brain potentials and recommended using the ear ipsilateral to the side being stimulated, to avoid distortion of the SEP (Tomberg et al. 1991a). Similarly, Tinazzi et al. (1997) recommended using the ipsilateral earlobe reference for recording 'genuine' cortical SEPs in lower limb topographic studies in the clinical domain.

Although the IFCN Committee report (Nuwer et al. 1994b) on recommended standards for short latency SEPs stated that the usual forehead reference site was the forehead or Fz position, they also noted that the ears or non-cephalic sites were preferred by some users and that this was acceptable. However, Zegers de Beyl and Brunko (1995), in a letter expressing their surprise about this recommendation to the editor of the journal Electro-encephalography and clinical Neurophysiology, recommended use of an ipsilateral or linked ear reference as an elegant solution to the dilemma of Fz/Fpz versus a non-cephalic reference.

However, irrespective of the electrode positioning, if several electrode placements or linkages are used for clinical recordings, separate norms are required for each (Legatt et al. 1987).

4.3.4   Variability

SEPs vary under different recording situations and for physiological reasons. The following are some examples.

Strenge (1986) demonstrated high correlation for cortical amplitudes and latencies (0.77-0.98) in a study of test-retest reliability of somatosensory evoked potential parameters on 86 neurologically normal subjects.

Shaw and Synek (1987) studied 11 subjects (16-46 years) on 3 successive occasions. They found greater variability in the N9-N20 and N13-N20 interpeak latencies than for absolute latencies, although the inherent fluctuation of the N20 was not greater than that of the N9 or N13. They considered that, as the interpeak latency was the interval between 2 discrete components, variability was a function of the spontaneous movement of both, thereby resulting in greater variability in the interpeak latency in some cases than in absolute latencies alone.

In a study on 20 healthy volunteers (aged 20 to 50 years) retested one week after the initial test, Bergamaschi et al. (1993a) noted that absolute and interpeak latencies were highly reliable, while amplitudes were less reliable. Sonoo et al. (1996), however, showed large intersubject variability in the N20 latency and the N20 onset to N20 peak interval, probably due to the fact that any of three distinct N20 subcomponents could become the highest N20 peak.

Nuwer et al. (1994b) recommended that reproducibility needs to be ensured by undertaking 2 to 3 separate runs and superimposing the traces. Automatic and visual artefact rejection needs to be ongoing during the study, to eliminate continuous low amplitude artefacts or occasional high amplitude transient artefacts. Latencies measured on independent repetitions should not differ by more than 0.25 msec for the short latency upper limb SEPs, while amplitudes should be within 20%.

4.3.4.1 Physiological differences

Age, gender and height
Cheron and Desmedt (1980) reported amplitude changes in healthy octogenarians, namely an amplitude decrease in the evoked potential in the neck and increase in the parietal components of the SEP, as well as slowing of nerve and spinal potentials; however, they considered central conduction time to be well-preserved.

Hume et al. (1982) reported that the N20 amplitude decreased between 10 and 49 years, then increased until the end of the seventh decade, the N14 amplitude being stable in the initial time period, then decreasing progressively. Furthermore, central conduction time remained constant from 10 to 49 years, but then increased by approximately 0.3 msec between the fifth and sixth decades. In the same year, in a study of 45 normal subjects (aged 15 to 60 years), Strenge and Hedderich (1982) found that those aged 40 to 60 years had significantly longer N13 and N20 latencies with significant prolongation of N9-N13 and N13-N20 conduction times.

In a large study of 130 male and 156 female neurologically normal subjects, 4 to 95 years of age, Allison et al. (1984) concluded that small developmental changes were seen in the somatosensory afferent pathway from the cervical spinal cord to thalamus, while large changes were seen in the somatosensory cortex. Increases in latency due to increased conduction time in older subjects, i.e., 'ageing' changes, were observed in the median nerve, cervical spinal cord and somatosensory cortex. Males showed a larger effect than females, which they attributed to arm and shoulder dimensions (Allison et al. 1983). This led them to suggest that age-related changes in human sensory conduction were not uniform, but different in specific areas and at different life epochs, being more pronounced in males (Allison et al. 1984). With respect to gender differences, Kakigi and Shibasaki reported higher amplitudes in topographic SEP mapping to median (1991) and posterior tibial nerve (1992) stimulation in aged subjects when compared with a younger group. In the posterior tibial nerve study they noted a tendency towards larger amplitudes in women and that gender differences were significantly large for some age-groups.

Nuwer et al. (1994b) suggested that in young children, the N9 and N13 potentials occurred early and central conduction was slow, while in older adults (over 55 years of age) reference ranges were 5-10% longer. Akyüz et al. (1996) detected a significant correlation between gender, height and SEP latencies, but none between height and central conduction time, findings in keeping with those of Meervaala et al. (1988).

This may be due to the use of peak latencies to calculate central conduction time, as Ozaki et al. (1994) reported a significant correlation between height and median nerve onset central conduction time, but not for height and peak central conduction time. The latter finding they ascribed to the inadequacy of the Fz reference for identification of the N13 (which could be confused with the N14) and the wide variation of the cortical N20-P20, resulting in peak central conduction with a wide range. This work was extended to include the ulnar nerve (Ozaki et al. 1996), where, once again, height was correlated with onset time.

Touge et al. (1997) found that amplitudes of cortical SEPs were generally smaller in a group of young normal volunteers (27.5±5.0 years) than in a group of aged normal volunteers (66.5±8.9 years), while latencies of the prerolandic P22, postrolandic P24 and pre- and postrolandic N60 were shorter in the younger group. Tanosaki et al. (1997) found that the onset to peak duration of the N20-P20 complex increased by 0.8 msec between the fourth and seventh decades. They suggested that the peak central conduction time (CCT) increase in older people reflected age-related changes in the N20-P20 profile, but not in the fastest central conduction; Sonoo et al. (1997) considered that increased central conduction time in the aged implied alteration of the intracortical processes in some way.

Temperature
The effect of temperature can be complex, as shown in an intra-operative study of 10 cardiac patients by Zeitlhofer et al. (1990), where absolute latencies (N13 and N20) and central conduction time increased with a decrease in temperature. For practical purposes, as cool limbs can result in slowed peripheral conduction, Nuwer et al. (1994b) recommended that limbs be kept warm during testing.

Sleep

Emerson et al. (1988) found that sleep prolonged the latency and altered the morphology of the N20 in normal subjects. The effect of sleep on short latency median nerve SEPs was also demonstrated by Addy et al. (1989) in a study of 6 patients being evaluated for seizure disorders and one control. They found the morphology of the cortical potentials to be similar during wakefulness and REM sleep, but significantly altered in non-REM sleep. Changes included an increase in the cortical absolute latency of the first major negativity and, in selected studies, lengthening of the second major positivity (probably due to double peaking), and diminishing of amplitude.

Nakano et al. (1995) also noted that central SEP latencies and morphologies in rapid eye movement sleep were almost the same as those recorded during the awake stage; during non-REM sleep, however, the latencies of the N16 and N20 were significantly prolonged, with the amplitude of the latter being decreased. As previously noted by Nuwer et al. (1994b), this could result in a latency asymmetry if one limb is tested with the subject asleep and the other while the subject is awake. Thus, as Santamaria et al. (1994) have suggested, the state of alertness needs to be controlled during SEP testing, particularly for older patients. Their conclusion was based on a study on 14 healthy older subjects (56-79 years), with a 17% (left) and 18% (right) increase in central conduction time, compared with a 12% and 8% increase in 10 healthy younger adults (26-36 years). These changes were so pronounced that for 45% of the older and 20% of the younger subject assessments, the central conduction time was prolonged beyond the 3 standard deviation upper limit (6.8 msec).

Handedness

Koike and Irie (1990) found an asymmetry related to handedness in healthy adults. Right-handed subjects undergoing right median stimulation showed an N20 situated 1.5 cm more medial than that to left median stimulation, there being little hemisphere asymmetry in non-right handers. In contrast, Kakigi and Shibasaki (1991, 1992) reported that stimulus side caused no differences in amplitude and topography with median or posterior tibial nerve stimulation.

However, Buchner et al. (1995b) subsequently reported higher N20 amplitudes to right-sided stimulation and higher P25 and N30 amplitudes to left-sided stimulation in approximately 70% of 50 normal right-handed subjects, as well as location asymmetries (N20 to right-sided stimulation was located predominantly parietally, but varied between parietal, centro-parietal and occipital areas to left-sided stimulation). No side differences were found for the subcortical N14 amplitudes and they attributed the cortical SEP differences to somatosensory cortex anatomical asymmetry.

4.3.4.2 Medication effects

Monaco et al. (1991) found that psychotropic drugs, for example oxiracetam, Naloxone, L-acetylcarnitine and others, affected some parameters of the early SEP components, particularly amplitude, and considered SEP recording to be a useful method for monitoring pharmacological activity in early stroke. Some anti-epileptic drugs (AEDs), for example carbamazepine and diphenylhydantoin, have been found to increase central conduction time or interpeak latencies in humans (Meervaala et al. 1987; Mavroudakis et al. 1991). Arezzo et al. (1989) reported that Vigabatrin (GVG) showed SEP central transmission slowing in dogs, but this has not been reproduced in humans (Hammond et al. 1988; Cosi et al. 1989; Liegeois-Chauvel et al. 1989, Meervaala et al. 1989, Hamilton-Bruce et al. 1991a). However, Chiappa and Jayakar (1995) emphasise that some results of the AED studies are controversial and non-uniform, and note that BAEPs and SEPs are very resistant to alteration by anything other than structural pathology in somatosensory tracts.

It should also be noted that Nuwer et al. (1994b), in the IFCN Committee report on recommended standards for short latency SEPs, consider that benzodiazepines or similar medications can be used to encourage relaxation (presumably provided that the subject does not sleep during part or all of the study).

4.4   SEP USE

In a brief review in 1990, Aminoff notes that evoked potential studies provide important information about the functional integrity of the major afferent systems, and, as such, are important for extending understanding of cerebral function and the characterisation of the distribution and pathophysiology of disease processes.

4.4.1   General

4.4.1.1   Conventional studies

Conventional evoked potentials provide sensitive quantitative extensions of the clinical neurological examination, and are commonly used in the diagnosis of multiple sclerosis, conversion symptoms, tumours of the nervous system, stroke, trauma, intra-operative procedures and ICU settings, as well as being used in the assessment of infants, where the sensory system cannot be assessed accurately (Chiappa and Ropper 1982b; Pillay 1984). In a study of brainstem vascular infarction, Towle et al. (1985) considered the most important aspect of multimodality EPs (SEPs and BAEPs) to be the immediate sensitivity to insult.

It should, however, be noted that concurrent clinical conditions can also affect the responses. For example, in a study of 50 acute stroke patients with proven diabetes mellitus and 50 with a history or findings suggestive of diabetes, Pavot et al. (1993) considered that an increase in SEP latency without a concomitant decrease in amplitude (the latter being their most common abnormality in stroke) could be ascribed to the diabetes, rather than the stroke.

4.4.1.2 Topographic studies

SEP mapping has been used mainly in research, in attempts to determine generators and clinical applications. As such, many studies have been undertaken on normal subjects and have included the utilisation of non-standard techniques or other tools. For example, Jones and Power (1984) assessed the effect of interfering tactile stimulation on scalp topography of human somatosensory evoked potentials and Tomberg et al. (1991b) used a nasopharyngeal electrode for generator determination. Buchner et al. (1995a) combined dipole source analysis and three-dimensional MRI to reveal somatotopy of the human hand somatosensory cortex, while Zifko et al. (1996) developed a method of performing median nerve SEP brain mapping during SPECT, with subsequent superimposition of an MRI scan for localisation of lesions in various disorders of the central nervous system.

As noted in the first chapter, clinical conditions studied with topographic or multichannel SEPs include cerebrovascular insufficiency and stroke, central nervous system tumours, coma and head injuries, epilepsy, multiple sclerosis, Down's syndrome, Huntington's disease and Parkinson's disease. They are also used for intraoperative localisation and identification.

Alternative methods of analysis include principal component and factor analysis. Duffy (1988) noted that these techniques were considered promising, but cautioned that there was no guarantee that the factors would prove to have direct biological meaning. Previously John et al. (1973) reported principal component analysis to be 'useful as a technique for meaningful neurophysiologic data condensation'. In 1989 they reported principal component analysis followed by Varimax rotation of visual evoked potentials (VEPs) able to show clear abnormalities in the group average z-score topographic maps of patients with senile dementia, schizophrenia, alcoholism, and unipolar and bipolar depression, while in 1993 they reported that, using standardised Varimax descriptors of event related potentials (ERPs), they could also separate normal from abnormal subjects with a wide variety of psychiatric disorders, with high, replicable accuracy.

Karniski (1992) used principal component analysis on SEP waveforms generated by right median stimulation of premature infants, and reported that the topographic maps of the 4 factor scores with the majority of the variance accounted for 4 independent generators. In a further study, Karniski et al. (1992) noted that one of the generators (N2) was large, easily identifiable and stable, and, as such, suggested that it might be used to evaluate functional status of the somatosensory cortex in term and pre-term infants at high risk of developing intracranial haemorrhage, as the latter could lead to abnormalities of tone and delays in motor development.

4.4.2 Stroke

While in the general section above, SEP use was categorised as conventional or topographic (mapped/multichannel) based on the author's terminology, the distinction is less clearcut than for EEGs. Thus, with respect to the research of others, whether it be for research purposes, potential clinical application or both, SEP studies in this section are not categorised but recording electrode numbers are given, where possible.

4.4.2.1 Sensitivity

Over the years, median nerve SEPs have been reported as having a range of sensitivities in cerebrovascular disease. In chronological order, some of these are: 85% (Miyoshi et al. 1971), 71% (Ignacio et al. 1982), 34% (Despland and Regli 1985), 75% (Hassel et al. 1986), 61% (Karnaze et al. 1987), 48% (Abbruzzese et al. 1988), 50% (de Weerd and Veldhuizen 1987a), 47% (Macdonell et al. 1989), 54% (Zeman and Yiannikas 1989), 44% (Gott et al. 1990), 48% (Kovala 1990), 45% (Kuntzer et al. 1991) and 77% (Lu and Yu 1993). Recording electrode numbers ranged from one to several.

The considerable variation seen could be due to a variety of factors, namely different study methods, operators and patient classifications. For example, irrespective of SEP methodology, in some studies patients were only included if the cerebrovascular disease was CT or MRI verified (Abbruzzese et al. 1988; Macdonell et al. 1989; Kuntzer et al. 1991). In most cases CT was more sensitive (41% (CT) versus 71% (SEP): Ignacio et al. 1982; 71% versus 61%: Karnaze et al. 1987; 83% versus 54%: Zeman and Yiannikas 1989; 80% versus 48%: Kovala 1990), however, as noted by Despland and Regli (1985), differences could also be due to timing of assessments. With respect to patient disease classification, considerable variation occurred, with cerebrovascular disease considered to be that resulting in transient neurological symptoms, lacunar, cortical and sub-cortical stroke.

With respect to differentiating between disorders, Abbruzzese et al. (1984) suggested that SEPs (2 scalp electrodes) could be useful in the differential diagnosis between multi-infarct and degenerative dementia, as the N13, N20 and CCT were increased with a decrease in cortical amplitude in the former and generally normal in the latter. In a study reported in 1988, Reisecker also found that SEP CCT (one scalp electrode) was significantly prolonged bilaterally in a group of 27 patients with multi-infarct dementia.

In 1985 Graff-Radford et al. reported that the profiles of clinical, neuro-psychological and SEP studies (14 scalp electrode positions) of patients with non-haemorrhagic thalamic infarctions revealed fairly consistent identifiable symptom clusters, when grouped according to lesion location on CT. They considered that recognition of such clusters could assist neurologists in patient assessment, as well as contributing to the understanding of complex subcortical structures. More recently, Macdonell et al. (1997) reported that SEPs discriminated between cortical and subcortical infarction in a study of 79 patients. In cortical infarction, waves subsequent to the N20 were lost in 45% of their patients, an abnormality not produced in subcortical infarction.

In 1985, Colon et al. undertook a study of the chronotopographical potential distribution of some SEP components to median nerve stimulation in cerebrovascular insufficiency on randomly selected patients. The study was limited to 7 patients and 10 controls, as the methodology was time-consuming. They studied the N20, P25, P45, P100, N140, P200 and P300 from 16 recording electrode sites, and found abnormalities in chronotopographic representation in 6 of 7 patients. They concluded, however, that an automated method was needed, including reliable artefact identification and rejection, before it could be introduced into routine clinical practice. While methods have been developed for this purpose (John et al. 1989; Pratt et al. 1994), the clinical utility of SEP brain mapping in stroke is not yet established, as noted previously.

Chu (1986) demonstrated that the combined use of median and tibial SEPs (one scalp electrode) was useful to determine the topographic organisation of the somatosensory system in the thalamus. In a median and tibial SEP study in 56 patients (26-67 years) with thalamic and thalamo-cortical radiation lesions, he showed significant change from the norm in short, middle or late latency SEPs ($p<0.05$) in all groups of patients (ventero-posterior, medial and lateral lesions).

While SEP CCT (one scalp electrode) and the left-right amplitude ratio have been reported normal in TIAs (Karnaze et al. 1987 (6 patients); Reisecker 1988 (44 patients)), de Weerd and Veldhuizen (1987a) concluded from a study of 12 patients with transient neurological symptoms, that extended recording of the SEP, i.e., F3/4, C3/4 and P3/4 (contralateral to side of stimulation) was useful, with SEPs revealing subclinical lesions in half the patients. Similarly, Buchner at al. (1992) reported that 7 of 30 middle cerebral artery stroke patients had 'pathological' amplitudes when using a montage with 3 scalp electrodes, while the amplitude recordings were normal when using a recording montage with only one scalp electrode.

4.4.2.2 Prognostic use

SEPs provide a more objective measure of sensory pathways than does a clinical examination, being particularly useful in patients with inattention, dysphasia or decreased levels of consciousness (Zeman and Yiannikas 1989).

As early as 1966 Larson et al. reported that clinical improvement correlated with SEP improvement in 4 of 6 stroke patients in whom serial investigations (5 to 10 scalp electrodes) were undertaken. Absence of cortical peaks was found to be the best predictor of an unfavourable outcome in the SEP study undertaken by La Joie et al. (1982). They used a one scalp electrode recording montage on 68 stroke patients with right hemiplegia and reported that the SEP was absent in 42 cases, and only one showed some functional gain in the right upper extremity at discharge. Similarly, in a study of 50 patients with cerebrovascular lesions, Regli and Despland (1982) reported that in all patients with an absent N20 (seen in patients with large infarcts of the postcentral parietal cortex and the underlying white matter), the N20 did not reappear in further recordings and no improvement was observed in sensory deficit.

In a study where SEPs (2 scalp electrodes) were assessed on 130 consecutive acute cerebrovascular accident patients by Pavot et al. (1986), carefully graded SEPs correlated well with functional outcome. De Weerd and Veldhuizen (1987a) concluded that extended recording of the SEP, i.e., F3/4, C3/4 and P3/4 (contralateral to side of stimulation), on patients with transient neurological symptoms (12 subjects from a study of 37 patients with cerebral ischaemia) provided diagnostic information. Furthermore, absence of the N20 indicated a poor prognosis, but this information, they considered, could be obtained from a single central or parietal electrode, a study which was easier and faster to perform in severely ill patients than the extended recording with additional electrodes.

An interesting perspective is provided by the findings of Chester and McLaren (1989), who, after assessing 26 patients with right cerebral infarction, concluded that the Barthel admission score was the best predictor of functional level after stroke rehabilitation, with knowledge of the median nerve SEP (one scalp electrode) and homonymous hemianopsia improving prediction. Of note, too, is the finding by Gott et al. (1990), in a study where 37 of 49 stroke patients were reassessed. They concluded that SEPs (one scalp electrode) were not significantly better in predicting stroke outcome than detailed neurological examination.

Two-electrode SEP studies have been shown in a study of 35 patients with acute stroke to be better than age, sex and side of cerebrovascular accident (CVA) in predicting functional outcome, correlating well with the Barthel Index (Zeman and Yiannikas 1989). In the same year in a study of 19 patients, Macdonell et al. found that, although SEP studies elicited on average 8 days after the event predicted recovery, they were not as sensitive as motor EPs ($0.01 < p < 0.05$). The results of their longitudinal study (1991), performed on 12 patients within the first week after stroke onset, 6 weeks, 3 months and 6 months later, showed that the major effect of stroke on median SEPs (2 scalp electrodes) occurred acutely and was little affected by secondary degenerative processes.

Kovala et al. (1991) drew a similar conclusion in a study of posterior tibial SEPs (one scalp electrode, 40 patients), where the number of amplitude abnormalities (including absent responses) remained the same during a one year follow-up period (latency decreases were considered to show only a 'nearly significant decrease'). In a further publication on the one year follow-up study of 35 of these patients, Kovala (1991) reported that occupational outcome correlated most closely with the amplitude abnormalities (absence or attenuation) and with overall abnormality in the tibial nerve SEPs (one scalp electrode). Tibial nerve SEPs were of greater prognostic value than median nerve SEPs (one scalp electrode), however, more prognostic information could be gained by the use of both.

Kuntzer et al. (1991), in a study of 64 patients with supratentorial deep or superficial ischaemic strokes, reported 29 of 64 (45%) with SEP abnormalities (using one scalp electrode). In their discussion they noted that in the group with absent SEPs, the functional disability was poorer than in the group with normal SEPs. Nonetheless, they considered SEPs were not sensitive enough because they could be normal in lesions associated with severe disability, as they depended on generators which could be unaffected (48% of their patients had normal sensation), with SEP abnormalities being related to the volume and location of the infarct.

After a study of 80 patients with spontaneous putaminal haemorrhage, Liu et al. (1991) found that one scalp electrode SEP studies performed within a week of onset were normal or had prolonged central conduction time in patients who made a good functional recovery (ADLs assessed at 6 months), while absent or attenuated SEPs were found in patients who were moderately or severely disabled. Lu and Yu (1993) studied median nerve SEPs (one scalp electrode) in 102 patients with unilateral cerebral haemorrhage or infarct in the basal ganglia, internal capsule, thalamus or cerebral hemisphere and reported an abnormal rate of 77%. They noted that CT scanning allowed a more direct, precise diagnosis to be made, but considered that SEPs functioned as an objective neurophysiological method of assessing neurological function in the affected limb, such that with an absent SEP, limb function recovery was poor, irrespective of lesion type (infarction or haemorrhage), size or location.

Soors et al. (1994), in a prospective study of 15 patients with a first ischaemic stroke in middle cerebral artery territory, found the combination of motor and somatosensory evoked potentials to be of more use prognostically, than either separately - the presence of both, despite a corresponding deficit, being good. In a study on 50 patients with acute middle cerebral artery infarction, Timmerhuis et al. (1996) reported that SEPs, magnetic evoked potentials and age were valuable prognostic parameters in predicting stroke outcome, however, in stepwise logistic regression, only magnetic evoked potentials and age contributed to clinical outcome.

4.5 SUMMARY

Sensory ageing changes in adults, where changes have been seen, have included an increase in cortical waveform amplitudes, latencies and central conduction time. Changes appear to be different for different parts of the nervous system and different ages, possibly due to deterioration with age or alteration of the intracortical (or other) processes or both. Gender differences appear in some cases to extend to longer latencies and smaller amplitudes in males, with size considered an influencing factor. A decrease in temperature results in slowing of peripheral and central conduction (the latter with hypothermia). The effect of sleep appears dependent on the sleep stage, with non-REM sleep resulting in an increase in latency and decrease in amplitude. Studies have also shown that conventional and topographic or multichannel SEPs appear to have diagnostic and/or prognostic ability in clinical settings, although, as studies have been conducted by various researchers in different laboratories in different countries with different equipment on various stroke types at different times, a range of findings has resulted. As such, the conclusion drawn is that responsible use of SEPs requires use of accepted consistent techniques and development of databases in the laboratories using these tests in clinical practice.

This and the foregoing chapters have provided a brief overview of the tests and assessments available to me to investigate stroke. The following chapters document the studies that I undertook to obtain new knowledge with respect to new investigations and to determine the relationship to conventional investigations in a routine clinical laboratory setting.

CHAPTER 5

ELECTROPHYSIOLOGICAL EQUIPMENT ASSESSMENT

5.1   INTRODUCTION

As discussed in the preceding chapters, computerisation in electrophysiology provides a number of challenges. Operators and clinicians need to develop varying degrees of computer literacy, in order to process and interpret data effectively. Information is presented to the reporting and/or referring clinicians in a very different form, on a video display rather than the traditional paper printout. Furthermore, the almost overwhelming quantitative data can be displayed as measures and/or topographic maps, providing a wide range of power and frequency information in raw or statistically manipulated form. These and other challenges need to be dealt with effectively before any computer-based equipment can reach full clinical potential. (Oken and Chiappa 1986; Duffy et al. 1986; Nuwer 1990a, 1997b.)

While brainmaps can be presented very elegantly, the equipment used may not be fully understood by the operators. Although full software documentation should be provided for system operation (English 1993), commercial companies may refuse to provide proprietary information. The data incorporated in the databases may have been collected at different sites (John et al. 1989), theoretically under the same recording conditions. However, publications may refer to the software package's proprietary name, rather than detail techniques exactly. Furthermore, although companies may claim that data was collected under strict conditions, extraneous noise may be introduced by, for example, the use of different amplifiers (Brandt 1992).

Equipment may also be provided with an elaborate series of self-diagnostic test procedures to verify integrity. Calibration signals can be displayed on the visual display unit or paper as traces or maps (monochrome or colour) and checked by inspection or measurement. Checks, however, should be based on an external calibrated source, using a signal generator to test the equipment independently, if they are to elicit the confidence of the user (Winter 1989).

The standard tests performed using the Cadwell Spectrum include EEG and visual, auditory and somatosensory evoked potentials. Acquisition of this equipment allowing these standard tests as well as the new computer analyses (topographic studies) thus necessitated performing laboratory checks prior to undertaking clinical studies. Although visual and auditory evoked potential studies did not constitute part of this clinical study on stroke patients, they were available for assessment of any patients, including those with stroke. As such, they were included in this assessment of the new equipment.

5.2   AIM

The aim of this part of the study was to test equipment performance with respect to accuracy and consistency in key areas, namely amplitude accuracy and voltage mapping consistency, and rectify any problems detected prior to commencement of studies on patients and controls.

5.3   METHODS AND MATERIALS

The hardware used in this assessment consisted of the Cadwell Spectrum 32™, with a Hewlett Packard Paintjet® colour and Canon LBP-8MarkIII® laser printer. The software included Neurometric Analysis (qEEG) and SEP Factor Analysis as marketed by Cadwell Laboratories Inc., as well as standard 1- to 3-channel evoked potentials (user selected). (Refer to appendix 5.1 for further details.)

5.3.1 Amplitude accuracy

5.3.1.1 Calibration check

The external signal source was a square wave output from a Krohn-hite Corporation model 5600 signal generator. The output was set to a selected value known to be accurate within 2%, previously confirmed by measurement on a cathode ray oscilloscope - a Tektronix Model 468 within current calibration and fed to the inputs of the Spectrum headbox. To reduce external interference, the signal generator was used in its battery operated-mode, with its ground connection coupled to the isolated ground of the input headbox.

For EEG and SEP Factor Analysis modes, all active inputs (excluding the A1A2 reference) were connected together. This was accomplished using a shorting plug on the pin headbox connector, rather than the individual electrode inputs, to facilitate future assessments. The balanced output of the signal generator was then connected between these shorted pins and the coupled A1A2 reference. The signal generator output was also connected to active inputs 1 to 3, for acquisition in the standard non-mapped VEP, auditory evoked potential (AEP) and SEP modes, with Fz as the reference and the ground connection as described above.

For the EEG acquisition mode, the signal generator output was set to 50μV (i.e., the same as the preset amplitude of the internally generated calibration signals on our polygraph machine). Initially for the evoked potential recording modes, an arbitrary level of 40 mV (10 Hz) for VEPs and 8 mV (200 Hz) for AEPs was used, with subsequent levels of 50μV for VEPs (10 Hz), AEPs (300 Hz) and SEPs (200 Hz). While the signal for the EEG mode was within the electrophysiological range, higher than physiological values were utilised in the evoked potential modes to minimise the effects of external noise and interference.

In the EEG mode the high frequency filters were set at 100 Hz, with a one second time constant, a notch filter of 50 Hz and a sensitivity of 10 μV/millimetre. VEP and AEP filters, however, were initially set at 10 KHz and 0.5 Hz with gains of 10000 and 2000 and sweep speeds of 200 msec and 10 msec, respectively. Subsequently, the following settings were used: 3-channel VEP filters set at 300 Hz and 0.5 Hz, 2-channel AEP filters at 3 KHz and 30 Hz, and 3-channel SEP filters at 3 KHz and 5.0 Hz, with gains of 20, 50 and 50, and sweep speeds of 200 msec, 10 msec and 50 msec, respectively. SEP Factor Analysis filters were preset by the manufacturer and unalterable, the high frequency filter being 500 Hz, the low frequency filter being 30 Hz, the sweep speed being 50 msec and the gain 20. While no internally generated calibration signal was provided for standard or mapped evoked potential montages, it was provided for EEGs, and the calibration mode was selected using a square wave 50μV signal.

The cursor was used for measurement of all signals on the screen and calibration responses were printed. Amplitude calibration checks were performed on all channels by measuring the square waves from take-off to peak for EEG, while evoked potential sine wave calibration signals were measured from peak to trough, a minimum of 5 waves being used. An average was taken (from the screen or hardcopy) and reported as percentage deviation, as would occur in routine practice.

5.3.1.2 Self-diagnostic amplifier gain check

The Spectrum's self-diagnostic amplifier gain check was also performed for EEGs and evoked potentials, to allow comparison with the results achieved using the external calibration signal. It was performed by selecting 'test utilities' through the utilities option from the main menu.

'Test utilities' allowed tests of the graphics board, averager (data acquisition) board and output/input/output board/stimulators, stimulator box, amplifiers, optical disk drive, printers, software versions and the system memory. The amplifier tests evaluated the data acquisition process from beginning to end, testing the structural integrity of the connections and electrical components of the headbox (pre-amplifier), amplifier and data acquisition board. (Cadwell Laboratories Inc. 1989.) Initially each option was selected in turn, and subsequently, where a particular problem was suspected or the hard-/software was changed, the relevant option(s) were selected. The results were recorded by means of the monochrome printer, from a still-frame on the monochrome screen.

5.3.2 Voltage mapping consistency

5.3.2.1 Calibration check

The external input signal employed was identical to that described above and was fed to all inputs simultaneously. The calibration signal was recorded onto a 650 megabyte Pioneer optical storage disk in the standard or uncompressed mode. A series of 4 voltage maps was plotted as close as possible to, and either side of, a square wave leading edge transition, at different scaling levels, for example ± 15.1 μV and $\pm 60.2 \mu$V. Performing an internal EEG calibration check with the optical disc recording mode selected allowed recording of the internal calibration signal onto the optical disc for mapping. SEPs were mapped at one second intervals from the same signal used for the amplitude accuracy check in the Factor Analysis montages (right and left). Other evoked potential software was not available or not assessed.

5.3.2.2 Fault simulation

A fault situation was simulated by introducing an arbitrary time delay, to demonstrate the effect of a sampling time error in a single channel.

5.4   RESULTS

5.4.1 Amplitude accuracy

EEG

The screen traces of the external calibration signal (21 channels in the qEEG montage) were printed on an A4 page using the laser printer, and the amplitudes of each trace were subsequently measured. Measurements ranged from 50μV to 54μV (0% to +8% variation), while measuring the same traces on the Spectrum's 35 cm colour display screen using the amplitude cursors with a potential resolution of 0.01μV in 50μV but with the minimum difference allowed by the mouse being 2.78μV (as set for routine use), gave a range of 47.3μV to 52.9μV (-5.4% to +5.8%). As the calibration mode had to be exited in order to measure the calibration signals at the time of the recording, assessment of the internal calibration signal on the visual display unit was by visual inspection. All signals appeared the same with respect to synchronicity and amplitude, and the self-diagnostic amplifier gain check showed that all test results fell within a $\pm 4\%$ range.

Evoked potentials tests

Using an external calibration signal, on initially testing the EP modes (1989), for the 1-channel VEP (40 mV calibration signal) the cursored screen response was 43.8 mV (+9.5%), while for the 1-channel AEP a response of 8.7 mV (+8.8%) was obtained with an 8 mV signal. No internal calibration option was provided, however, the self-diagnostic amplifier gain check indicated that all channels fell within $\pm 4\%$. Subsequent to a customised EP software upgrade from the manufacturer in 1989, the response was 42.2 mV (+5.5%) for VEPs and 8.1 mV (+1.3%) for AEPs. Using an external 50μV calibration signal, assessment of the 21 channel Factor Analysis program for amplitude accuracy gave a range of 47.3μV to 51.5μV (-5.4% to +3.0%) for the right median nerve program and 48.5μV to 51.7μV (-3.0% to +3.4%) for the left median nerve, when read from the screen. Three-channel VEP measures ranged from 50.5μV to 50.8μV (+1.0% to +1.6%) when measured with the screen cursor, 2-channel AEPs from 49.4μV to 51.4μV (-1.2% to 2.8%) for screen measurements (cursored), and 3-channel SEPs from 50.1μV to 51.4μV (+0.2% to +2.8%).

5.4.2 Voltage mapping consistency

EEGs

The four overlapping triangular cursor markers in Figure 5.1[1] indicate the times at which voltage mapping was performed on identical (synchronous) external calibration signals, showing a variation of one colour increment across the map with the scale set at $\pm 15.1 \mu V$. With each colour gradation representing $1.9 \mu V$, this single colour change could represent a variation in plotted voltage between $0.1 \mu V$ and $3.8 \mu V$ (0.7% to 25.2%). No variation was seen with the scale set at $\pm 60.2 \mu V$. As the calibration mode had to be exited in order to undertake mapping, no live internally generated calibration signals were available for mapping. Mapping of the internally generated signals retrieved from the optical disk was attempted, but the signals were distorted due to the inability of the system to remontage the signals appropriately and mapping was unsuccessful. The simulated fault in Figure 5.2 demonstrates the effect of a sampling time error, where variation in shading is seen in the F3 channel.

Evoked potential studies

For SEP mapping, the plots showed a one colour change in 24/50 (48%) and 23/50 (46%) of the maps ($\pm 10 \mu V$ scale) for the right and left SEP Factor Analysis montages respectively, with a single colour change representing $0.1 \mu V$ to $2.5 \mu V$ (1.0% to 25.0%).

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[1] *All graphics were sharpened for clarity, when printed.*
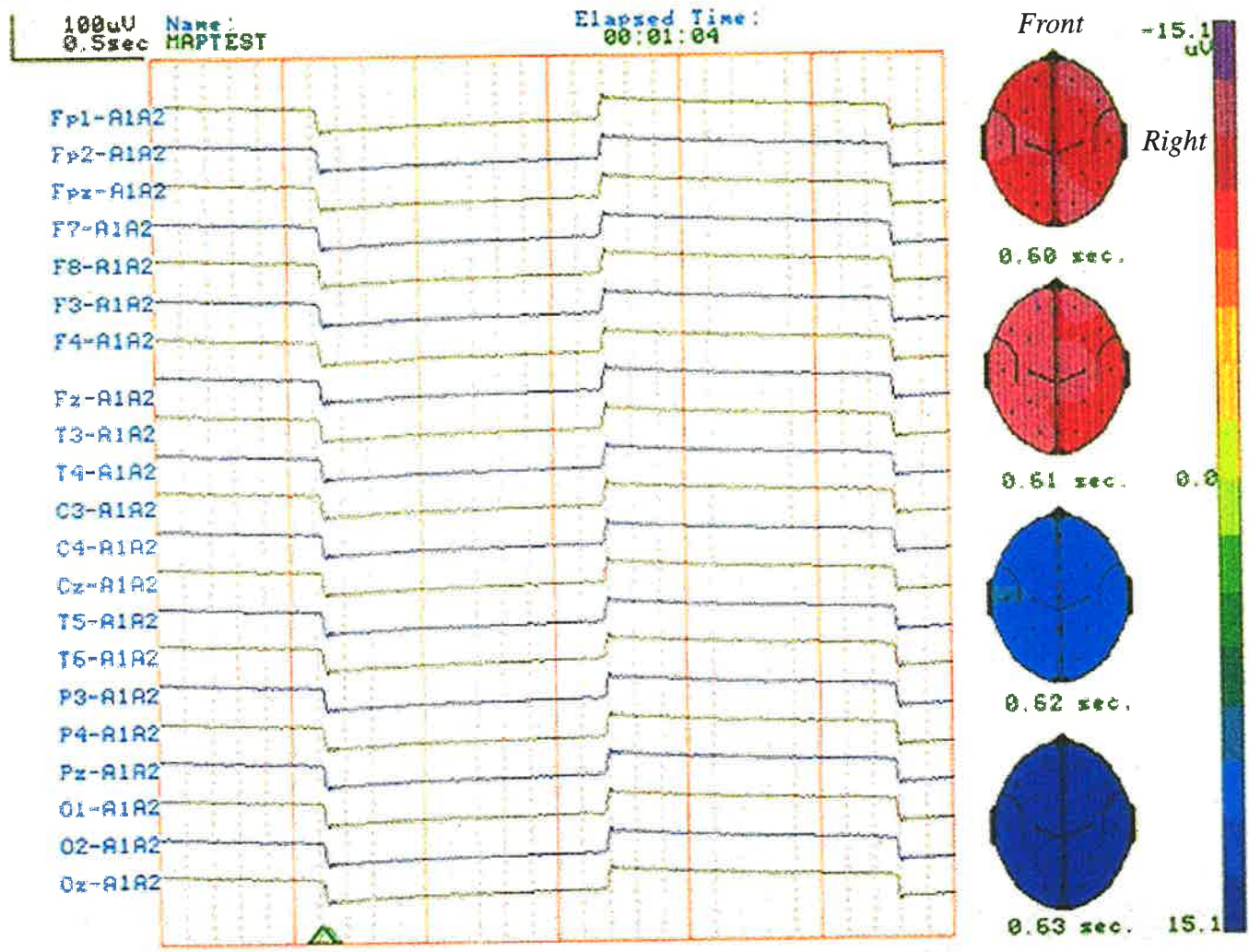
FIGURE 5.1   Voltage mapping at the calibration signal transition.
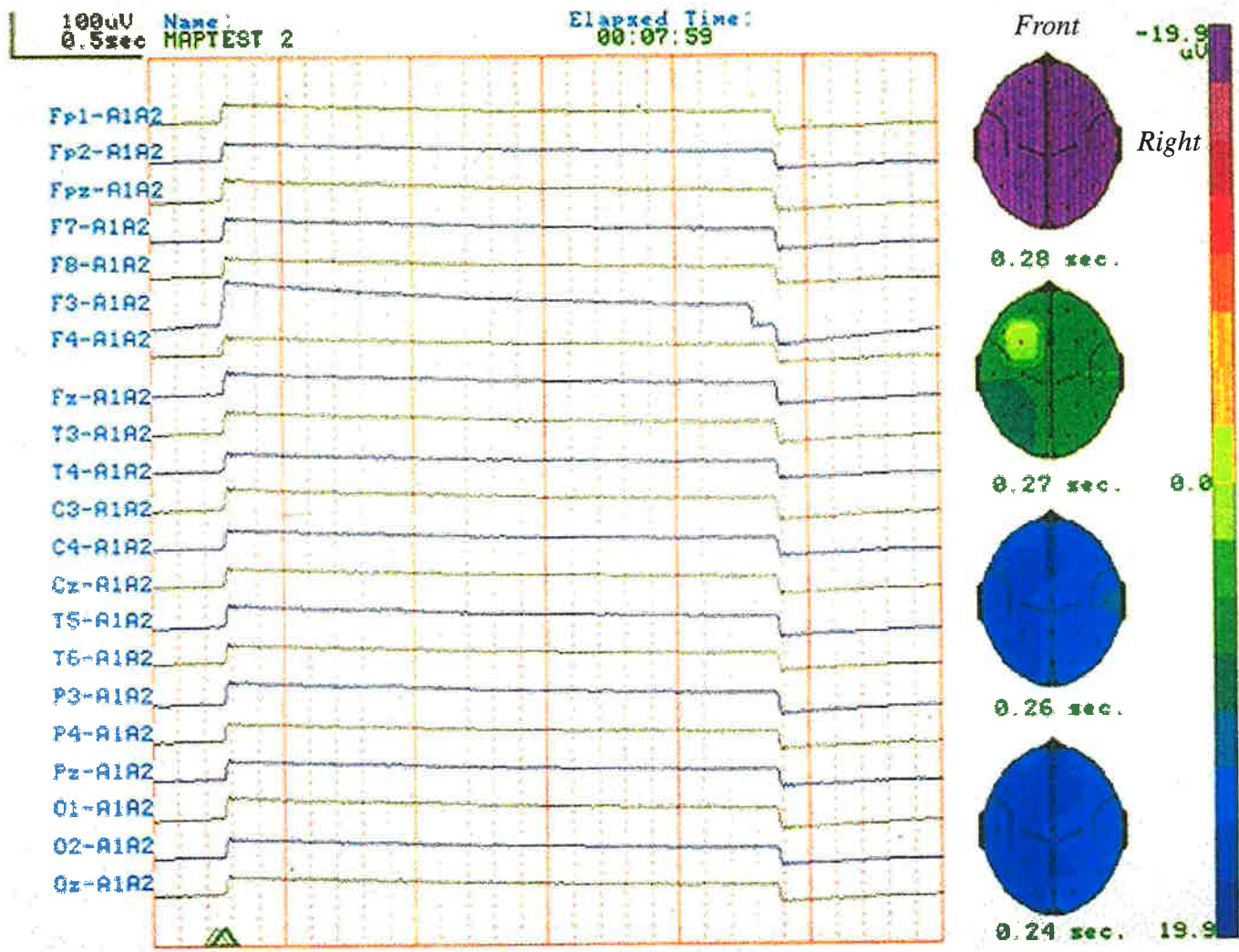
FIGURE 5.2   Voltage mapping with a simulated fault condition in the F3 channel.

5.5   DISCUSSION

5.5.1   Amplitude accuracy

EEG

For EEG, amplitudes of the externally generated signal varied between -5.4% and +5.8% on the screen, and 0% and 8% on the paper report, limits which exceeded the maximum 1% channel-to-channel variation and the 0-2 μV variation allowable for additional 'noise', as recommended by the IFCN Committee (Nuwer et al. 1994b). Screen-cursored 21-channel SEP amplitudes varied from -5.4% to +3.0% and -3.0% to +3.4%, right and left respectively. The self-diagnostic amplitude check for both, however, yielded values well within the ±4% limits.

For both screen and hardcopy, the degree of accuracy is limited, the former by the thickness of the screen traces and the mouse tracking speed, and the latter by the resolution to which the printed waveforms can be measured, with other variables such as inter- and intra-operator variability and calibration signal noise able to affect both.

While exact (measured) amplitude may not necessarily be considered the most critical factor in the visual inspection of the EEG, with emphasis being on the frequency domain and differentiation between slow and fast rhythms as well as amplitude estimation, accuracy cannot be disregarded. This is highlighted during mapping, when amplitude is recorded as colour which may be perceived as a hotspot emphasised by statistical assessment, for example, z-scores using a normative database which may have been recorded in another laboratory/laboratories. Furthermore, where patients are referred for follow-up studies, amplitudes would be compared with those of earlier studies, thus it is important that assessment of the maps takes these variables and potential inaccuracies into account.

Evoked potential studies

For evoked potentials, where both latency and amplitude are routinely measured, amplitude accuracy assumes greater significance. With an identical signal being fed into each channel at a known amplitude, the processed signals should all be equal and equivalent to that input. An accuracy of $\pm 5\%$ is typically expected of other electrophysiological measurement equipment such as ECG at The Queen Elizabeth Hospital, while the self-diagnostic gain check on the Spectrum specifies a $\pm 4\%$ limit. However, the initial 1-channel montages tested with the external calibration signal fell outside these limits, the VEP channel being in error by 9.5% and the AEP channel in error by 8.8%. This was considered to be due to a problem with the gain calibration during manufacture and rectification was by means of a customised montage-specific software upgrade from the manufacturer, although only the AEP measurements subsequently fell within the Cadwell specified $\pm 4\%$ limits.

This occurred initially despite the system's self-test of amplifier gains indicating that no channel was in error by more than $\pm 4\%$, highlighting the inadequacy of internally generated checks. The only real test of the accuracy of a system's signal processing is with an accurate, externally calibrated signal source for all montages used, although not all laboratories may have routine access to such equipment. Ideally a quality assurance scheme, administered by an accreditation agency using an external signal generating device that can be tested blinded in each laboratory, would allow laboratories to ascertain their accuracy and to upgrade to maintain it, if necessary.

5.5.2 Voltage mapping consistency

EEG

Voltage mapping consistency was checked to determine whether colour changes would be present across the head when mapping the same signal. The colour topographic maps plotted on identical (synchronous) external calibration signals during this test are demonstrated in Figure 5.1, and ideally should show a uniform colour over the entire plot. However, scaling needs to cover the range of electrical activity, and in the example the voltage selected is determined by plot amplitude before and after the waveform transition.

As seen in Figure 5.1, a variation of one colour gradation occurred in 3 of the 4 plots representing 0.7% (0.1 μV) to 25.2% (3.8 μV), using a range of ± 15.1 μV. Thus a perceptual error may occur, as the full range is scaled for only 16-shade colour variations. When the scaling was altered, for example to $\pm 60.2\mu$V, the maps plotted were a uniform colour throughout. More detailed determination of the actual errors involved would necessitate plotting a large range of amplitudes on varying scales, and assessment of the effects of background noise and the 'ringing' effect seen on the calibration signal.

Mapping of the stored internally generated EEG calibration signals could not be undertaken due to the manner in which they were montaged, and Cadwell Laboratories Inc. recommended using an external signal. Duffy and Maurer (1989) recommended that every system must provide means for complete calibration and the inability of the Spectrum to allow use of the recalled calibration signal is seen as a severe limitation.

The simulated fault in Figure 5.2 demonstrates that if problems were to exist with synchronicity, variations of greater than one shade could be seen during mapping, as also illustrated by Winter (1989). While such 'hills' (or 'holes') at single electrodes should not be allowed to affect the interpretation (Nuwer and Jordan 1987), if several channels were in error and undetected, misinterpretation could occur, as it could for the polygraph EEG. As noted by Walter et al. (1984), reading and interpretation of scales is essential, and from this section of the study it is concluded that alteration of scaling for enhancement of abnormalities could result in erroneous conclusions from the evaluation of a plot generated by a system with a fault, if users were unaware of the problem.

SEP

One-shade colour variations were also noted for SEP mapping of the external signal, reflecting a 1.0% to 25.0% variation, and were present in almost half the SEP maps. While these one shade variations would not be expected to affect proper clinical interpretation, once again users need to be aware that maps showing electrical variability in the subject's brain activity, together with the variations already shown, could be misleading particularly if scaled inappropriately. As discussed previously, no internal calibration signals were provided for evoked potentials.

Pottinger (1993) has indicated that the issue of external or internal calibration checks is debatable. This study demonstrates, however, that checking using an external calibration signal is necessary to test all parts of the system. However, for independent laboratories that do not have ready access to a signal generator, an internal calibration signal may be the conventional method of assessment, as it is for polygraph EEG machines. An internal calibration signal is available on the Spectrum, but only for assessment of EEG amplitudes and channel alignment. The system's inability to map stored calibration signals is seen as a limitation, as is the lack of such a signal for the evoked potentials.

5.6   CONCLUSION

Clarification of the functioning of equipment within accepted limits is necessary to provide ongoing confidence in the results produced. Assessment of amplitude accuracy and topographic voltage mapping consistency was undertaken, using an input signal of known voltage. Some of the limits were determined and problems were identified and rectified, where possible. This study emphasises the need for systems to be calibration-checked in the laboratories in which they are used, with an independent external signal generator. While newly acquired equipment should be tested comprehensively, the external checks described can readily be performed at regular intervals, for example when routine preventative maintenance procedures are performed or at the installation of software upgrades.

Mapping should not be the sole basis of the interpretation of results. Maps should only be used as an aid to viewing the data obtained, particularly where altered scaling is used to illustrate an abnormality. Furthermore, the reader of such maps needs to be fully aware of the type and degree of any manipulation of the graphics. Data from control subjects should be illustrated in the same way as that of the patients, to allow comparative assessment under the same conditions. Checks such as these provide greater awareness of amplitude, timing, scaling and resolution issues; they improve confidence in the interpretation of results, and are therefore considered an essential part of laboratory practice. (Richards and Hamilton-Bruce 1991, 1994 (refer to appendices 5.2, 5.3).)

CHAPTER 6

QUANTITATIVE EEG (qEEG): INTRA- AND INTER-OPERATOR VARIABILITY

6.0 INTRODUCTION

The qEEG has been reported as a sensitive, accurate and reliable method of evaluating brain function (Jonkman et al. 1985; John et al. 1988a; Sebban et al. 1988) and various studies have been undertaken on variability over the years.

Intra-operator (intra-rater/-electroencephalographer) reliability, when interpreting the EEG visually, can vary greatly, so much so that Woody (1966) considered the electroencephalographer in his study inconsistent in his ability to duplicate his interpretations. This, he considered, added support for the use of electronic analysers. Intra-rater visual EEG performance correlations have also been reported by Hooijer et al. in 1990. These were 0.62 for alpha frequency, 0.72 for the amount of alpha and 0.81 for the amount of theta, using the Spearman correlation coefficient ($p < 0.05$) on the EEGs of patients with senile dementia. They reported that inter-rater coefficients were slightly lower (0.52, 0.69 and 0.77, respectively), however, concomitant intra- and inter-rater spectral analysis comparisons were not given.

Inter-electroencephalographer visual EEG interpretation variability was demonstrated by Houfek and Ellingson (1959), who reported only 69% complete agreement between 2 electro-encephalographers in a study of 140 patients. Volavka et al. (1971) found that when 7 electroencephalographers were presented with 98 EEG recordings independently, average inter-rater coefficients for reporting abnormal/borderline/normal ranged from 0.40 to 0.63, while those for paroxysmal feature detection ranged from 0.19 to 0.50. Struve et al. (1975) reported that complete interpretive agreement between themselves ranged from 88% to 92%. Williams et al. (1990) reported 50% - 89% total agreement with 62 electroencephalographers reading 8 EEG recordings, while Spillane (1995) reported a 62% consensus of opinion among 5 technicians and 3 clinicians reading 16 EEGs.

Thus although qEEG intersession studies abound (John et al. 1983; Gasser et al. 1985; Woerner et al. 1987; Eskenasy-Cottier et al. 1988; Sebban et al. 1988; Kohrman et al. 1989; Hooijer et al. 1990), reproducibility studies for intra- and inter-operator variability do not.

Gotman et al. reported that 3 readers gave very consistent EEG canonogram (topographically meaningful representations of the ratios for each of 16 EEG channels) reports in 1975, however, as highlighted by Nuwer (1990a, 1992a), reproducibility of results needed to be demonstrated, with artefacts, normal variants and other problems needing to be identified and avoided.

As part of the process of evaluation of the proposed new diagnostic EEG tests, I considered it necessary to undertake various assessments of validity, prior to undertaking my clinical study. These included initial intra- and inter-operator reliability studies as documented in this chapter, and intersession studies, as documented in chapter 7. Such assessment would also allow observation and documentation of artefacts and physiological activity seen on qEEG and overall would result in new knowledge, as well as providing the opportunity for staff to gain experience in using a method new to the laboratory.

6.0.1   Aim

The aim of the study was to determine whether the new test (qEEG) would vary significantly when:

1) re-analysed by one operator

2) analysed by three different operators interested in using the method and prepared to participate blinded to the subjects' details.

Additionally, the study aimed to allow:

3) observation and documentation of some of the artefacts and physiological activity as brainmaps.

6.1   METHOD

6.1.1   Subjects

The study was performed with the approval of The Queen Elizabeth Hospital Ethics' Committee. Ten volunteer subjects were provided with an information sheet (refer to appendix 6.1) and consent form (refer to appendix 6.2) in order to be able to give informed written consent. Subjects included colleagues, friends and relatives recruited by verbal and written advertisement and were unrecompensed. When the tests were booked, the study was explained to the subjects. They were screened verbally using a questionnaire (refer to appendix 6.3) to identify medication, drugs, alcohol, diseases and other medical disorders which could affect the EEG and result in exclusion from the study.

At the time of the EEG test, the questionnaire was completed formally and a clinical examination was performed on the subjects by a qualified medical officer from the Department of Neurology. The clinical screen by the medical officer consisted of taking a brief medical history and assessment of cranial nerves (1-12), the motor system (power, tone, co-ordination and reflexes), the sensory system (join position and vibration sense, pain, light touch and temperature) and gait (walking, heel-toe and Romberg testing) (refer to appendix 6.3). Exclusion was based on signs or symptoms of nervous system dysfunction, or a disorder or treatment that could affect the nervous system.

6.1.2   Equipment

EEGs were recorded on the Cadwell Spectrum AT 386, using the Cadwell Electrocap (with electrode positions corresponding to those of the International 10-20 system) and a linked-ear reference. The recording electrodes used for the Neurometric method were Fp1/z/2, F7/3/z/4/8, C3/z/4, P3/z/4, T5,3,4,6, O1/z/2.

Twenty-one channel EEG recordings were performed using the electrodes detailed above, with additional channels to assist in ECG and ocular artefact detection. Filters were set at 70 Hz and 0.3 Hz, the sensitivity at 10 μV/mm and a 50 Hz notch filter was used. The EEG was recorded on a 230 megabyte ISI optical storage disc using the standard (uncompressed) mode and retrieved later for computerised analysis.

6.1.3 Subject and electrode preparation

Subjects were seated and the scalp and forehead were wiped with an isopropyl alcohol wipe. The frontopolar electrode positions were marked using the 10-20 International System and a measuring tape to determine the positions. Head circumference was measured by means of a tape provided with the Cadwell Electrocap, to determine the size of cap required (large, medium or small). The appropriate cap was selected, fitted (utilising the frontopolar electrode markings to assist in positioning) and secured by means of cap straps, as well as additional taping to the forehead. Electrode electrical contact was made with the scalp by injecting eci ELECTROGEL™ EEG electrode paste into the cap electrode wells, subsequent to rubbing with a manufactured blunted syringe needle. Impedances were checked on the Cadwell Spectrum AT 386 and electrode contact was adjusted by further rubbing and/or paste injection, until measures less than or equal to 5 kOhms were obtained.

In addition, an ECG electrode was placed on each wrist and ocular electrodes were placed, one at the outer canthus of the right eye and one below the right eye, subsequent to preparation of the skin with an isopropyl alcohol wipe and Omni Prep paste to achieve low impedances; eci ELECTROGEL™ EEG paste was used to provide the electrical contact. These electrodes were utilised to enhance operator artefact detection during recording and subsequently at analysis.

6.1.4 Recording

For the recording, subjects remained seated and were requested to relax, but remain alert. The recording was performed with the subject's eyes closed, but 'eyes-open' short annotated rest-breaks (lasting approximately 30 seconds) were allowed during recording to reduce fatigue and enhance co-operation. Where drowsiness was suspected due to characteristic changes on the EEG or ocular electrodes or by observation of the subject, the subject was requested to respond verbally, or to open the eyes.

Recording lasted 10-30 minutes, depending on impedance checks and trace quality. If electrode malfunction was suspected during the recording, due to a change in impedance at a spot check during or routine check at the end of the recording, or due to drift, pop or other irregularities, impedances were checked and the electrode contact improved, if necessary, to re-establish electrode contact to less than or equal to 5 kOhm, prior to continuing the recording. At the end of the recording, the subject was disconnected from the equipment and allowed to leave.

6.1.5 Analyses

Neurometric Analysis
The EEG was retrieved from the optical disc by Neurology staff not involved with the study and the operators had no knowledge of the subject's identity or clinical details (other than that the subjects were healthy controls) to avoid possible bias. Analysis of each trace was performed consecutively by the operators using the artefact reject mode as well as visual scrutiny to attempt to avoid inclusion of artefact. Up to 48 epochs (2.5 second segments of the EEG) were selected from the 'eyes-closed' section of the EEG by me for the intra-operator study and independently by each of 3 operators (a Neurologist, a Neurology Registrar and myself) for the inter-operator study.

Neurometric reports displayed the data as Absolute Power, Relative Power, Power Asymmetry and Coherence and full Neurometric analysis could only be performed when 24 or more epochs were selected, with the maximum number for selection being set at 48. Examples of artefact or physiological activity were mapped using the frequency mapping program provided by Cadwell in the Review EEG Analysis options and printed using the colour printer.

Discriminant Analysis

The Neurometric Analysis Discriminants reports were provided as follows:

'This patient's discriminant scores ... ':

'lie within the normal limits expected for an individual of this age'
- considered normal (N),

'lie outside of the normal limits expected for an individual of this age'
- considered abnormal (A),

'do not allow a confident determination of the presence of abnormalities'
- considered borderline (B)

OR

'At this time there is no appropriate discriminant function to evaluate this patient's data'
- categorised as unable to classify (U)

Further statistical analyses

1. <u>Intra-operator studies:</u> Variability of the quantitative data generated by Neurometrics was assessed by paired comparisons for each subject using the Cadwell T-Score Analysis Package, as a 2-tailed t-test ($p \leq 0.05$). This allowed comparison of all four mono- and bipolar parameters (delta, theta, alpha and beta) for Absolute Power using the t-test, as well as z-score differences for the derived parameters Relative Power, Power Asymmetry and Coherence.

2. <u>Inter-operator studies:</u> The results were analysed in two ways. Firstly, results were compared for two operators at a time using the Cadwell T-Score Analysis Package as a 2-tailed t-test ($p \leq 0.05$), correlated (paired) where the number of epochs was the same in both tests and independent (unpaired) where they differed, to determine the variability between operators. Subsequently all data were analysed simultaneously by means of analysis of variance (ANOVA), using the Statistical Package for the Social Sciences (SPSS 1990a, 1990b). The monopolar and bipolar Absolute Power raw measures were analysed using one-way ANOVA and the Neurometric Analysis Discriminants report results were analysed using the Friedman two-way ANOVA - the results for the latter being coded as 1 - normal, 2 - abnormal, 3 - borderline and 4 - unable to classify.

6.2   RESULTS

6.2.1   Clinical assessment

Ten control subjects were assessed (mean age 33.8 years, standard deviation (SD) 9.4 years, range 16.6 - 53.9 years) and none was found to have a condition requiring exclusion.

6.2.2 Intra-operator study

Neurometric analysis was performed twice on all recordings and examples of some of the results obtained are provided:

Figure 6.1 illustrates 2 epochs (epoch 20 of a total of 48 in each analysis) selected from the EEG recording of a healthy 34 year old control (Q61) for qEEG analysis. On the left are the monopolar traces from 21 electrodes (referenced to linked ears in the qEEG montage) and one ocular trace (bottom), while on the right is the more limited bipolar montage. The top traces are from the first analysis (Q61(1)) and the bottom from the second analysis (Q61(2)).

Figure 6.2a shows the qEEG z-score measures from the same control (Q61), for monopolar and bipolar measures for the first analysis (Q61(1)). The three measures falling at or outside the 1.96 SD lower limits are highlighted. Figure 6.2b shows the qEEG z-score measures from the same control (Q61), for monopolar and bipolar measures for the second analysis (Q61(2)). The four measures falling outside the 1.96 SD upper or lower limits are highlighted.

Figure 6.3a shows the monopolar and bipolar qEEG z-score maps from the Neurometric analysis for the same control for the first analysis (Q61(1)). Figure 6.3b shows the monopolar and bipolar qEEG z-score maps from the Neurometric analysis for the same control for the second analysis (Q61(2)).

Some of the artefacts and physiological activity recorded have been mapped in Figure 6.4. The maps on the left were recorded from an epoch where the subject (Q77, a healthy 31 year old male control) felt drowsy. The top left map shows ocular artefact frontally in the delta frequency range, the second map down on the left shows some central slowing in the theta frequency range, alpha frontal spread is seen in the third map on the left, while the bottom left map shows muscle artefact particularly in T4, in the beta frequency range map. In the maps on the right (Q89, a healthy 52 year old male control), mu rhythm is most pronounced centrally in the alpha frequency range map (third from the top), but is also seen in the beta frequency range map (bottom right) and minimally in the central region of the theta frequency range map.
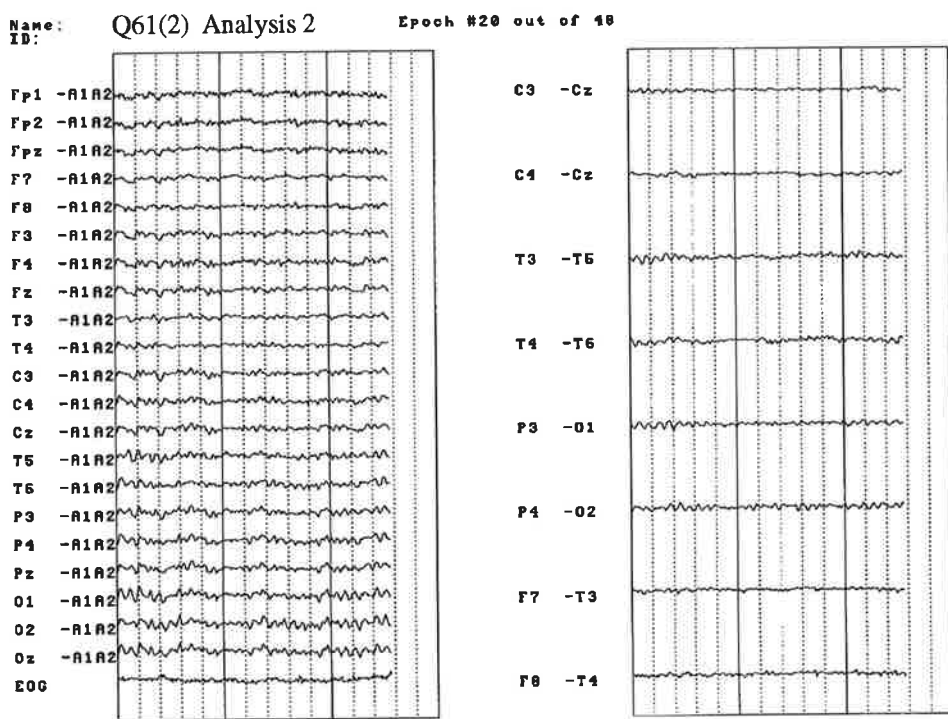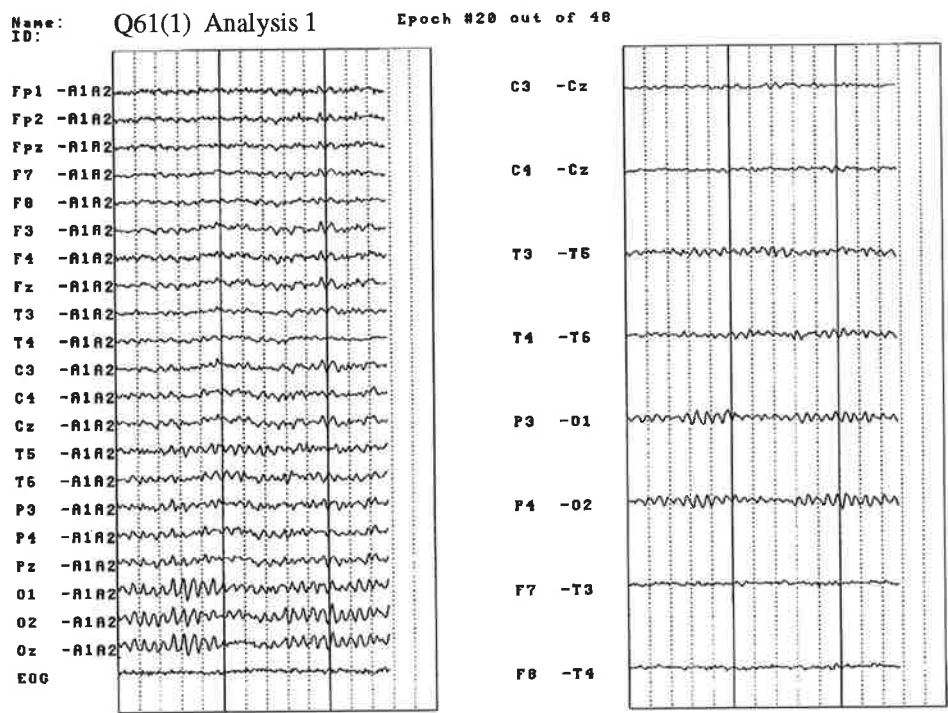
FIGURE 6.1   Monopolar (left) and bipolar (right) qEEG epochs from Neurometric analyses 1 (Q61(1)) and 2 (Q61(2)) of an EEG recording from a healthy 34 year old female volunteer, during the intra-operator study.

Name: Q61(1) Analysis 1
Age: 34.2 yrs   Recorded: 10/31/90
                              # Epochs: 48

Monopolar Z Score Measures

		Fp1	Fp2	F7	F8	F3	F4	C3	C4	Fpz	Fz	Cz
Absolute	Δ	-1.55	-1.55	-1.00	-1.19	-0.68	-0.71	-0.33	-0.39	-1.51	-0.83	-0.66
Power	θ	-1.18	-1.32	-0.63	-0.99	-0.46	-0.69	-0.50	-0.75	-1.24	-0.65	-0.88
	α	-1.46	-1.48	-1.22	-1.28	-1.23	-1.27	-1.10	-1.13	-1.48	-1.37	-1.37
	β	-0.85	-0.43	-0.79	-1.02	-0.63	0.10	-0.35	-0.35	-0.76	-0.68	-0.67
Relative	Δ	-0.08	-0.10	0.39	0.42	0.64	0.44	0.78	0.80	-0.02	0.64	0.83
Power	θ	0.99	0.56	1.19	0.96	1.13	0.53	0.75	0.49	0.83	1.07	0.78
	α	-0.70	-0.83	-0.87	-0.79	-1.06	-1.22	-1.05	-1.00	-0.76	-1.13	-1.07
	β	1.10	1.69	0.46	0.52	0.43	1.41	0.65	0.83	1.25	0.60	0.58

			Fp1/Fp2		F7/F8		F3/F4		C3/C4			
Interhem.	Δ		-0.27		0.39		0.15		0.31			
Power	θ		0.44		0.66		0.71		0.93			
Asymmetry	α		0.20		0.32		0.18		0.14			
	β		-1.26		0.40		**-2.40**		-0.01			
Interhem.	Δ		0.37		0.47		-0.00		0.45			
Coherence	θ		-0.01		0.11		-0.14		0.26			
	α		-0.11		-0.33		-0.79		-0.62			
	β		-0.63		0.84		-0.80		0.45			

		T3	T4	T5	T6	P3	P4	O1	O2	Pz	Oz
Absolute	Δ	-0.36	-0.15	-0.00	0.12	-0.25	-0.18	0.15	0.12	-0.39	0.21
Power	θ	-0.60	-0.32	-0.34	-0.10	-0.46	-0.48	-0.25	-0.19	-0.69	-0.22
	α	-0.93	-0.55	-0.42	-0.15	-0.96	-0.87	0.00	0.23	-1.02	0.10
	β	-0.54	-0.33	0.09	0.42	-0.13	-0.03	0.38	0.52	-0.28	0.44
Relative	Δ	0.01	0.59	0.53	0.25	0.80	0.76	0.16	-0.10	0.82	0.11
Power	θ	0.54	0.36	0.20	0.08	0.54	0.56	-0.21	-0.48	0.63	-0.32
	α	-0.71	-0.36	-0.45	-0.20	-0.98	-0.93	-0.01	0.25	-0.95	0.08
	β	0.26	0.21	0.72	0.79	1.00	1.11	0.57	0.42	0.98	0.49

			T3/T4		T5/T6		P3/P4		O1/O2		
Interhem.	Δ		-0.03		-0.17		-0.13		0.01		
Power	θ		-0.02		-0.37		0.01		-0.11		
Asymmetry	α		-0.13		-0.65		-0.27		-0.83		
	β		-0.03		-0.69		-0.27		-0.40		
Interhem.	Δ		0.65		1.14		0.99		1.80		
Coherence	θ		-0.94		0.68		0.49		1.34		
	α		-0.25		-1.55		-1.14		-0.40		
	β		-0.76		-0.42		-0.17		0.69		

Name: Q61(1) Analysis 1
Age: 34.2 yrs   Recorded: 10/31/90
                         # Epochs: 48

Bipolar Z Score Measures

		Central		Temporal		Parietal Occipital		Frontal Temporal	
		C3/Cz	C4/Cz	T3/T5	T4/T6	P3/O1	P4/O2	F7/T3	F8/T4
Total Absolute Power		-1.37	-1.30	-0.62	-0.39	0.14	0.53	-1.35	-1.04
Total Power Asymmetry		-0.16		-0.48		-1.00		-0.56	
Relative	Δ	0.18	0.25	0.56	0.05	-0.70	-1.24	0.20	0.22
Power	θ	0.48	0.80	0.10	-0.08	-0.94	-1.48	0.75	0.70
	α	-0.38	-0.64	-0.34	-0.13	0.48	1.01	-0.48	-0.65
	β	0.52	0.58	0.56	0.64	0.51	0.02	0.44	0.64
	Δ+θ	0.23	0.48	0.31	-0.09	-0.91	-1.44	0.35	0.33
	Combination	-2.09	-0.97	-1.44	-4.16	-0.73	0.19	-0.89	-0.80
Interhem.	Δ		-0.22		0.37		0.02		-0.54
Power	θ		-0.70		-0.24		-0.11		-0.66
Asymmetry	α		0.23		-0.63		-1.17		-0.19
	β		-0.13		-0.49		-0.20		-0.48
	Combination		-0.84		-0.63		-0.04		-1.33
Interhem.	Δ		**-3.09**		0.87		1.39		0.52
Coherence	θ		-1.07		0.54		0.39		0.29
	α		0.68		**-2.43**		-0.13		-1.02
	β		0.48		0.55		1.22		0.63
	Combination		1.63		1.38		0.54		-0.19
Overall			0.79		0.32		0.03		-1.20

FIGURE 6.2a   Monopolar (left) and bipolar (right) qEEG z-score measures from Neurometric analysis 1 (Q61(1)) of an EEG recording from a healthy 34 year old female volunteer, during the intra-operator study. Measures falling outside the 1.96 SD upper or lower limits are highlighted.

Monopolar Z Score Measures

	Fp1	Fp2	F7	F8	F3	F4	C3	C4	Fpz	Fz	Cz
Absolute Power Δ	-1.58	-1.69	-1.09	-1.17	-0.83	-0.78	-0.38	-0.33	-1.64	-0.90	-0.64
θ	-0.97	-1.06	-0.59	-0.84	-0.31	-0.58	-0.54	-0.68	-0.94	-0.52	-0.88
α	-1.49	-1.43	-1.25	-1.19	-1.23	-1.08	-1.08	-1.48	-1.36	-1.33	
β	-0.72	-0.34	-0.78	-0.84	-0.57	0.10	-0.34	-0.21	-0.61	-0.57	-0.60
Relative Power Δ	-0.21	-0.37	0.31	0.27	0.44	0.33	0.74	0.76	-0.29	0.49	0.81
θ	1.30	0.94	1.31	1.04	1.35	0.69	0.72	0.45	1.29	1.23	0.72
α	-0.81	-0.81	-0.90	-0.76	-1.07	-1.19	-1.01	-1.01	-0.82	-1.16	-1.04
β	1.17	1.73	0.50	0.62	0.49	1.39	0.68	0.93	1.34	0.70	0.63

	Fp		F7/F8		F3/F4		C3/C4	
Interhem. Power Asymmetry Δ	0.09		0.26		-0.08		-0.01	
θ	0.28		0.47		0.78		0.61	
α	-0.42		-0.01		0.01		-0.00	
β	-1.16		0.13		**-2.33**		-0.42	
Interhem. Coherence Δ	0.39		0.62		0.12		0.63	
θ	0.26		0.38		0.23		0.14	
α	-0.19		-0.28		-0.68		-0.60	
β	-0.52		0.82		-0.69		0.15	

	T3	T4	T5	T6	P3	P4	O1	O2	Pz	Oz
Absolute Power Δ	-0.36	-0.07	0.04	0.24	-0.16	-0.03	0.29	0.28	-0.26	0.36
θ	-0.62	-0.28	-0.52	-0.11	-0.59	-0.54	-0.35	-0.17	-0.77	-0.24
α	-0.96	-0.48	-0.46	-0.20	-0.51	-0.84	0.13	0.30	-0.95	0.22
β	-0.53	-0.29	0.21	0.46	-0.07	0.01	0.44	0.54	-0.31	0.49
Relative Power Δ	0.83	0.61	0.60	0.38	0.85	0.86	0.13	-0.07	0.89	0.08
θ	0.52	0.31	-0.03	0.09	0.42	0.42	-0.47	-0.56	0.47	-0.52
α	-0.75	-0.32	-0.52	-0.40	-0.93	-0.93	0.12	0.30	-0.87	0.20
β	0.30	0.18	0.92	0.86	1.04	1.11	0.46	0.32	0.87	0.37

	T3/T4		T5/T6		P3/P4		O1/O2	
Interhem. Power Asymmetry Δ	-0.11		-0.29		-0.28		-0.11	
θ	-0.08		-0.64		-0.22		-0.52	
α	-0.25		-0.62		-0.18		-0.64	
β	-0.06		-0.54		-0.23		-0.31	
Interhem. Coherence Δ	0.76		1.26		1.14		**1.96**	
θ	-0.54		0.52		0.34		1.36	
α	-1.36		**-2.36**		-1.00		-0.26	
β	-0.71		-0.46		-0.39		0.67	

Bipolar Z Score Measures

	Central		Temporal		Parietal Occipital		Frontal Temporal	
	C3/Cz	C4/Cz	T3/T5	T4/T6	P3/O1	P4/O2	F7/T3	F8/T4
Total Absolute Power	-1.31	-1.23	-0.67	-0.39	0.19	0.61	-1.29	-1.03
Total Power Asymmetry	-0.16		-0.67		-1.08		-0.46	
Relative Power Δ	0.02	0.14	0.63	0.10	-0.84	-1.40	0.33	0.07
θ	0.39	0.81	0.08	0.02	-0.99	-1.45	0.81	0.81
α	-0.60	-0.64	-0.40	-0.22	0.57	1.02	-0.75	-0.58
β	0.87	0.66	0.60	0.70	0.43	0.06	0.55	0.64
Δ+θ	0.08	0.13	0.35	-0.01	-1.00	-1.50	0.47	0.27
Combination	-1.45	-0.75	-1.11	-4.02	-0.62	0.31	-0.57	-0.47
Interhem. Power Asymmetry Δ	-0.34		0.30		-0.00		-0.06	
θ	-0.86		-0.50		-0.32		-0.60	
α	0.07		-0.68		-1.16		-0.58	
β	0.24		-0.58		-0.47		-0.34	
Combination	-0.45		-0.31		-0.33		-1.52	
Interhem. Coherence Δ	-1.82		1.18		1.34		0.63	
θ	-1.25		0.22		0.21		0.40	
α	0.76		**-2.26**		-0.06		-1.13	
β	0.65		0.68		1.19		0.54	
Combination	0.51		1.30		0.59		-0.05	
Overall	-0.58		0.30		-0.01		-1.06	

FIGURE 6.2b   Monopolar (left) and bipolar (right) qEEG z-score measures from Neurometric analysis 2 (Q61(2)) of an EEG recording from a healthy 34 year old female volunteer, during the intra-operator study. Measures falling outside the 1.96 SD upper or lower limits are highlighted.
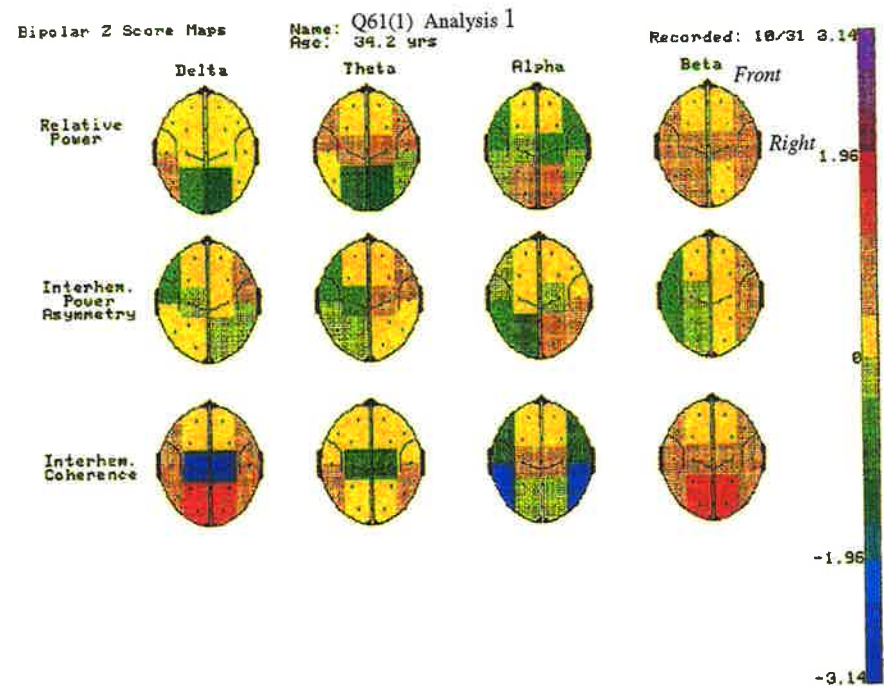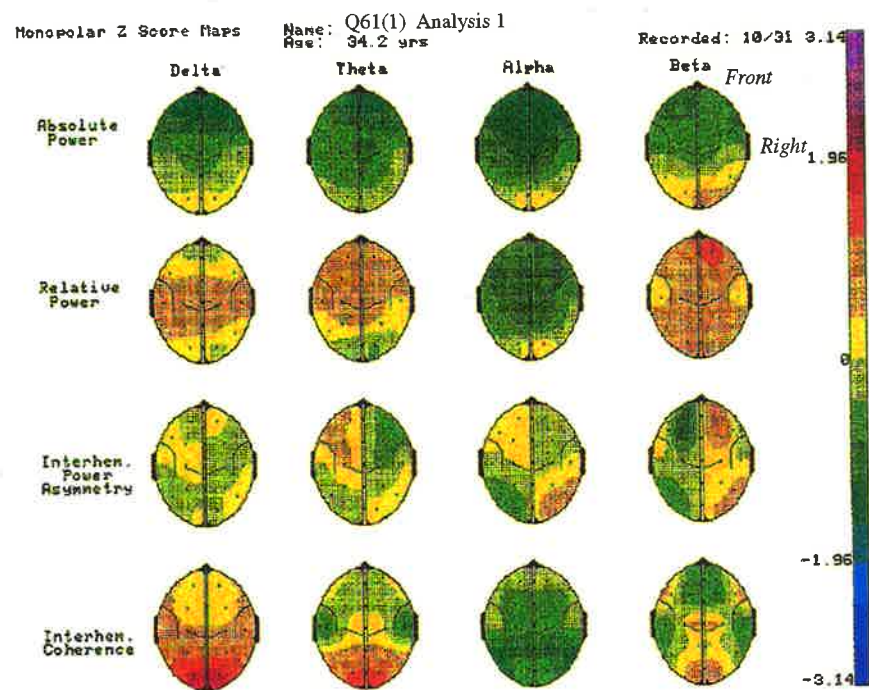
FIGURE 6.3a   Monopolar (left) and bipolar (right) qEEG z-score maps from Neurometric analysis 1 (Q61(1)) of an EEG recording from a healthy 34 year old female volunteer, during the intra-operator study. Scale: 3.14 SD (magenta) to -3.14 (deep blue).
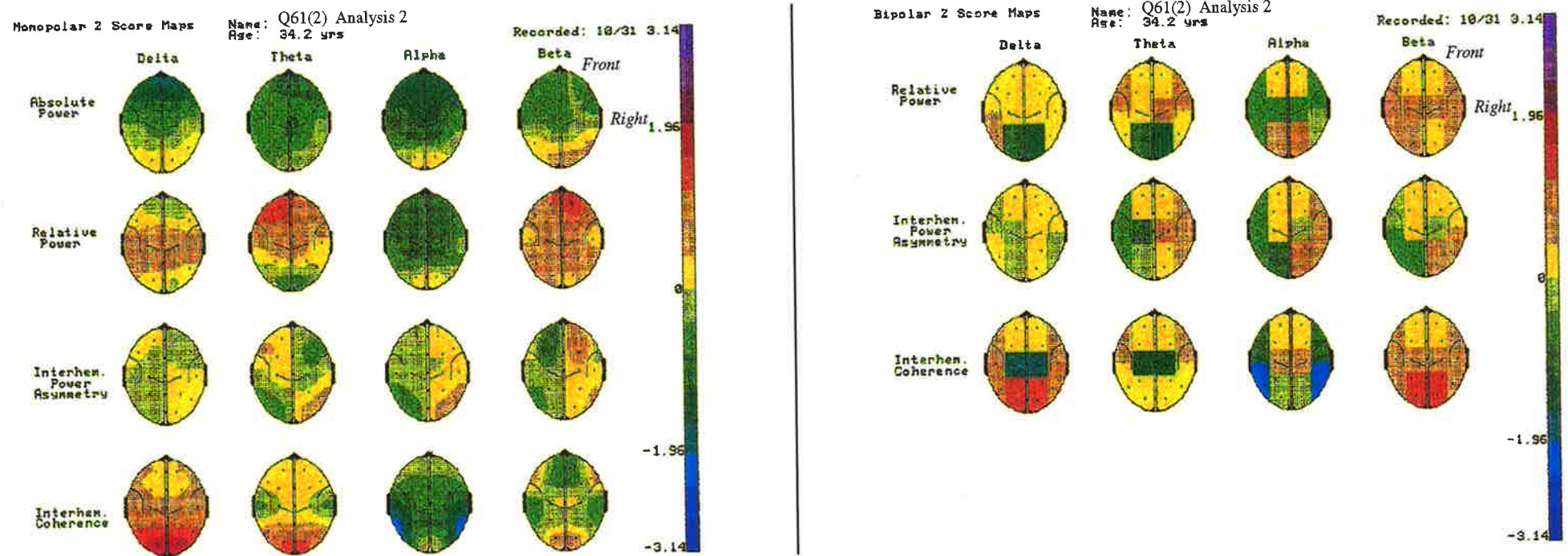
FIGURE 6.3b   Monopolar (left) and bipolar (right) qEEG z-score maps from Neurometric analysis 2 (Q61(2)) of an EEG recording from a healthy 34 year old female volunteer, during the intra-operator study. Scale: 3.14 SD (magenta) to -3.14 (deep blue).
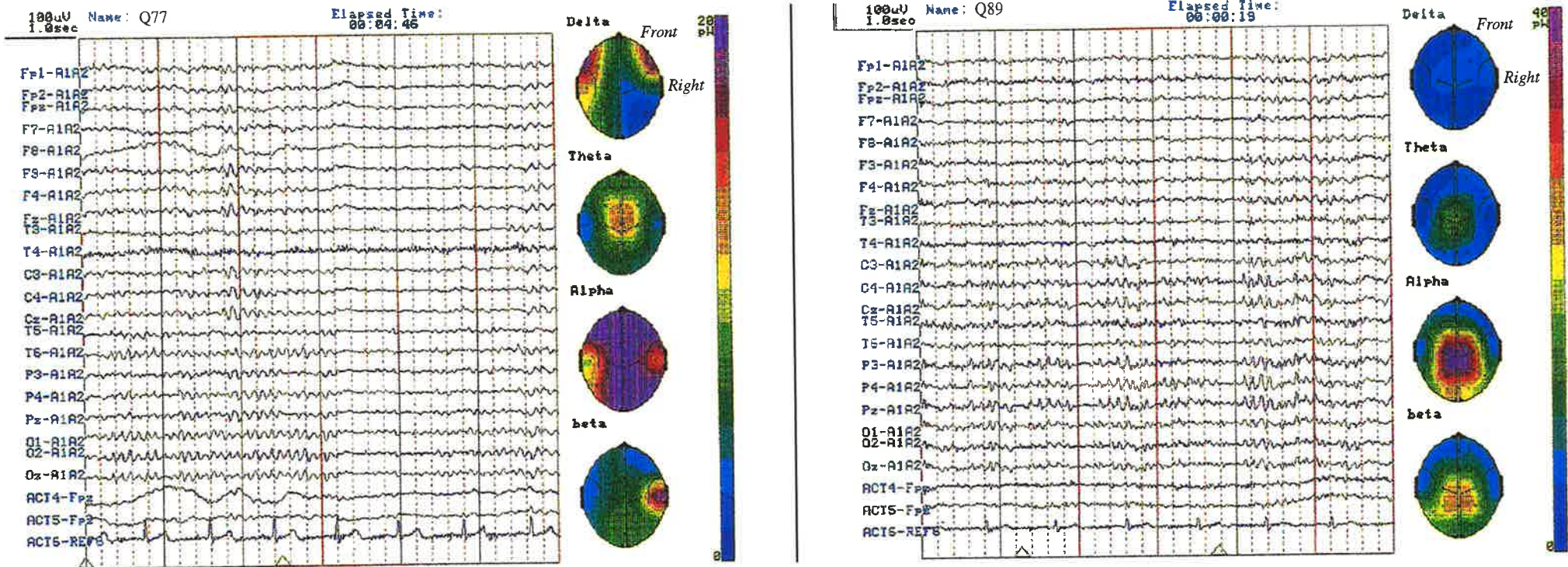
FIGURE 6.4   On the left, EEG frequency maps illustrate ocular artefact in the top map (delta frequency range), drowsiness in the second and third maps (theta and alpha frequency ranges, respectively) and muscle artefact in the fourth map (beta frequency range) all recorded from the same epoch from a healthy 31 year old male volunteer (Q77). On the right, EEG frequency maps illustrate mu activity mainly in the third and fourth maps (chiefly alpha and beta frequency ranges, respectively) all recorded from the same epoch from a healthy 52 year old male volunteer (Q89).   Scale: 0 to 20 pW on the left and 0 to 40 pW on the right.

Using the Cadwell T-Score Analysis Package in the intra-operator study, the maximum number of significant differences for all subjects was 5, 3, 1 and 1 of 21 monopolar and 2, 0, 0, and 1 of 8 bipolar Absolute Power scores in the delta, theta, alpha and beta frequency ranges, respectively ($p \leq 0.05$, 2-tailed t-test). Relative Power and Power Asymmetry showed no significant differences in any of the frequency ranges ($p > 0.05$, 2-tailed t-test), and Coherence showed only 1 significant difference out of 4 scores in the bipolar montage in the alpha frequency range ($p \leq 0.05$, 2-tailed t-test). Discriminant analysis showed 9 of 10 reports in agreement (3 normal, 3 borderline, 2 abnormal and 1 unable to classify), with one of the normals showing different significant levels ($p \leq 0.025$ versus $p \leq 0.10$). Only one report changed from normal to borderline on re-analysis ($p \leq 0.05$).

6.2.3 Inter-operator study

Comparison of the data from two operators, i.e., operators 1 and 2, 2 and 3, or 1 and 3 using the Cadwell T-Score Analysis Package showed considerable variation in monopolar Absolute Power scores, with the maximum number of significant differences for all subjects being 13, 18, 21 and 13 for 21 scores in the delta, theta, alpha and beta frequency ranges, respectively ($p \leq 0.05$, 2-tailed t-test). Relative Power, by comparison, showed this for only 1 of 21 scores and coherence for 1 of 8 scores, in the theta and beta frequency ranges, respectively ($p \leq 0.05$, 2-tailed t-test). No other significant differences were seen ($p > 0.05$, 2-tailed t-test). Bipolar scores reflected these results, with the maximum number of significant Absolute Power differences being 4, 8, 8 and 4 for 8 scores in the delta, theta, alpha and beta frequency ranges, respectively. Relative Power and Power Asymmetry values showed no significant differences, while for Coherence 1 of 4 scores in the alpha frequency range was significantly different.

The Absolute Power raw measures were further analysed using oneway ANOVA on the monopolar and bipolar scores. The multiple range test (Tukey procedure) gave a range difference of 3.50 and, at the 0.05 level, no two groups were found to be significantly different. Only Absolute Power was analysed in this way, as the other measures (Relative Power, Power Asymmetry and Coherence) were derived from Absolute Power.

Discriminant analysis classified 7 of the 10 EEGs the same (3 normal, 1 borderline, 2 abnormal and 1 unable to classify), the remaining 3 being classified as normal or borderline. The Neurometric Analysis Discriminants reports were analysed using the Friedman two-way ANOVA and yielded mean ranks of 1.95 for operators 1 and 2 and 2.10 for operator 3. There was no significant difference between mean rank for the operators (chi-square=0.15, p=0.928).

6.3   DISCUSSION

6.3.1   qEEG brainmapping

Visual assessment and comparison of qEEGs is difficult due to the large number of measures generated for each subject. Moreover, some measures are likely to be abnormal by chance (Oken and Chiappa 1986; Abt 1990; Jonkman et al. 1992b). For example, Monopolar Absolute Power has 84 measures per subject (21 electrodes, 4 frequency ranges) so that by chance, at the 0.05 level, 7 of these measures may fall outside the 1.96 SD limit (Hamilton-Bruce et al. 1991b (refer to appendix 6.5)), using the formula and Basic program, as documented by Desbiens et al. (1990).

With respect to artefact, as stated by Lee and Buchsbaum (1987), the ideal EEG recording does not contain muscle or ocular activity. However, if present, when mapped the artefacts are seen as frequency shifts and regional patterns, not as specific analogue signals. Thus separate mapping of artefacts, as well as physiological activity, for example the frequency change seen with drowsiness as well as mu rhythm, provides a guide for those interested in interpretation and also a reminder to avoid inclusion of such activity in a qEEG analysis. As such, illustrative examples were mapped when noted in some sections of some of the traces; these have provided a reference point for those undertaking brainmapping in the laboratory and also for teaching purposes.

6.3.2 Intra-operator study

The Cadwell T-Score Analysis Package (the Neurometrics brainmapping software for comparison of 2 qEEG analyses supplied for the Spectrum) showed that most variability in the qEEG intra-operator analyses occurred in Absolute Power in both the mono- and bipolar studies. In a study to determine reliability of spatial distribution of EEG amplitude over time within a session on 24 healthy right-handed subjects, Burgess and Gruzelier (1993) concluded that spatio-temporal reliability was more than adequate for group comparisons, but insufficient to allow topographical comparisons in a single individual, with the poorest reliability after 40 minutes being in the delta frequency band. Thus the variability in Absolute Power in my study could reflect amplitude variability of individual EEG recordings and the selection of different epochs on the separate occasions.

In contrast, Relative Power, Power Asymmetry and Coherence showed less variation. This may be reflective of the stability of these measures or due to the use of difference z-score assessment with a concomitant lack of independence for the comparisons (the same subjects were used in the first and second assessments). However, as the subjects had all been screened clinically and accepted for inclusion in the study, the method could be reflective of stability. This hypothesis could be tested by repeating the study with a larger sample, or developed further by performing other similar studies, for example inter-operator and intersession studies and assessing studies on patients where differences would be anticipated.

Discriminant analysis showed agreement, with 9 of 10 reports being the same, one changing from normal ($p \leq 0.025$) to borderline on re-analysis ($p \leq 0.025$), a report which would nonetheless be considered normal in our clinical laboratory.

Thus, for analyses other than those of Absolute Power, variability is low. Comparison with the work of others, however, is difficult as the methods of analysis (visual versus quantitative) are different. Thus, for future comparative assessments, correlation analyses would also need to be undertaken.

6.3.3 Inter-operator study

For the initial analysis, the Neurometrics Cadwell T-Score Analysis Package supplied for the Spectrum was used. This allowed comparison of analyses from only two operators at a time. When the maximum number of significant differences between any 2 operators was pooled, most significant differences were shown in Absolute Power, as was also seen in the intra-operator study.

This could be a reflection of:

a) the increased number of abnormalities seen when using the t-test to compare more than 2 variables (Zar 1984)

b) the use of the t-test for Absolute Power comparisons and difference z-score measures for comparison of Relative Power, Power Asymmetry and Coherence, as discussed in section 6.3.2

c) the selection of different epochs by different operators, given the variable nature of the EEG.

Following preliminary analysis, the oneway ANOVA was performed on the non-derived Absolute Power measures and showed no significant differences between the operators at the 0.05 level for both mono- and bipolar raw measures.

Statistical analysis of the Discriminant Analysis reports showed no significant differences between operators, with 70% showing complete agreement, i.e., all normal, borderline, abnormal or unknown. 30% showed minor disagreement, i.e., the subject was classified normal or borderline, both of which are considered normal in our clinical laboratory. No major disagreement (normal or borderline versus abnormal in the same subject) was shown in this study. This compared well with previous results of visually analysed interoperator studies, where agreement ranged from 50% to 92% (Houfek and Ellingson 1959; Struve et al. 1975; Williams et al. 1990; Spillane 1995), although my subjects were all healthy volunteers, rather than patients.

6.4   CONCLUSION

6.4.1   Intra-operator variability

Assessment of intra-operator variability showed that most significant differences occurred in the Absolute Power Mono- and Bipolar measures, whereas Relative Power, Power Asymmetry and Coherence showed few significant differences.

6.4.2   Inter-operator variability

Differences in Absolute Power between operators were detected using the Cadwell T-Score Analysis Package to compare 2 operators at a time, reflecting the findings of the intra-operator study. However, when comparing the qEEG analyses of 3 operators simultaneously, no statistically significant differences were detected with respect to both the raw measures and discriminant reports. While this may indicate that this method of analysis could be used interchangeably between these operators in our laboratory, it may also be that further studies with a larger sample would detect significant differences and confirm the findings of the t-test comparisons. The lack of difference in the difference z-score measures for Relative Power, Power Asymmetry and Coherence is also reflective of the findings in the intra-operator study, but as the same database was used, no firm conclusions can be drawn with respect to this aspect of the study.

Thus my assessment of topographic qEEG was initiated with baseline studies of intra- and inter-operator variability and mapping of artefact. This has allowed operators to obtain experience in using the equipment and in the method of Neurometric analysis, and extended knowledge in the field (Hamilton-Bruce 1991; Hamilton-Bruce et al. 1991b; Hamilton-Bruce et al. 1991c (refer to appendices 6.4-6.6)).

CHAPTER 7

qEEG: INTERSESSION VARIABILITY

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7.0 INTRODUCTION

Following the initial intraoperator and interoperator qEEG studies documented in Chapter 6, the next stage was to undertake qEEG intersession or test-retest studies on a group of healthy subjects. Findings from previous studies have been varied. John et al. (1983) observed that Absolute Power measures showed more significant intersession changes than Relative Power in children. At the 0.05 level, they found significant intersession differences in 18 of 152 Absolute Power measures (12%) compared with 3 of 152 Relative Power measures (2%). Sebban et al. (1988) also reported few intersession changes in Relative Power in healthy young adults, although they did find a significant increase in slow alpha Relative Power (6 - 8) Hz, which they considered due to habituation. Similarly, Nagata et al. (1992) noted that Absolute Power showed greater variability than Relative Power in a study of stroke patients.

In contrast, Pollock et al. (1991) reported higher intersession reliability coefficients in adults for absolute rather than relative amplitude measures in all frequency bands except delta, where the test-retest reliability over a 4.5 month interval was lower than those of other bands, Fein et al. (1984) previously having reported similar findings in 9 - 13 year old boys over a 1 - 3 year period. However, many of these studies are not strictly comparable, with variations in both methods and algorithms.

Furthermore, as some measures may be abnormal by virtue of chance (Oken and Chiappa 1986; Abt 1990; Hamilton-Bruce et al. 1991b; Jonkman et al. 1992b), these statistical findings could be misinterpreted. One way of addressing this issue would be by the reduction of the p-value for individual comparisons to maintain the usual p-value (0.05) for the analysis as a whole, one of the simplest methods being that of division of the usual p-value by the number of comparisons being made (Oken and Chiappa 1986; Jonkman et al. 1992b). Thus the effect of using a lower cut-off point needed to be determined in my study. In addition, in the intra- and inter-operator studies, some of the healthy subjects had been assessed by the Neurometric Analysis Discriminants method to have an abnormal EEG, thus it was also determined that this method should be compared not only with itself, but also with the standard visual method of EEG analysis.

As the intraoperator and interoperator comparative data analysis of the qEEG raw measures was limited to the Cadwell T-Score Analysis Package, in order to undertake further statistical analyses, computer programs to convert the data files and execute the analyses needed to be developed. This would also allow results to be interpreted more readily with respect to those of other intersession qEEG studies (John et al. 1983; Gasser et al. 1985; Woerner et al. 1987; Eskenasy-Cottier et al. 1988).

Assessment also needed to be extended to the statistical software - Neurometric Analysis. This program performed the analyses independently of the operator once the epochs were selected, thus statistical software consistency could be checked by re-analysing the same epochs from one study many times, or the same epochs from many studies twice. As laboratory tests for stroke usually involve only one or two follow-up studies, the test-retest method provided a similar comparison for the intersession and statistical software consistency studies.

7.0.1 Aim

The aim of this section of the thesis was to determine:

1) intersession and intermethod EEG variability for quantitative and visual analyses on healthy subjects

2) the effect of reducing the usual p-value (<0.05) and

3) statistical software consistency when qEEG epochs were re-analysed.

7.1 METHOD

7.1.1 Subjects

Twenty healthy volunteer subjects were assessed. Subject details with respect to ethics, consent, clinical examination and exclusion criteria are detailed in Chapter 6. In addition, as this was an intersession study, subjects were informed that a second test would be performed approximately 2 weeks after the first.

7.1.2 Equipment

The Spectrum AT 386 was used for recording the EEG and performing the quantitative analyses. Hardware, software and machine settings were the same as those used for the intra- and inter-operator studies, as discussed in Chapter 6.

For visual analysis, the EEG was printed using a Nihon Kohden 4317F EEG machine, a 17-channel, microprocessor-controlled EEG machine with 2 additional marker channels (Nihon Kohden Corporation, n.d.). The machine was interfaced with the Spectrum by means of individual direct current connectors; sensitivity was set at $30\,\mu V/mm$ and the time constant to direct current.

The EEG was printed using the standard (16 channel) laboratory montages, i.e., parasagittal average (Pa), temporal average (Ta), parasagittal (P), temporal (T), fronto-occipital (FO) and central plus frontal and occipital (C+), as documented in TQEH Neurophysiology Laboratory standard operating procedures manual (Hamilton-Bruce 1994). One minute of trace was printed for each of the averaging montages, the remainder of the trace being divided between the four remaining montages.

To further analyse the qEEG Neurometric Analysis intersession data, additional hardware and software were used. The hardware was a locally-made IBM cloned Protech, with a 25 MHz Intel 80386-25CPU, 4 Mb RAM, 80387-25 maths coprocessor, 120 Mb hard disk, and one 1.2 Mb and one 1.44 Mb floppy disk drive and VGA screen, and was linked to a Canon LBP-8III laser printer via a selection box.

Software included:

a) Microsoft® MS-DOS® version 5.0 (Microsoft Corporation 1991), as the operating system

b) Microsoft® QuickBASIC™ version 4.5 for IBM® personal computers and compatibles (Microsoft Corporation 1990) used for the conversion of the raw ASCII (American standard code for information interchange) data (pre- or post-upgrade configuration) from the Spectrum to data files for subsequent statistical analysis with SPSS

c) SPSS/PC+™ version 4.0 Base (SPSS Inc. 1990a) and SPSS/PC+ Statistics™ version 4.0 (SPSS Inc. 1990b) were used for data management, file handling routines and statistical procedures for the analysis of Spectrum qEEG files

d) GB-STAT™ (Friedman 1991), an integrated data-management, statistical analysis and graphics package used for independent user-friendly checking of basic statistics.

7.1.3   Recording

Studies were conducted as described in Chapter 6, with each study being repeated within a few weeks of the initial study.

7.1.4   Intersession EEG analysis

I performed Neurometric Analysis on all EEGs as described in Chapter 6. Each of the printed EEGs was assessed independently by an experienced Neurophysiologist/ Neurologist (Andrew Barham Black (ABB)), also without knowledge of the subject's identity. The second analysis was made with no knowledge of the first, for both methods.

Subsequent to an upgrade, Neurometrics reported the data as Absolute Power, Relative Power, Mean Frequency, inter- and intra-hemisphere Power Asymmetry and Coherence. The reports for the Neurometric Analysis Discriminants have been described in Chapter 6.

Assignment of records by visual analysis was as follows:

consistent delta activity (>10%) approaching or above background alpha amplitude *OR* episodic theta and alpha *OR* asymmetrical theta
- considered abnormal

some theta of higher amplitude than background alpha, but no consistent asymmetry and no episodic theta
- considered borderline

domination of the EEG by alpha or beta frequencies and absence of the above
- considered normal.

7.1.5 Statistical software consistency

After the first Neurometrics Analysis was performed, the same epochs were re-analysed.

7.1.6 Statistical analyses

7.1.6.1 Subject analyses

Intersession variability of the quantitative data generated by Neurometric Analysis was assessed for each subject using the Cadwell T-Score Analysis, correlated (paired) where the number of epochs was the same in both tests and independent (unpaired) where they differed (2 tails, $p \leq 0.05$). Monopolar and bipolar assessments were made, assessing the total and maximum number of significant differences detected, respectively.

The effect of changing the p-value was documented for the bipolar assessment, the new p-values being determined by dividing the usual p-value of 0.05 by the number of electrodes (4 and 8), then rounding the result to the nearest 2 or 3 decimal points, as appropriate.

7.1.6.2 Group analyses

Comparison was by means of the paired samples t-test and Pearson's correlation coefficient, using SPSS (2 tails, $p \leq 0.05$). As correlation reflects a concomitant change in the data from one session to the next, this analysis was only undertaken for comparison with the work of John et al. (1983), rather than for clinical application. As such, it was limited to the parameters assessed and reported in their study. Raw ASCII data (SPECTRUM .S32 files) were converted internally to analyse the qEEG intersession data using SPSS (O'Halloran and Hamilton-Bruce 1995). GB-STAT was used on a limited basis to verify in-house programming for analysis of data.

7.1.6.3 Comparison of reports

Association between the Neurometric Analysis Discriminants reports, visual reports, and the Neurometric Analysis Discriminants and visual reports was assessed for each group by means of Cohen's Kappa statistic, using SPSS.

7.1.6.4 Statistical software consistency

The monopolar, bipolar and multivariate measures for the parameters Absolute and Relative Power, Mean Frequency, Power Asymmetry and Coherence were compared using the correlated Cadwell T-Score Analysis software. The results were printed for evaluation.

7.2   RESULTS

Eleven female and nine male healthy subjects (mean age 33.9 years, SD 10.9 years, range 19.0 - 56.0 years) were assessed. The repeat studies were performed 7 to 23 days after the initial study (mean 10.3 days, SD 4.2 years). None of the subjects was found to have a condition requiring exclusion.

7.2.1   Subject analyses

T-Score analyses were correlated (paired) for 16 subjects and independent (unpaired) for 4, the latter where fewer than 48 epochs were selected (n=47) for individual qEEG analyses. The results are not presented, as a total of 15,200 monopolar and 3,840 bipolar measures and 9520 T-Score/Difference Z-score Measures were generated; instead, for each parameter within each frequency band, the maximum number of significant differences between studies are tabulated.

Table 7.1 shows the total number of significant differences in measurements in each parameter for all electrodes, using the monopolar T-Score Analysis software (2 tails, $p \leq 0.05$), with Absolute Power showing the largest number of significant differences throughout.

Table 7.1: **Total number of significant differences between monopolar measures in the two studies using the T-Score Analysis software (2 tails, p≤0.05).**

Parameter	n.o.e.	Delta (%)	Theta (%)	Alpha (%)	Beta (%)
		Total number of significant differences in measurements in each parameter for all electrodes			
MAP	420	93 (22.1)	147 (35.0)	147 (35.0)	201 (47.9)
MRP	420	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
MMF	420	9 (2.1)	2 (0.5)	0 (0.0)	7 (1.7)
MPA	160	6 (3.8)	2 (1.2)	1 (0.6)	2 (1.2)
IMPA	160	2 (1.2)	0 (0.0)	1 (0.6)	3 (1.9)
MCoh	160	1 (0.6)	2 (1.2)	1 (0.6)	4 (2.5)
IMCoh	160	3 (1.9)	3 (1.9)	2 (1.2)	0 (0.0)

n.o.e.: number of electrodes (20 subjects each with 21 electrodes for the first 3 parameters and 8 electrodes for the remainder)

MAP/MRP	-	Monopolar Absolute Power/ Monopolar Relative Power
MMF	-	Monopolar Mean Frequency
MPA/IMPA	-	Inter-/Intra-hemisphere Monopolar Power Asymmetry
MCoh/IMCoh	-	Inter-/Intra-hemisphere Monopolar Coherence

For bipolar measures, using the Cadwell T-Score Analysis Package, the maximum number of significant differences between the 2 studies were 7, 7, 8, and 7 of 8 bipolar Absolute Power scores in the delta, theta, alpha and beta frequency ranges, respectively ($p \leq 0.05$, 2-tailed t-test). Use of a lower p-value, i.e., 0.01 or 0.005 did not change this. For Relative Power, the maximum number of significant differences between the 2 studies were 0, 1, 1 and 1 of 8 scores; lowering the p-values (0.01 or 0.005) resulted in a change to a score of zero for all frequency bands. Power Asymmetry showed the maximum number of significant differences to be 1, 1, 1 and 2 of 4 scores, with use of either of the lower p values reducing the single significant difference found in the alpha frequency band to zero, all other differences remained unchanged. Similarly, for Coherence, where the maximum number of differences was one for all frequency bands, use of either lower p-value resulted in a change to zero in only the alpha frequency band. To provide an individual perspective, the subject with the least differences throughout showed significant differences in Absolute Power only, i.e., 1, 1, 0 and 2 in the delta, theta, alpha and beta frequency ranges. At the $p \leq 0.01$ level, these differences changed to 0, 0, 0 and 2, while at the $p \leq 0.005$ level, the 2 significant differences in the beta frequency changed to 1.

7.2.2 Group analyses

Table 7.2 shows the electrode positions where significant differences (2-tails, $p \leq 0.05$) are found in the intersession comparison using the t-test (SPSS).

Table 7.2. Intersession comparison by means of the t-test (SPSS) for each electrode position, those with significant differences are tabled (2-tails, p ≤ 0.05).

Parameter	Delta	Theta	Alpha	Beta
MAP, 21 electrodes	ns	ns	ns	$Fp_{1,z,2}$
MRP, 21 electrodes	ns	ns	ns	ns
MMF, 21 electrodes	T_4, F_z	ns	ns	ns
MPA, 8 electrodes	T3/4	ns	$Fp_{1/2}$, $T_{3/4}$	$Fp_{1/2}$
IMPA, 8 electrodes	ns	ns	ns	ns
MCoh, 8 electrodes	ns	ns	$O_{1/2}$, $T_{5/6}$	ns
IMCoh, 8 electrodes	Fp_2/F_4	ns	ns	ns
BAP, 8 electrodes	ns	ns	ns	$T_{3/5}$
BRP, 8 electrodes	ns	$T_{4/6}$	ns	ns
BPA, 4 electrodes	ns	ns	ns	ns
BCoh, 4 electrodes	$C_3C_z{:}C_4C_z$	ns	ns	ns

ns: no significant difference

MAP/MRP	-	Monopolar Absolute Power/Monopolar Relative Power
MMF	-	Monopolar Mean Frequency
MPA/IMPA	-	Inter-/Intra-hemisphere Monopolar Power Asymmetry
MCoh/IMCoh	-	Inter-/Intra-hemisphere Monopolar Coherence
BAP/BRP	-	Bipolar Absolute Power/ Bipolar Relative Power
BPA	-	Bipolar Power Asymmetry
BCoh	-	Bipolar Coherence

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Intersession comparison for the four frequencies by means of correlation for each electrode position indicated positive correlation (2 tails, $p \leq 0.05$) for the parameters Monopolar and Bipolar Absolute and Relative Power, as illustrated below for Bipolar Relative Power.

Table 7.3: Bipolar intersession variability - correlation coefficients for Relative Power (2-tails, $p \leq 0.05$).

Frequency	Delta	Theta	Alpha	Beta
LF	0.86	0.93	0.94	0.92
LT	0.93	0.86	0.92	0.93
LC	0.86	0.94	0.95	0.95
LP/O	0.92	0.86	0.92	0.92

LF	-	left frontal	:	F_7/T_3
LT	-	left temporal	:	T_3/T_5
LC	-	left central	:	C_3/C_z
LP/O	-	left parieto-occipital	:	P_3/O_1

7.2.3 Comparison of reports

Noteworthy changes in the qEEG, using the Neurometric Analysis Discriminants reports, were 4 reports assessed as abnormal in the initial study and borderline on retest. For visual assessment 6 initially borderline results were considered abnormal on retest, with only one of the abnormal Neurometric Analysis Discriminants and visual reports being from the same subject. All other changes were between the categories of normal and borderline. Statistical comparison of Neurometric Analysis Discriminants intersession reports showed significant association ($p \leq 0.05$) with a kappa of 0.45, while comparison of visual analyses yielded a kappa of 0.32. Comparison of the quantitative method with the visual assessment, however, showed little agreement, with a kappa of -0.04 for the initial study, and 0.19 for the retest.

7.2.4 Statistical software consistency

The printed results consisted of more than 20,000 measures. Visual scrutiny showed them to be identical. Comparing the raw measures by means of the T-Score Analysis software showed no differences between analyses 1 and 2, for all measures through all frequencies for the 20 subjects. Measures were reported as 0.0 in all cases.

7.3   DISCUSSION

7.3.1   Subject analyses

Assessment of subject intersession variability using the T-Score Analysis software showed that most significant differences occurred in the Absolute Power measures, findings in keeping with those of John et al. (1983) and Sebban et al. (1988). Relative Power, Mean Frequency, Power Asymmetry and Coherence showed fewer significant differences. These findings also reflect those of my intra- and interoperator studies (Chapter 6; Hamilton-Bruce 1991; Hamilton-Bruce et al. 1991b; Hamilton-Bruce et al. 1991c (refer to appendices 6.4, 6.5 and 6.6, for the last 3 references, respectively)), where Absolute Power differences in qEEG analyses were attributed to the selection of epochs of different amplitude and the detection of fewer differences in the other parameters was attributed to reliability or lack of independence for the comparisons. However, Relative Power, Power Asymmetry and Coherence measures are not as stable in the current study, which may have been reflective of some intersession differences in the EEG.

The largest difference in monopolar Power Asymmetry was found in a subject showing a significant change with slow wave activity, including 3 Hz delta components of widespread distribution, on re-test. The neurological examination and questionnaire did not reveal a significant clinical history, but she volunteered information at the time of the second test that she felt stressed at work that day and was menstruating.

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Significant oscillations in EEG correlations as a function of menstrual cycle (with phase synchronisation) have been reported by Solís-Ortiz et al. (1994), although Corsi-Cabrera et al. (1997) did not detect significant differences between recording sessions when menstrual sessions were randomly distributed among the group. Visual assessment of the record from the subject in question in my study revealed paroxysmal slow activity ('a period of widespread asymmetrical delta activity on retest'), which was confirmed by independent assessment (a second Neurophysiologist/Neurologist in the Neurology Department, Grant Hartnell Purdie (GHP)), indicating that this type of activity may be present within the population and does not necessarily indicate clinical abnormality.

As noted previously, with the generation of many raw measures in a quantitative report, some differences may occur by chance alone (Oken and Chiappa 1986; Abt 1990; Hamilton-Bruce et al. 1991b; Jonkman et al. 1992b). Using Neurometrics and allowing for the number of cells in the matrices, Jonkman et al. (1992b) indicated that a probability of less than 0.01 may be more acceptable. However, the use of different probability cut-offs in my study (0.05, 0.01 and 0.005) did not affect the number of Absolute Power parameters declared significant in my study, and only a few changes were noted in the other parameters.

7.3.2 Group analyses

Group intersession comparison by means of the paired t-test (SPSS) for each electrode showed only a few significant differences scattered through the frequencies and parameters (Table 7.2). This is in contrast to the t-test findings in the individual studies where most cells in Table 7.1 showed changes. The latter reflects a difference between the epochs selected from an individual trace (attributable to a variety of causes) and the former a difference between groups.

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Differences, where present, could be due to true biological change, chance or contamination of the EEG, separately or in combination. Commonly occurring artefacts include eye movement, blink, muscle, movement, poor electrode contact and ambient electrical fields with the delta frequency range, for example, being more prone to eye movement contamination than the other bands (Gasser et al. 1985; Kahn et al. 1988; Pollock et al. 1991). Neurometric Analysis, however, excludes low delta and high beta to minimise some of these (John et al. 1983).

Where significant differences are due to chance, clustering would not be expected. Thus, for example, with Monopolar Mean Frequency for delta, a significant change in 2 unrelated electrodes (T4 and Fz) in a total of 21 electrodes in healthy subjects in a single intersession study (Table 7.2) would not be interpreted as showing biologically meaningful change between sessions. Similar conclusions may be drawn for the other non-clustered differences. Some clustering does appear in this study in Absolute Power, for example, in the beta frequency, at the 3 frontopolar electrode positions (Fp1,z,2) for the monopolar montage and the left temporal region (T3/5) in the bipolar montage. Monopolar Power Asymmetry, a derived parameter, also shows this and it could be reflective of some EMG activity. While a variety of techniques may be employed to obtain relaxation, complete elimination of muscle tension artefact cannot always be achieved. Gasser et al. (1985) also reported that the beta frequency was, to some extent, less reliable. Coben et al. (1990) reported more or less continuous muscle artefact in one or several channels seen commonly in normal and patient (mild probable Alzheimer's disease) groups; they therefore removed entire channels if EMG artefact was judged to exceed 20μV for the majority of the time, an option not available to SPECTRUM users.

Overall, however, with only 14 significant changes in 102 comparisons through 4 frequencies, many, if not most of these changes could have occurred by chance. As the clinical section of this thesis also entails the use of healthy control subjects, analyses can be replicated on a separate database. Differences, if due to chance, would not be anticipated to be reproduced in exactly the same way.

With respect to intersession data correlation, the measures for all electrode positions through all frequencies showed positive correlation for monopolar and bipolar Absolute and Relative Power. John et al. (1983) reported Relative Power intersession correlations on learning disabled children as varying from 0.52 (theta, left frontal) to 0.97 (alpha, left temporal) between tests carried out one week apart. The comparable Relative Power correlations carried out on 20 healthy subjects in my study varied from 0.86 (delta: left frontal and central; theta: left temporal and parieto-occipital) to 0.95 (alpha and beta: left central) for seven to twenty-three days between tests, as documented in Table 7.3. Gasser et al. (1985), using different software, reported Relative Power correlations ranging from 0.37 (delta, C4) to 0.90 (beta2, Pz) in children who underwent tests approximately 10 months apart. Hooijer et al. (1990) reported intersession correlations ranging from 0.50 (alpha) to 0.68 (theta) on 20 patients with senile dementia of the Alzheimer's type who were retested after 24 hours. Overall, my results on healthy adult subjects compare well with these earlier studies, although it should be noted that adult findings may not be comparable with those of children.

7.3.3 Comparison of reports

Differences from the database may also occur due to different selection of subjects, the quality of electrophysiological data, correctness of classification, choice of comparative parameters and mental activity (Kahn et al. 1988; John et al. 1989; Kohrman et al. 1989; Logar et al. 1993). While fewer qEEGs than EEGs were classified abnormal, using a database not generated in my department may partly account for the four initial abnormal qEEG classifications. However, unless referred to a normative database, evaluation of quantitative measures and topographic maps of EEG measures is difficult (John et al. 1989).

Thus a laboratory needs to decide whether to use a database collected elsewhere or develop its own. In the case of the former, it should be noted that the algorithms developed in other laboratories to allow for age, gender and other significant factors may not be applicable to the new data; thus database software needs to be issued with this caveat, although this would not necessarily avoid inappropriate use.

With respect to individual laboratory reference range development, the software needs to be available or written to allow the database to be used appropriately. However, collection of adequate reference data is time-consuming and expensive, and therefore may not be performed routinely; furthermore, control groups may not necessarily reflect all the changes seen in patient groups.

For within-method intersession assessment, agreement was shown for qEEG Neurometric Analysis Discriminants and visual reports, respectively. The changes that were noted could be due to EEG changes on retest and/or intra-operator variability. If the Neurometric Analysis Discriminants method of reporting was to be considered for use in my laboratory, the lack of agreement between the methods would need to be investigated further. However, as it was not developed initially for stroke assessment and is not available in my laboratory for clinical use, this issue will not be pursued further.

7.3.4 Statistical software consistency

The re-analysis of epochs yielded identical results, as anticipated with a process involving digital reprocessing of data. This process is, however, dependant on the software. If, as part of an upgrade, changes were made which affected the measures used in the report, quantitative analysis of data would need to be repeated to allow comparison with pre-upgrade studies and manufacturers would be expected to emphasise this. Laboratory staff would also need to remember to re-analyse work done at any stage pre-upgrade for comparison with post-upgrade studies, a requisite that could be overlooked with a change of staff and/or the passage of time, if not emphasised.

Thus databases and subsequent software changes need to be examined before and during incorporation of such equipment into the laboratory's battery of tests, and at intervals thereafter, for example after an upgrade, in order to develop and maintain user confidence in the equipment (Richards and Hamilton-Bruce 1994 (refer to appendix 5.3)).

7.4   CONCLUSION

To determine intersession qEEG and EEG variability, 20 healthy subjects underwent EEG recordings twice. The recordings were analysed quantitatively and visually. qEEG differences were maximal for Absolute Power in individual intersession studies. A few intra-individual changes were also seen in parameters considered to be more reliable (Relative Power, Power Asymmetry and Coherence), probably reflective of fluctuation and change in the EEG. Physiological features (slow wave activity) noted in one volunteer were considered to account for some of the changes seen, although such changes were not necessarily indicative of underlying pathology. Altering the significance level ($p \leq 0.05$ to $p \leq 0.01$ and $p \leq 0.005$) did not markedly affect the number of statistically significant differences detected.

Group intersession comparison showed changes that mostly could be ascribed to chance or non-meaningful statistical differences in low frequency parameters, for example delta in healthy subjects. The design of the clinical section of this thesis will allow subject and group analyses to be replicated on a different sample and thereby assess whether the findings were due to chance. Although within-method reports (visual and quantitative analyses) showed significant association, between method reports (visual versus quantitative) did not, the latter being a comparison of methods of analysis using different criteria. With respect to Neurometric Analysis Discriminants, this method of reporting was not considered appropriate for stroke localisation and, as such, will not be used in the clinical section of this thesis. The software showed consistency with respect to statistical analyses, however, upgrades could affect analyses and, as such, need to be monitored.

The data illustrated some of the differences that may be seen in a group of healthy subjects. These need to be taken into account when establishing the limitations of the technology, in order to allow better utilisation of the modality clinically. The work in this chapter has verified some of my earlier findings and increased knowledge in intersession variability (Hamilton-Bruce et al. 1992, 1995 (refer to appendices 7.1 and 7.2, respectively)), prior to using qEEG (Neurometric Analysis) in the clinical study.

CHAPTER 8

CONVENTIONAL AND TOPOGRAPHIC qEEG AND SEP STUDIES IN STROKE PATIENTS AND CONTROL SUBJECTS -

AIM AND METHOD

8.0   AIM

8.0.1   Main aims

The main aims were to assess CT, EEG, topographic qEEG, conventional (3-channel) and topographic (21-channel) SEP studies for:

1) diagnostic lateralising ability in acute ischaemic stroke patients with no previous history of stroke within the first 48 hours of the stroke (the first session), by determining true and false positive test results, sensitivity, specificity and positive and negative predictive values

2) differentiation of cortical from non-cortical acute ischaemic stroke, using univariate and multivariate analyses

3) differentiation of cortical from non-cortical acute ischaemic stroke after exclusion of patients identified by CT as having had a previous stroke which had not been detected during the clinical assessment, as having subsequently developed haemorrhagic stroke, and as having any other disorders which could have affected the results

4) differentiation of cortical from non-cortical acute ischaemic stroke after exclusion of patients with no radiological evidence (CT or MRI) of acute ischaemic stroke

5) differentiation of cortical from non-cortical acute ischaemic stroke after exclusion of patients identified by CT as having had a previous stroke which had not been detected during the clinical assessment, as having subsequently developed haemorrhagic stroke, as having any other disorders which could have affected the results, and with no radiological evidence (CT or MRI) of acute ischaemic stroke

6) determining whether diagnostic and differentiation effects observed in the first session in all subjects and in the total patient group respectively (aims 1 and 2), were sustained in the second session

7) determining the prognostic value of the studies (CT and electrophysiological studies) with respect to stroke patient outcome as measured by the Barthel Index

8) determining the effects of inclusion of nominated studies (CT, EEG) in the analyses for differentiation and prognosis in the first session.

8.0.2 Additional aims

9) determining qEEG intersession variability in the control subjects independently and also in aggregate

10) determining the prognostic value of the modified Canadian Neurological Score and Functional Independence Measure with respect to stroke patient outcome, as measured by the Barthel Index

11) determining conventional SEP reference ranges for healthy control subjects

12) determining differences in the conventional SEPs between stroke patients and control subjects

13) determining differences in the conventional SEPs between cortical and non-cortical stroke patients

14) determining the prognostic value of the conventional SEPs with respect to stroke patient outcome, as measured by the Barthel Index.

8.1 METHOD

8.1.1 Subjects

8.1.1.1 Patients

Type

The study was performed prospectively on acute ischaemic stroke patients with no previous history of stroke, admitted consecutively to TQEH between 1992 and 1994.

Inclusion and exclusion criteria

Inclusion in the study was based on:

a) fulfilment of clinical criteria for acute unilateral ischaemic stroke (within 48 hours of onset) at the time of admission, as assessed by a qualified medical officer from the Neurology Department

b) agreement of the patient's clinical manager

c) informed signed consent from the patient or relative (refer to appendices 8.1 (patient information sheet) and 8.2 (patient consent form))

d) my availability to coordinate all assessments and investigations and to perform all electrophysiological studies.

Exclusion from the study was based on:

a) the finding of haemorrhagic stroke on the first CT

b) history of previous stroke

c) history of other disorders or diseases which could affect the central nervous system.

8.1.1.2 Controls

Type

For the control database, healthy volunteers were recruited from hospital staff and friends, as well as local residents and workers between 1992 and 1994, by advertisement for middle-aged to elderly subjects (refer to appendix 8.3 for an example of an advertisement). Control subjects were not paid for volunteering, but were thanked verbally and by letter (refer to appendix 8.4).

Inclusion and exclusion criteria

Controls were provided with an information sheet (refer to appendix 6.1) and consent form (refer to appendix 6.2) and screened verbally by me prior to clinical assessment (refer to appendix 6.3). They could be excluded if taking medication or non-prescription drugs expected to affect the EEG or if a disorder or disease was discovered which could affect the nervous system at any stage up to the time of the clinical screen prior to electrophysiological investigations.

Verbal screening also covered the intake of alcohol and alcoholism. However, as stroke patients may have ingested alcohol prior to the stroke, the controls' recent alcohol intake was merely noted, and provided it was limited to moderate social drinking (one or two/'a few glasses') one to two days before the electrophysiological studies, this was not used as a reason for exclusion from the study.

Full screening was by assessment of the completed questionnaire and subsequent examination by a qualified medical officer in the Neurology Department, to allow exclusion of subjects as detailed above (refer to appendix 6.3, section: medical and neurological screen). Potentially questionable findings were referred to one experienced Neurologist/Neurophysiologist (ABB) for a final decision on inclusion or exclusion.

8.1.2 Investigations and assessments

8.1.2.1 Patients

Timing

Patients were entered in the trial and the initial investigations were performed within the first 48 hours. Investigations were repeated on patients who were willing to undergo repeat studies before discharge or within approximately 2 weeks of the event.

Clinical assessment

Two clinical assessments were performed by a qualified medical officer in the Neurology Department including completion of a clinical screen (refer to appendix 8.5) and assessing the modified Canadian Neurological Score for each clinical assessment (refer to appendix 8.6). The patient's medication was not altered in any way through participation in the study.

The first clinical assessment was performed within 48 hours of the stroke, the second being timed to coincide with the radiological and electrophysiological studies.

Radiological investigations

These included:

a) a non-contrast CT, performed by the duty radiographer in the Radiology Department at The Queen Elizabeth Hospital, within 48 hours of the stroke for the first session and within 2 weeks for the second session

b) an MRI, if requested by the patient's clinical manager, performed by the duty radiographer at the Flinders Medical Centre, Adelaide, when a booking time was available. (MRI assessment was not a part of this study and 'radiological' or 'radiology' will refer to CT, unless otherwise specified.)

Clinimetric assessments

These included:

a) the modified Canadian Neurological Score performed by a qualified medical officer in the Neurology Department at the time of the clinical assessment, the maximum score being 11.5

b) the Barthel Index assessment (refer to appendix 8.7) performed by qualified Occupational Therapists (Cherie Archer (CA) and Stacey George (SG)) from the Occupational Therapy Department, the maximum score being 100. These assessments were undertaken during the hospital stay on completion of the first radiological and electrophysiological studies and approximately three months later - the second assessment being a telephonic interview with the patient or carer

c) the Functional Independence Measure (refer to appendix 8.8) was assessed by qualified medical officers from Rehabilitation Medicine or the Director of the Rehabilitation Medicine (RL), the maximum score being 126. These assessments were undertaken during the hospital stay after completion of the first radiological and electrophysiological studies and again 6 or more months later - the latter assessment being a telephonic interview with the patient or carer.

Electrophysiological assessments

These were performed by me within 48 hours of the stroke and repeated within approximately 2 weeks of the stroke. The date of the second session was determined by the patient's length of stay and the availability of booking times for the studies and assessments.

The studies included:

a) a conventional EEG

b) a topographic qEEG (a few additional topographic qEEGs were also recorded in some cases to allow visualisation of change over time)

c) a conventional SEP

d) a topographic SEP.

8.1.2.2 Controls

The controls underwent the same electrophysiological investigations as the stroke patients, but did not undergo radiological investigations or clinimetric testing. Clinical assessment was undertaken as detailed in 8.1.1.2. The date of the second session was determined by subject and laboratory availability, the intention being to repeat the investigations approximately one to two weeks after the first session.

8.1.3 Equipment and techniques

8.1.3.1 Radiology

The CTs were performed in the Department of Radiology at The Queen Elizabeth Hospital using a Siemens Somatom Plus, and MRIs, when undertaken, were performed using a Siemens Magnetom Impact 1 Tesla in the Department of Radiology at Flinders Medical Centre, Adelaide. Standard departmental protocol was followed for these investigations.

8.1.3.2 Electrophysiology

Electroencephalographic studies were performed on the Cadwell Spectrum 386 AT, using the method detailed in Chapters 6 and 7.

SEP studies were also performed on the Cadwell Spectrum 386 AT, using the Cadwell Electrocap (based on the 10/20 system) for the 21-channel topographic SEPs, with an earlobe reference contralateral to the side being stimulated. The Erb's Point electrode was connected to Fp1, as recommended by Cadwell, as no spare channels were available. The conventional 3-channel SEP method used Fz as the reference electrode, the active recording electrode being C3'/C4' (between C3 and P3, two centimetres posterior to C3, and between C4 and P4, two centimetres posterior to C4, respectively) for right and left median nerve stimulation, respectively, as well recording over Erb's Point and the second cervical process (C2).

Filters ranged from 30 Hz to 500 Hz (preset and unalterable) for topographic SEP software used, 5 Hz to 2 KHz for conventional scalp recorded SEPs and 10 Hz to 3 KHz for Erb's Point and C2 recordings. Sweep speed was 5 msec/div for conventional SEPs and 10 msec/division for topographic SEPs (unalterable in the case of the latter). Stimulation was at a rate of 9.72 Hz for the topographic SEPs (preset and unalterable) and 4.86 Hz for the conventional SEPs, pulse width being 100μseconds for both.

A minimum of 1000 responses per trial was averaged for the topographic studies and 250 responses per trial for the conventional studies, with at least two trials per arm being performed. On completion of the last trial, a grand average of all trials was performed for both topographic and conventional SEPs. Neither patients nor controls were sedated for any of the electrophysiological studies. 21-channel SEPs were retrieved and mapped using Cadwell standard and sequence mapping options (4 and 12 voltage maps per page, respectively) plotted at operator selected times and printed in colour using a Hewlett Packard Paintjet printer. 3-channel conventional SEPs were labelled (Erb's Point, C2, C3'/C4') and printed using a Canon LBP-8III laser printer, as were the 21-channel traces.

Arm length was measured by means of a tape measure from C2 to the styloid process of the radius. Arm temperature was measured on the medial surface of the middle of the fore-arm, using an Anritsu digital surface thermometer HLC-80P.

8.1.4 Diagnostic classification

Final diagnostic classification was made by one experienced Neurologist (ABB), following the second clinical assessment. CT scans and reports were all checked by the same Neurologist. Where the CT scans or official CT reports were unclear, they were reviewed without clinical details by a consultant radiologist at TQEH for a final opinion. In any ambiguous case, a final diagnosis was made (ABB) after a full review of all the clinical and CT information.

The infarct was deemed cortical if the first or second CT showed a clinically appropriate recent cortical hypodensity or, in the absence of such, if there was persuasive clinical evidence of cortical involvement such as aphasia, agnosia and apraxia, as identified during the clinical assessment. Otherwise the stroke was categorised as non-cortical. MRI findings, where positive, were used to assist in classification.

Subjects with previous strokes (identified by CT, not clinical history) and non-stroke disorders, and those with negative radiology (CT and MRI) studies were identified for exclusion from the database during re-analysis of some of the data.

8.1.5 Analyses and interpretation of test results

8.1.5.1 Radiology

Unblinded assessment of the CT, for the patient's unit record, was performed visually by a qualified Radiologist or Radiologist-in-training in the Department of Radiology, at The Queen Elizabeth Hospital. All CT scans and reports were also checked by the Neurologist (ABB) before determining the final diagnostic classification; unclear scans or reports were dealt with as detailed in 8.1.4.

The first CT was subsequently interpreted blinded at the end of the study, by a senior registrar (Sinead Hanley (SH)), for the purpose of this study, with CTs from this stroke project being randomly interspersed with CTs on patients sent to Radiology for CTs for any disorder other than ischaemic stroke.

MRIs were reported unblinded by Radiologists from TQEH or Flinders Medical Centre.

8.1.5.2 Electrophysiology

Neurometric qEEG

Subsequent to the departure of the patient or control, the Neurometric method was used for topographic qEEG analysis. Where possible, forty-eight 2.5 second epochs were selected from the resting eyes-closed section of the EEG, with use of the artefact reject mode assisting this selection. Where 48 epochs could not be achieved, fewer were accepted, a minimum of 24 being required for full Neurometric assessment.

For the qEEG measures, highlighting (by the software) indicated those falling at or outside the 1.96 standard deviation limit of the Neurometric normative database. Z-score measures and maps for Absolute Power, Relative Power, Power Asymmetry and Coherence were produced by comparing the patient's data with the Neurometric normative database.

Conventional SEPs

The conventional SEP absolute latency variables were EP, N13, N20, P22, P25, P28, N30 and P45. Absolute latencies were measured in milliseconds, from the time of stimulation to the peak or trough (negativity or positivity, respectively) of the major waves, as listed. The conventional SEP interpeak latency variables assessed were EP-N13, N13-N20, N20-N30 and N20-P45. These were calculated by subtraction of the shorter peak latency from the longer peak latency in each case.

The three SEP amplitude (A) variables (measured in microvolts) were:

a) A1 - measured from baseline to the peak of the N20. Absence of the N20 was recorded as 0.00 microvolts

b) A2 - measured from the peak of the N20 to the trough of the P22/P25/P28 complex, whichever was present and most prominent. Absence of the N20 and P22/P25/P28 complex was recorded as 0.00 microvolts

c) A3 - the sum of the amplitudes of three components:

- N20 to P22/P25/P28 (peak (or baseline in the absence of a peak) to trough, as described above) - component 1,

- P22/P25/P28 (whichever was most prominent) to N30 (trough to peak) - component 2, and

- N30 to P45 (peak to trough) - component 3.

Absence of any part of components 2 or 3 was recorded as 0.00 microvolts.

Topographic SEPs

Twenty-one channel SEPs were mapped using the Cadwell standard mapping protocol for the 2 first major negativities and 2 first major positivities (one page of 4 maps), as well as the Cadwell sequence mapping protocol, mapping at 1 second intervals, to display changes between 15 and 50 milliseconds (3 pages of 12 maps per page).

Interpretation of electrophysiology results

For each study, i.e., EEG traces, qEEG printouts (measures and maps), conventional SEP traces and topographic SEPs (traces and maps) for stroke patients and controls were randomised (Diem and Seldrup 1982) for interpretation of the electrophysiological studies, which was performed with the interpreter blinded to the status of the subject.

Polygraph EEGs were assessed visually and interpreted by one experienced Neurologist/Neurophysiologist (ABB). The EEG was considered abnormal (diagnostic) if there was consistent (>10%) ipsilateral delta approaching or above background alpha amplitude, or episodic theta and alpha, or asymmetrical theta. Topographic qEEGs were interpreted by me. The topographic qEEG was considered abnormal if there was increased (≥ 1.96 SD) ipsilateral delta or theta at 2 or more adjacent electrode sites in 2 or more parameters (absolute power, relative power, power asymmetry); or if these abnormalities were present in 1 parameter and in both frequency bands; or if there was decreased ipsilateral alpha (≤ 1.96 SD) in one parameter together with increased ipsilateral delta or theta in 1 (or more) parameter(s).

SEP interpretation was by one experienced Neurologist/Neurophysiologist (Con Yiannikas (CY)). Traces were superimposed and, using laboratory reference range data, N13-N20 interpeak and interside latency differences of more than 0.7 msec, N20-P22/P25/P28 interside amplitude differences of more than 50% or absence of SEPs were determined to be abnormal, as were morphology changes, i.e., absence or decreased amplitude (more than 50%) of later waves up to the P45. 21-channel traces and SEP maps were assessed at the same time.

Clinimetric outcome assignment

Prior to analyses being undertaken, the Barthel Index scores were dichotomised as follows: outcome assignment of 'poor' was considered to be indicated by a Barthel Index of less than or equal to 35 for the first session and less than or equal to 60 for the second session (Chua et al. 1995), the latter assessed approximately 3 months after the stroke, when the patient was out of hospital.

8.1.6 Statistical analyses

8.1.6.1 Radiological and electrophysiological categorical data assessment

Validity and characterisation

To assess the individual studies, namely CT, EEG, topographic qEEG, conventional (3-channel) and topographic (21-channel) SEPs, for lateralisation in stroke patients, validity and characterisation were assessed by determining true and false positive test results, sensitivity, specificity and positive and negative predictive values for the first and second sessions.

Cortical/non-cortical stroke prediction

To analyse the data further, a technique was needed to determine the association between the binary dependent variable (outcome, i.e., type of stroke) and a set of independent variables (indicator or predictor variables, i.e., radiological and electrophysiological studies). As the data were fragmented, i.e., for every individual not all the measures were necessarily present, a number of steps were undertaken prior to the multivariate analysis. Furthermore, as logistic regression is not available in most routine laboratories, a chi-square test was performed as an initial screen of the categorical data, to determine significant univariate associations. Logistic regression was then used to develop univariate associations when possible, and to identify candidate prediction variables for subsequent entry into multivariate logistic modelling.

The general mathematical formula used for the probability of outcome was:

probability (p) = $e^\psi / (1 + e^\psi)$

where ψ = $B_0 + B_1X_1 + B_2X_2 + ... + B_nX_n$

B_0 = the constant

B_1 to B_n = coefficients estimated for the respective variables

X_1 to X_n = predictor variables (CT, EEG, qEEG, cSEP and tSEP)

where 1 or 0 was entered for the predictor variable when the result was diagnostic or non-diagnostic, respectively, and qEEG was the topographic qEEG, cSEP the conventional SEP and tSEP the topographic or mapped SEP.

The probability of an event not occurring
= (1 - probability of the event occurring)

The univariate inclusion limit for multivariate logistic regression was taken at the default value of $p \leq 0.15$ by convention, and all candidate variables with $p \leq 0.15$ were considered for multivariate stepwise logistic regression.

Automated model building in the multivariate logistic regression analysis was by means of mixed stepping. The stepping procedure began with no terms in the model (refer to the equation below). At each subsequent step, the model was assessed using a likelihood ratio procedure, and a further term, if indicated (i.e., $p \leq 0.15$), was included. Iteration proceeded until no further terms passed the inclusion criteria and convergence was achieved. Once a final model was identified by this stepping procedure, it was re-estimated using all available individuals with complete data on the variables selected by the stepwise procedure to confirm the conclusion. Radiological and electrophysiological results, as well as age and gender, were included in this definition of predictor variables. This provided a model with variables which, in aggregate, were most suited to detecting cortical stroke.

Thus, statistical analyses to determine whether radiological and electrophysiological variables (CT (blinded and unblinded interpretations for the first session, unblinded only for the second session), EEG, topographic qEEG, conventional and topographic SEPs) for sessions 1 and 2 were predictive of cortical stroke, using the second clinical assessment of cortical or non-cortical stroke as the outcome variable, were:

the chi-square test ($p \leq 0.05$) and univariate logistic regression ($p \leq 0.15$), to determine candidate variables (CT, EEG, topographic qEEG, conventional and topographic SEPs) for multivariate analysis

and

multivariate logistic regression ($p \leq 0.05$) on independent variables identified in the univariate analyses

Gender was coded 1 for male and 0 for female.

For the analysis of CT data, evidence of acute ischaemic stroke was considered diagnostic and was classified as 1 for cortical stroke and 0 for non-cortical stroke.

For electrophysiology studies, ipsilateral abnormalities were considered diagnostic and scored as 1, all other results were scored as 0.

Epi Info Version 5.01 (Dean et al. 1990) was used to obtain chi-square values from 2x2 tables containing the outcome and predictor variables. Strengths of association were presented as p-values, with Yates' correction for continuity. When expected values were less than 5, p-values were derived from a Fisher's Exact test. Systat/Logit Version 2.01 (Systat, Inc. 1991) was used for univariate and multivariate analyses of categorical data and the procedure was performed independently for both sessions.

Stroke outcome prediction

To determine whether radiological and electrophysiological test variables at each session were predictive of stroke patient outcome (as measured by the Barthel Index), the statistical procedures described above were used. The test variables were CT (blinded and unblinded interpretations for the first session, unblinded only for the second session), EEG, topographic qEEG and conventional and topographic SEPs.

8.1.6.2 Clinimetric categorical data assessment

To determine whether the clinimetric variables (modified Canadian Neurological Score and Functional Independence Measure) could predict stroke patient outcome (as measured by the Barthel Index), the statistical procedures described above were used.

8.1.6.3 Control qEEG intersession studies

Control qEEG intersession studies were undertaken using the method described in Chapter 7.

8.1.6.4 SEP metric data assessment

The SEP absolute latency variables were EP, N13, N20, P22, P25, P28, N30 and P45; SEP interpeak latency variables were EP-N13, N13-N20, N20-N30, N20-P45. The three SEP amplitude variables (measured in microvolts) were A1 - measured from baseline to the peak of the N20, A2 - measured from the peak of the N20 to the trough of the P22/P25/P28, whichever was the largest, and A3 - the sum of the amplitudes: N20 to P22/P25/P28, P22/P25/P28 to N30 and N30 to P45. Amplitudes were log transformed to normalise all the data and, by convention, one was added when using logarithms, to avoid taking a logarithm of zero, i.e., $\ln(A1+1)$, $\ln(A2+1)$ and $\ln(A3+1)$. For application in the laboratory, a reverse exponentiation was made.

SEP measures, arm length, temperature and age measures were described by means of medians and ranges (minima and maxima).

SEP control reference ranges

Absolute, interpeak and interlimb latencies and absolute and interlimb amplitude differences were assessed using repeated measures analysis of variance to identify significant factors. A significance level of ≤ 0.01 was used to declare significance, due to the large number of statistical conclusions to be reached.

In a manner similar to that discussed in Snedecor and Cochran (1971), the population 95% confidence interval for a variable with no significant factors was calculated as follows:

$$\mu^* \pm 1.96 \sqrt{\text{s.e.}(\mu^*)^2 + (\sigma^*)^2}$$

where μ^*, s.e. (μ^*) and σ^* are the sample estimates of the corresponding population mean, standard error of the mean and standard deviation.

The population 95% confidence interval for a variable with significant factors was calculated as follows:

$$\mu^*(x) \pm 1.96 \sqrt{\text{s.e.}(\mu^*(x))^2 + (\sigma^*)^2}$$

where (x) represents the appropriate significant effect as a scalar or vector depending on the number of predictors determined by the repeated measures analysis of variance

and $\mu(x)^*$, s.e.$(\mu^*(x))$ and σ^* are the sample estimates of the corresponding population mean, standard error of the mean and standard deviation.

Comparison of patient and control conventional SEP data, including stroke type (cortical/non-cortical) prediction

Repeated measures analysis of variance was also selected as the method most suited to the multivariate analysis of the metric conventional SEP data performed on two occasions, to determine significant factors and to determine differences between the patients and controls and, separately, cortical and non-cortical stroke. The factor side had two levels as did arm length and temperature (right versus left); the two levels for session were those of time, i.e., session 1 versus session 2. Age and gender were also included as factors. The linear model incorporating all these factors was fitted to each SEP variable in turn, to determine which, if any, were significant ($p \leq 0.01$).

Stroke outcome prediction

To assess the ability of the conventional SEP variables to predict stroke outcome and to develop a predictive model, logistic regression analysis was used. Stroke outcome for this analysis was defined as 'poor' when the second Barthel Index was ≤ 60 or the patient had died, and 'good' when >60.

BMDP Statistical Software Programs V and LR (Dixon 1992) were used for all analysis of variance and logistic regression analyses of SEP metric data, respectively.

CHAPTER 9

CONVENTIONAL AND TOPOGRAPHIC qEEG AND SEP STUDIES IN STROKE PATIENTS AND CONTROL SUBJECTS -

RESULTS

9.0 RESULTS

9.0.1 Subject information

9.0.1.1 Stroke patients

52 patients were assessed for this study. A further 19 were referred to the laboratory during the study, as clinical managers requested electrophysiological studies. However, these subjects either missed the 48 hour cut-off for entry to the trial, were known to have a past history of stroke, or were considered to have had a transient ischaemic attack, a psychiatric disorder (anxiety attack), demyelination or migraine and therefore were not included in the study.

Of the 52 patients assessed in the study, one was considered to have had bilateral occipital and brainstem stroke. This patient was excluded, as the bilateral stroke precluded lateralisation. The remaining patients consisted of 20 female and 31 male patients aged 44.3 to 87.1 years (median 70.2 years; mean 70.2 years, SD 10.0 years). Stroke was CT confirmed in 36 patients and MRI confirmed in one further patient with negative CTs. 37 of the 51 cases were considered to have had unilateral cortical strokes and 14 unilateral non-cortical strokes. The cortical stroke cohort consisted of 16 females and 21 males, aged 44.3 to 87.1 years (median 70.2 years; mean 70.4 years, SD 10.0 years). The 14 non-cortical stroke patients consisted of 4 females and 10 males aged 46.9 to 81.5 years (median 70.4 years; mean 69.8 years, SD 10.2 years).

The territories affected in the cortical strokes were 20 left and 14 right middle cerebral arteries, one left anterior cerebral artery, and one left and one right posterior cerebral artery. The non-cortical strokes consisted of 1 left middle cerebral penetrating artery, 2 left cerebellar, 2 left and 1 right lacunar, 2 left and 1 right brain-stem and 1 left and 4 right site-unknown strokes.

Forty-five of the 51 patients, 18 females and 27 males aged 44.3 to 87.1 years (median 70.5 years; mean 70.5 years, SD 10.1 years), underwent repeat radiological and all electrophysiological studies, 4 to 15 days after the initial studies. Some underwent limited additional testing (CTs and EEG), and in one the topographic SEP studies were marred by artefact and therefore excluded.

9.0.1.2 Controls

Sixty-six subjects volunteered as controls. One was excluded on the basis of a clinical history of moderately severe head injury with post-traumatic amnesia lasting 24 hours or more, at the age of 22 (some 40 years previously). Sixty-five healthy non-patient controls were thus assessed clinically and electrophysiologically. This control group consisted of 28 females and 37 males aged 40.4 to 95.8 years (median 64.8 years; mean 64.3 years, SD 9.6 years). Fifty-one controls, 21 females and 30 males aged 40.4 to 95.8 years (median 64.4 years; mean 64.2 years, SD 10.3 years), underwent all investigations on a second occasion, 5 to 16 days after the first.

9.0.2 Stroke patients' radiological, electrophysiological and clinimetric results

9.0.2.1 Validity and characterisation

Validity and characterisation results are tabulated below.

Table 9.1: True and false positives and negatives, using stroke and control data.

Test	True +ve 1	True +ve 2	False -ve 1	False -ve 2	False +ve 1	False +ve 2	True -ve 1	True -ve 2
CT	23/51	32/47	28/51	15/47	-	-	-	-
CTb	17/49	-	32/49	-	-	-	-	-
EEG	31/51	24/46	20/51	22/46	9/65	6/53	56/65	47/53
qEEG	31/51	20/46	20/51	26/46	1/65	0/53	64/65	53/53
cSEP	22/51	19/45	29/51	26/45	2/54	3/51	52/54	48/51
tSEP	22/50	20/44	28/50	24/44	3/54	5/51	51/54	46/51

True +ve	: true positive (TP)	: +ve in stroke patients
False -ve	: false negative (FN)	: -ve in stroke patients
False +ve	: false positive (FP)	: +ve in healthy controls
True -ve	: true negative (TN)	: -ve in healthy controls

CTb	: CT scan read blinded

Table 9.2: Sensitivity, specificity and predictive values using the stroke and control data.

Test	Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
	1	2	1	2	1	2	1	2
CT	45.1	68.1	-	-	-	-	-	-
CTb	34.7	-	-	-	-	-	-	-
EEG	60.8	52.2	86.2	88.7	77.5	80.0	73.7	68.1
qEEG	60.8	43.5	98.5	100	96.9	100	76.2	67.1
cSEP	43.1	42.2	96.3	94.1	91.7	86.4	64.2	64.9
tSEP	44.0	45.5	94.4	90.2	88.0	80.0	64.6	65.7

Sensitivity	Number of true positives in stroke patients (TP/(TP+FN))
Specificity	Number of true negatives in healthy controls (TN/(TN+FP))
Positive predictive value (PPV)	Number of true positives in total number of positives (TP/(TP+FP))
Negative predictive value (NPV)	Number of true negatives in total number of negatives (TN/(TN+FN))

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9.0.2.2 Session 1

Assessments were undertaken within the first 48 hours of the event. The 37 cortical strokes showed appropriate lateralising abnormalities in 21 initial CTs assessed unblinded and 14/35 blinded. Only 35 CT scans were assessed blinded, as one CT scan had been destroyed after the patient's death and another could not be found at the time. 27 EEGs, 30 qEEGs, 19 conventional SEPs and 19 topographic SEPs were abnormal in the 37 cortical strokes. Thirty-seven cortical stroke patients underwent the MCNS and results ranged from 1.5 to 11.5, with a median of 7; 35 underwent the BI, which ranged from 0 to 100, with a median of 58; 36 underwent the FIM, which ranged from 18 to 126, with a median of 90. One patient, who had not undergone repeat studies, died after leaving hospital.

In the non-cortical group, appropriate lateralising abnormalities were seen in 2/14 CTs assessed unblinded and in 3/14 blinded, 4/14 EEGs, 1/14 qEEGs, 3/14 conventional SEPs and 3/13 topographic SEPs. 14 non-cortical stroke patients underwent the MCNS and results ranged from 5 to 10.5, with a median of 9; 13 underwent the Barthel Index, which ranged from 2 to 100, with a median of 88; 14 underwent the FIM, which ranged from 51 to 126, with a median of 113.

None of the 51 CTs read unblinded lateralised contralaterally, while 5 lateralised contralaterally when read blinded. These patients were considered to have had asymptomatic previous cerebrovascular events on the basis of the CT, 2 being cortical (1 right and 1 left middle cerebral artery) and 3 non-cortical (1 cerebellar and 2 left lacunar) strokes. Four EEGs were reported as showing bilateral changes, as were three qEEGs. No EEGs lateralised contralaterally, while 1 qEEG, 3 conventional SEPs and 4 topographic SEPs lateralised contralaterally.

9.0.2.3 Session 2

Forty-five patients underwent both radiology and electrophysiology testing a second time. The remainder withdrew from the study after the first session. Those not repeated in full were all cortical stroke patients, with CT confirmation of their stroke, some of whom underwent limited additional testing (two had repeat CTs and one a repeat EEG and qEEG).

The CTs were repeated 4 to 15 days after the first CT (median 7 days; mean 7.5 days, SD 2.0 days), EEGs and qEEGs 4 to 15 days after the first EEG and qEEG (median 7.0 days; mean 7.0 days, SD 1.9 days) and SEPs 4 to 15 days after the first SEP (median 7 days; mean 6.9 days, SD 1.9 days).

Patients with cortical stroke showed diagnostic lateralising abnormalities as follows: 26/33 CTs unblinded (blinded assessments were not performed on the CTs from the second session), 21/32 EEGs, 20/32 qEEGs, 18/31 conventional SEPs and 16/31 topographic SEPs. One patient's left middle cerebral artery ischaemic stroke transformed into a haemorrhagic stroke (seen on the second CT) and another had previously undergone a leucotomy. Two died before the assessment of the second Barthel Index, another died prior to the second FIM and one other was uncontactable for the second FIM, having moved leaving no forwarding address. MCNS results ranged from 1.5 to 11.5, with a median of 7.5; the BI ranged from 6 to 100, with a median of 98 and the FIM ranged from 19 to 126, with a median of 120.

The non-cortical stroke patients showed diagnostic lateralising abnormalities as follows : 6/14 CTs, 3/14 EEGs, 0/14 qEEGs, 1/14 conventional SEPs and 4/13 topographic SEPs. 14 non-cortical stroke patients underwent the MCNS and results ranged from 5 to 11.5, with a median of 10; 13 underwent the BI (one was not assessed), which ranged from 65 to 100, with a median of 100 and 14 underwent the FIM, which ranged from 68 to 126, with a median of 123.

Contralateral abnormalities were reported in 3 EEGs, 1 qEEG, 3 conventional SEPs and 6 topographic SEPs and bilateral abnormalities were reported in 7 EEGs, 4 qEEGs, 2 conventional SEPs and 1 topographic SEP, for both groups.

Five patients underwent MRI investigation on request from their clinicians. In 3 cases (one classified as left anterior cerebral artery and 2 as right non-cortical, site unknown), both CTs were negative, as were the MRIs. In one patient (right middle cerebral artery stroke), the CTs and MRI were positive and in the remaining patient the CTs were negative and the MRI positive, for left cerebellar stroke.

9.0.3 Control electrophysiological results

9.0.3.1 Session 1

Electrophysiological studies of the controls showed lateralising abnormalities in 9/65 EEGs, 1/65 qEEGs, 2/54 conventional SEPs and 3/54 topographic SEPs. Non-lateralising abnormalities were reported in 17 EEGs and 4 qEEGs.

9.0.3.2 Session 2

Of the 65 controls who underwent EEGs and qEEGs, 53 underwent repeat studies. Ten had been referred for EEG and qEEG only from a single session research study being undertaken in another department at TQEH on the same day, however, the researcher involved did not want them to return for a second study within one to two weeks of the first, as he wanted them to return for further studies in his department, at a different time. SEP numbers were further decreased as, due to a delay in acquisition of SEP software, only the conventional SEPs were assessed in one of the controls (in both sessions) and neither conventional nor topographic SEPs in either session in another control. A further two were from interstate (Victoria) and unable to stay for the second session of all tests.

EEGs and qEEGs were repeated after 5 to 16 days (median 8 days; mean 9.8 days SD 3.6 days), while SEPs were repeated after 5 to 16 days (median 8 days; mean 9.6 days SD 3.3 days). These studies yielded lateralising abnormalities in 6/53 EEGs, 0/53 qEEGs, 3/51 conventional SEPs and 5/51 topographic SEPs. Non-lateralising abnormalities were reported in 19 EEGs, 1 qEEG and 1 topographic SEP study.

9.0.4 Variability in control qEEG intersession studies

The maximum number of significant differences in monopolar qEEG intertest measures (Cadwell T-Score Analysis software, 2-tailed t-test ($p \leq 0.05$)) in the 53 controls (that were tested twice) was seen in Absolute Power, where, for all frequencies, for one or more controls, there were 21 changes (21 electrodes). Mean Frequency showed the second highest number of changes, namely 13, 9, 0 and 1, while Relative Power showed 2, 12, 0 and 1, for the delta, theta, alpha and beta frequency bands, respectively. The remaining parameters showed fewer changes, namely 3, 1, 1 and 2 for Interhemisphere Power Asymmetry; 2, 2, 0 and 2 for Intrahemisphere Power Asymmetry; 3, 1, 1 and 1 for Interhemisphere Coherence and 1, 0, 0 and 1 for Intrahemisphere Coherence, for the delta, theta, alpha and beta frequency bands, respectively.

Intersession comparison of the controls by means of the t-test (SPSS group analysis) for the beta frequency showed a significant difference between the sessions for O2 only. Monopolar Power Asymmetry correlation existed for 2 of 8 electrode pairs in delta, 6 of 8 in theta, and bipolar Power Asymmetry correlation in delta existed for 2 of 4 electrodes. The remaining inter- and intrahemisphere Power Asymmetry and all Coherence frequencies, other than 1 of 4 in bipolar delta, were correlated ($p \leq 0.05$). Table 5 shows bipolar intersession variability correlation coefficients for the parameters documented in Chapter 7.

Table 9.3: Bipolar intersession variability - correlation coefficients for Relative Power (2-tails, p≤0.05).

Frequency	Delta	Theta	Alpha	Beta
LF	0.68	0.84	0.90	0.84
LT	0.86	0.87	0.89	0.87
LC	0.92	0.95	0.92	0.94
LP/O	0.89	0.90	0.92	0.90

LF   - left frontal   : F_7/T_3

LT   - left temporal   : T_3/T_5

LC   - left central   : C_3/Cz

LP/O - left parieto-occipital : P_3/O_1

9.0.5 Illustrative cases

9.0.5.1 Case 1

qEEG studies on an acute ischaemic cortical stroke patient

A 70 year old female patient (Q130) with receptive and expressive dysphasia was admitted approximately an hour after the event and assessed clinically as having a left cortical infarction. The CT was performed 3 hours after the event and showed no evidence of recent or old infarction or ischaemia (Figure 9.1, upper left CT).

The qEEG was performed 7 hours after the event, and the monopolar z-score maps showed some increased delta and theta in the left temporo-parietal area in interhemisphere Power Asymmetry (Figure 9.1, uppermost pair of monopolar z-score qEEG brain maps (Q130-1) as an oblique view from above the left hemisphere, the midline shown by a double line). Absolute and relative power measures and maps also localised increased slow activity to the left hemisphere in 2 or more adjacent electrode sites (not illustrated). The qEEG performed two days later (Figure 9.1, second pair of monopolar z-score qEEG brain maps (Q130-2), showed extension of the delta and theta abnormalities.

Six days after the stroke, both the topographic qEEG and CT were repeated. qEEG delta and theta were still increased (Figure 9.1, third pair of monopolar z-score qEEG brain maps (Q130-3)). The CT (Figure 9.1, upper right CT) showed a hypodensity adjacent to the frontal horn of the left lateral ventricle and was reported as showing evidence of infarction in the left middle cerebral artery territory (left postero-lateral-frontal cortex, extending to the frontal horn in 5 cuts). A final topographic qEEG (Figure 9.1, fourth pair of monopolar z-score qEEG brain maps (Q130-4)), performed thirteen days after the initial study, showed residual slow activity of similar distribution to that of the first topographic qEEG (Q130-1).

Front   **Front**

Left   *Left*

Q130 Session 1 CT   Q130 Session 2 CT
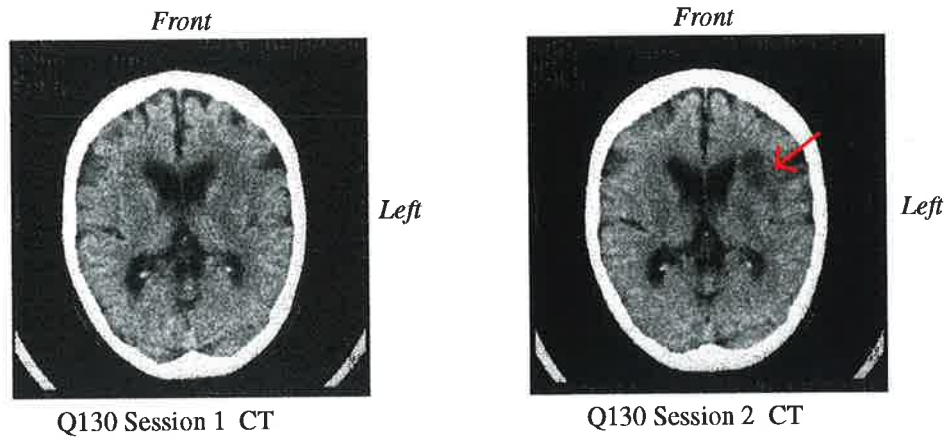
Monopolar Z Score Maps   Name: Q130
Age: 70.2 yrs

Delta   Theta
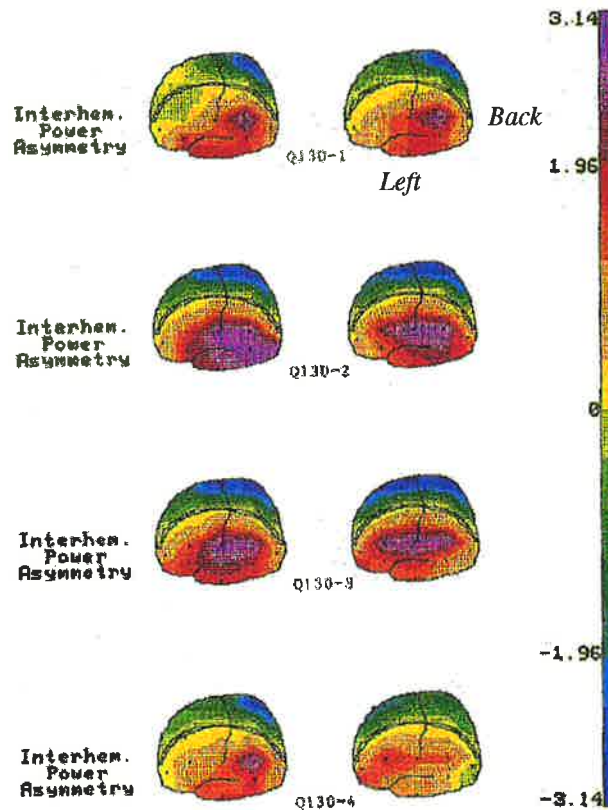
FIGURE 9.1   Top left: a CT performed on a 70 year old female patient (Q130) 3 hours after left cortical stroke and reported as showing no evidence of recent or old infarction. Top right: a CT performed 6 days later, showing infarction in left middle cerebral artery territory (arrow). Below: interhemisphere Power Asymmetry monopolar z-score EEG maps, showing increased slow activity in the left temporo-parietal area; the top map, Q130-1, was performed 7 hours after the event, with studies Q130-2, -3 and -4 performed 2, 6 and 13 days later, respectively.

Scale: 3.14 SD (magenta) to -3.14 SD (deep blue).

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9.0.5.2 Case 2

SEPs on an acute ischaemic cortical stroke patient

A 56 year old female (Q133) was admitted within 48 hours of sudden onset of right hemiplegia and global aphasia. The CT, performed within 48 hours of the event, showed an extensive, but ill-defined frontal hypodensity in 4 cuts, one cut being illustrated in Figure 9.2 (top). The second CT (performed 7 days later) showed an extensive well-defined hypodensity in the frontal and temporal lobes extending deeply to the lateral ventricle seen on 8 cuts in the second assessment (not illustrated). These findings, together with the clinical findings described above, were considered consistent with an area of infarction in the distribution of the left middle cerebral artery, and the patient was diagnosed as having left middle cerebral artery stroke.

The SEPs to left median nerve stimulation fell within the reference range; standard mapping shows the major negative, positive, negative and positive responses at 20, 24, 30 and 46 milliseconds (all latencies are automatically rounded by the SEP mapping software), as illustrated in figure 9.2 (upper traces and 4 maps). In contrast, the response to right median nerve stimulation was reported as absent in the conventional study, with mapping showing extended negativity at 24 milliseconds, maximal in the left fronto-temporal region extending centrally, with no further clearly defined activity, as illustrated in Figure 9.2 (bottom traces and 4 maps). Repeat SEP studies (not illustrated) performed 7 days later were still abnormal, confirming the results of the first study.

Front
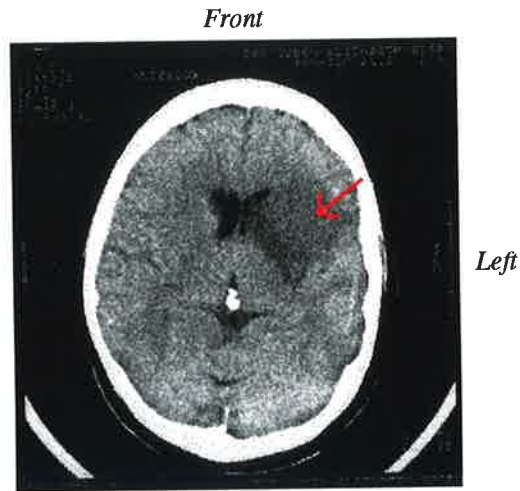
Left

Q133 Session 1 CT

Q133 Session 1 SEPs to left median nerve stimulation.
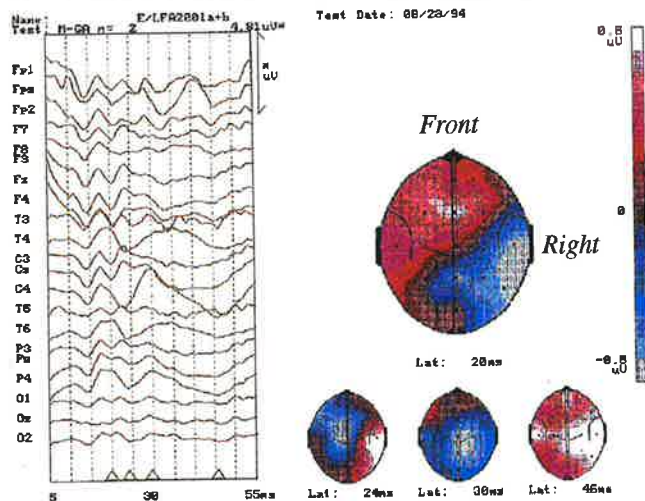
Q133 Session 1 SEPs to right median nerve stimulation.
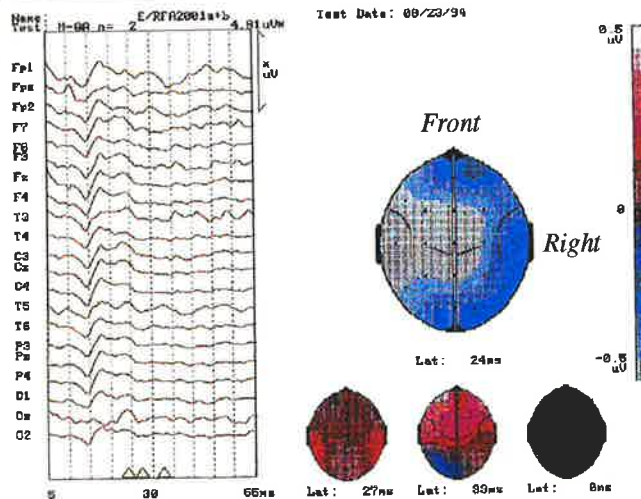
FIGURE 9.2   Top: a CT performed within 48 hours of left cortical stroke on a 56 year old female patient (Q133) showing extensive, but ill-defined frontal hypodensity (arrow). Middle: trace and mapped SEPs to left median nerve stimulation were reported as normal. Bottom: trace and mapped SEPs to right median nerve stimulation were reported as abnormal. Scale: top white 0.5 μV and bottom pale blue -0.5 μV. (Note: Fpz was recorded from the ipsilateral Erb's Point in each case.)

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SEPs on a healthy control subject

By comparison, Figure 9.3 shows trace and topographic SEPs recorded on two occasions on a 62 year old healthy female control (Q213). On the first occasion the major negative, positive, negative and positive SEPs to left median nerve stimulation were recorded and mapped at 19, 24, 31 and 47 milliseconds, those to right median nerve stimulation at 20, 24, 30 and 46 milliseconds, respectively (Figure 9.3, left top and bottom respectively). On the second occasion (14 days later), major negative, positive, negative and positive SEPs to left median nerve stimulation were mapped at 19, 24, 31 and 48 milliseconds, those to right median stimulation at 20, 24, 30 and 47 milliseconds, respectively (Figure 9.3, right top and bottom, respectively; test dates are those of the analysis date (grand average and map plotting), not the recording date). Conventional SEPs were normal on both occasions and no CT was performed.
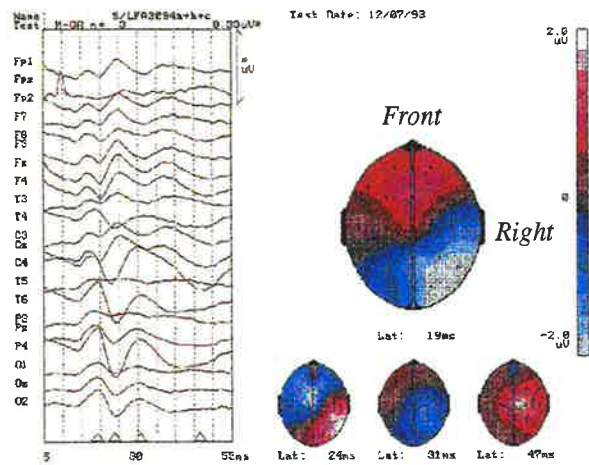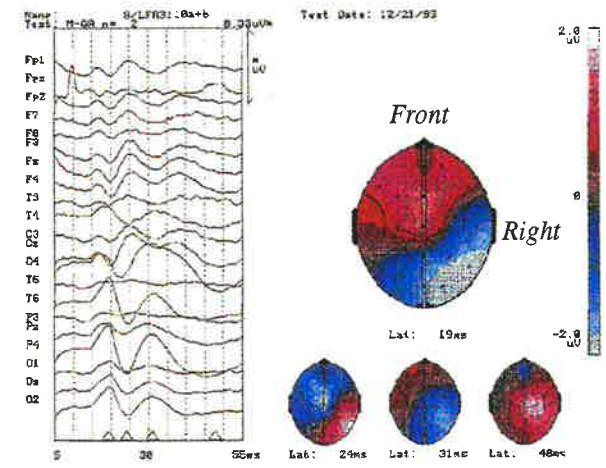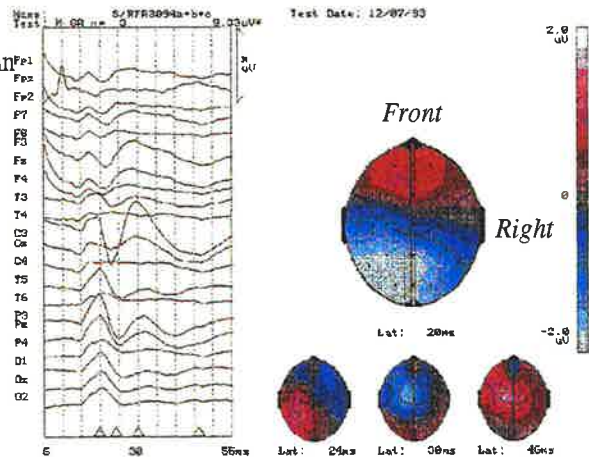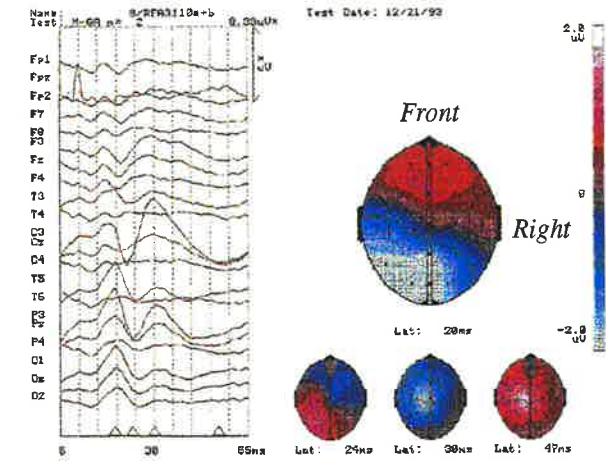
FIGURE 9.3 Left: trace and mapped SEPs to left (top) and right (bottom) median nerve stimulation of a healthy 62 year old female volunteer (Q213). Right: corresponding traces and maps on the second occasion of testing. All trace and mapped SEPs were reported as normal. Scale: top white 2.0 μV and bottom pale blue -2.0 μV. (Note: Fpz was recorded from the ipsilateral Erb's Point in each case.)

9.0.5.3 Case 3

SEPs on an acute ischaemic non-cortical stroke patient

A 73 year old male (Q144) was admitted within 12 hours of sudden onset right-sided hemiparesis (arm more affected than leg) which resolved gradually within 4 days. The CT was performed on the same day and showed two ill-defined left corona radiata hypodensities illustrated (arrows) in Figure 9.4a (top) which were confirmed by the second CT, 8 days later, as illustrated (arrows) in Figure 9.4b (top). These findings, together with the clinical findings described above, were considered consistent with a classification of left lacunar stroke.

In the first session, the SEPs to left median nerve stimulation fell within the reference range for the conventional study, with standard mapping showing the major negative, positive, negative and positive responses at 21, 27, 34 and 43 milliseconds, as illustrated in figure 9.4a (upper traces and 4 maps). In contrast, the response to right median nerve stimulation was reported as abnormal in the conventional study, with mapping showing the major responses at 23, 32 and 47 milliseconds, as illustrated in Figure 9.4a (bottom traces and 4 maps).

For the second session, the conventional SEP was reported as normal to both left and right median nerve stimulation. The topographic SEP latencies to right median nerve stimulation were the same as those in the first study and were again reported as abnormal, those to left median nerve stimulation being the same or similar, i.e., 21, 28, 33 and 43 milliseconds, to those of the earlier study (Figure 9.4b, upper and lower traces and maps, respectively).

Front
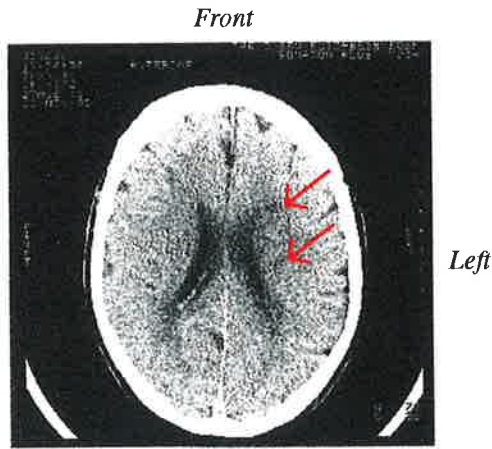
Left

Q144 Session 1 CT

Q144 Session 1
SEPs to left median
nerve stimulation.
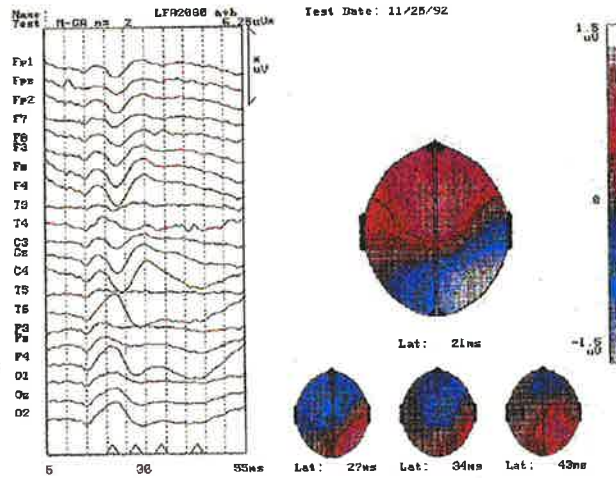
Q144 Session 1
SEPs to right median
nerve stimulation.
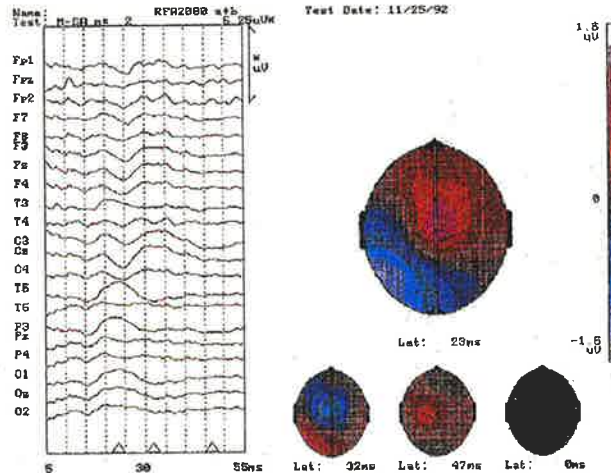
FIGURE 9.4a   Top: a CT performed within 12 hours of left non-cortical stroke on a 73 year old male patient (Q144) showing two ill-defined left corona radiata hypodensities (arrows). Middle: trace and mapped SEPs to left median nerve stimulation were reported as normal. Bottom: trace and mapped SEPs to right median nerve stimulation were reported as abnormal. Scale: top white 1.5 μV and bottom pale blue -1.5 μV.

(Note: Fpz was recorded from the ipsilateral Erb's Point in each case.)

Front
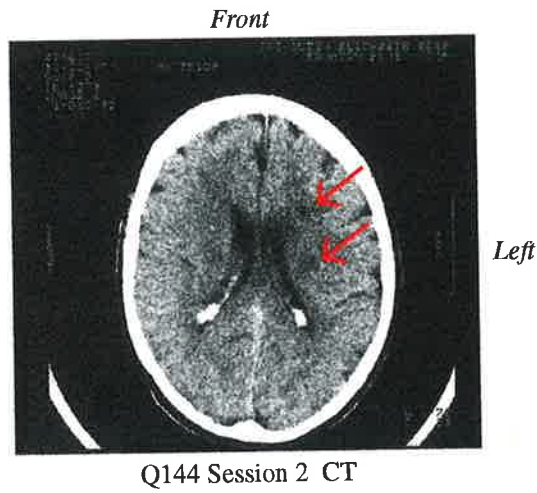
Q144 Session 2 CT

Q144 Session 2
SEPs to left median
nerve stimulation.

Front
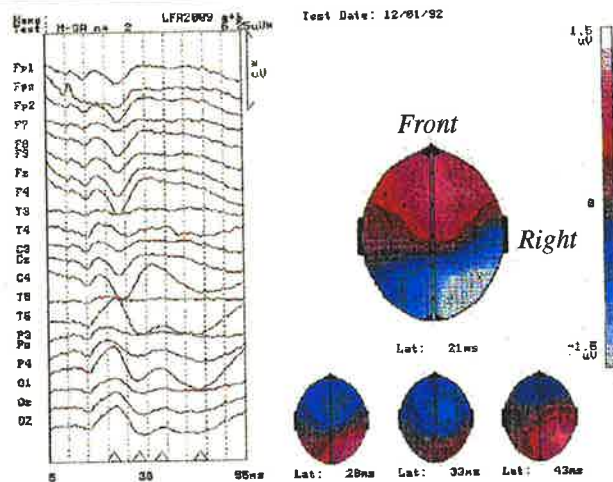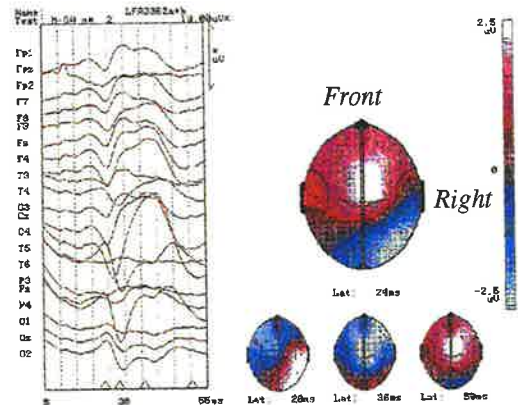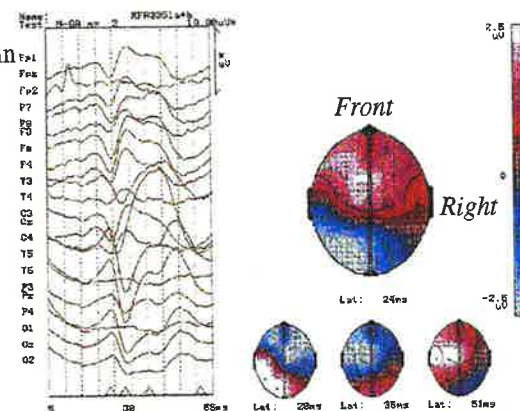
Right

Q144 Session 2
SEPs to right median
nerve stimulation.

Front

Right

FIGURE 9.4b   Top: a CT performed 8 days after the first CT (Figure 9.4a) on a 73 year old male patient (Q144) with left non-cortical stroke, confirming the left corona radiata hypodensities. Middle: trace and mapped SEPs to left median nerve stimulation were reported as normal. Bottom: trace and mapped SEPs to right median nerve stimulation were reported as abnormal. Scale: top white 1.5 μV and bottom pale blue -1.5 μV.

(Note: Fpz was recorded from the ipsilateral Erb's Point in each case.)

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SEPs on a healthy control subject

By comparison, Figure 9.5 shows trace and topographic SEPs recorded on two occasions from a healthy 69 year old male control (Q249). On the first occasion the major negative, positive, negative and positive SEPs to left median nerve stimulation were recorded and mapped at 23, 28, 35 and 49 milliseconds, while those to right median nerve stimulation were mapped at 24, 28, 35 and 51 milliseconds (left top and bottom traces and maps, respectively). On the second occasion (12 days later), major SEPs to left median nerve stimulation were recorded at 24, 28, 36 and 50 milliseconds, while those to right median nerve stimulation occurred at 24, 28, 36 and 51 milliseconds (right upper and lower traces and maps, respectively). Conventional SEPs were normal on both occasions and no CT was performed.

FIGURE 9.5   Left: trace and mapped SEPs to left (top) and right (bottom) median nerve stimulation of a healthy 69 year old male volunteer (Q249). Right: corresponding trace and mapped SEPs from the second session. All trace and mapped SEPs were reported as normal. Scale: top white 2.5 μV and bottom pale blue -2.5 μV.

(Note: Fpz was recorded from the ipsilateral Erb's Point in each case.)

CHAPTER 10

CONVENTIONAL AND TOPOGRAPHIC qEEG AND SEP STUDIES IN STROKE PATIENTS AND CONTROL SUBJECTS -

RESULTS OF UNIVARIATE AND MULTIVARIATE STATISTICAL ANALYSES

10.0 RESULTS

10.0.1 Prediction of cortical stroke using radiological and electrophysiological categorical data

10.0.1.1 Session 1

Univariate analysis

The results of the univariate analyses of the radiological and electrophysiological categorical data (chi-square test and logistic regression) using CT 1 (blinded and unblinded interpretations), EEG 1, qEEG 1, cSEP 1 and tSEP 1 (collected within the first 48 hours) are summarised in Table 10.1.

Table 10.1 **Univariate chi-square and logistic regression (L.R.) results of the first session of radiological and electrophysiological investigations**

Test	Chi-square*	Chi-square* p-value	L.R. p-value	L.R. estimate	L.R. s.e.
CT 1	5.78	0.016	0.013	2.064	0.833
CT 1b	0.81	0.367	0.225	0.894	0.737
EEG 1	6.64	0.010	0.006	1.910	0.698
qEEG 1	20.30	0.000	0.000	4.020	1.119
cSEP 1	2.59	0.108	0.064	1.353	0.730
tSEP 1	2.08	0.149	0.087	1.258	0.736

* Yates corrected/Fisher's exact test

Multivariate analysis

Multivariate analysis of the radiological and electrophysiological data was undertaken subsequently. All categorical variables with a univariate logistic regression p-value≤ 0.15 (i.e., CT 1, EEG 1, qEEG 1, cSEP 1 and tSEP 1) were entered in the stepping procedure. The variables which in aggregate provided a model for detecting cortical stroke were qEEG 1 (p=0.001) and CT 1 (p=0.028). The model developed was as follows.

Model 10.1   **Prediction of cortical stroke using radiological and neurophysiological categorical data.**

$$\psi = -1.671 + 4.350(\text{qEEG 1}) + 2.441(\text{CT 1})$$

where a diagnostic test result = 1 and a non-diagnostic test result = 0

Thus the model could be used to calculate the probability of cortical stroke, as described in chapter 8.

Example 10.1a

Where the qEEG is diagnostic and the CT is non-diagnostic in the first session (as for patient Q130 in figure 9.1), and assigned one and zero, respectively:

$$\psi = -1.67 + 4.350(1) + 2.441(0) = 2.68$$
and $p = 0.936$

Thus there is a predicted 94% chance that the patient has cortical stroke. For this patient the second CT confirmed left cortical (middle cerebral artery) stroke.

Example 10.1b

Where both the qEEG and CT are non-diagnostic (assigned zero in each case) in the first session, as in the case of patient Q137:

$$\psi = -1.671 + 4.350(0) + 2.441(0) = -1.671$$
and $p = 0.158$

Thus there is a predicted 16% chance that the patient has cortical stroke. For this patient, the second CT indicated a left brainstem stroke.

10.0.1.2 Session 2

Univariate analysis

The second assessment occurred an average of 7.5 days (SD 2.0 days) between the first and second CTs, an average of 7.0 days (SD 1.9 days) days between the first and second EEG tests (EEG/qEEG)) and average of 6.9 days (SD 1.9 days) between the first and second SEP tests (cSEP and tSEP). The results of the univariate analyses (chi-square and logistic regression) using CT 2, EEG 2, qEEG 2, cSEP 2 and tSEP 2 are summarised in Table 10.2.

Table 10.2 **Univariate chi-square and logistic regression results of the second set of radiological and electrophysiological investigations.**

Test	Chi-square*	Chi-square* p-value	L.R. p-value	L.R. estimate	L.R. s.e.
CT 2	4.30	0.038	0.020	1.600	0.688
EEG 2	5.55	0.019	0.012	1.897	0.752
qEEG 2	12.44	0.000	**	**	**
cSEP 2	8.27	0.004	0.009	2.890	1.100
tSEP 2	0.87	0.350	0.211	0.875	0.700

* Yates corrected/Fisher's exact test

** Due to the singularity of the qEEG 2 matrix, qEEG 2 was rejected during the L.R. procedure and does not appear in the final model, despite being highly predictive of cortical stroke in the univariate analysis. A subset of selected measures from the qEEG 2 Neurometric report (Coherence, Coherence Combined Central, Overall All, Interhemisphere Power Asymmetry All, Relative Power All) was thus analysed by means of univariate logistic regression, to determine the strongest substitute variable. The results of these analyses are presented in Table 10.3.

Table 10.3 Univariate chi-square and logistic regression results of the second set of Neurometric investigations.

Test	L.R. p-value	L.R. estimate	L.R. s.e.
CA 2	0.022	0.781	0.341
CCC 2	0.060	0.571	0.304
OA 2	0.002	1.418	0.468
PAA 2	0.006	-0.832	0.305
RPA 2	0.008	0.778	0.293

CA 2	:	coherence all (session) 2
CCC 2	:	coherence combined central (session) 2
OA 2	:	overall all (session) 2
PAA 2	:	interhemisphere power asymmetry all (session) 2
RPA 2	:	relative power all (session) 2

Multivariate analysis

Multivariate analysis using all of the above the predictor variables ($p \leq 0.15$) resulted in only OA being left in the model (p=0.003). Thus OA 2 was selected as the surrogate variable to replace qEEG 2 for the multivariate L.R. procedure. Multivariate analysis was then undertaken by entering categorical variables (with a univariate L.R. $p \leq 0.15$ (i.e., CT 2, EEG 2 and cSEP 2)) and the qEEG 2 replacement variable (OA 2) in the stepping procedure. The resultant model for detecting cortical stroke contained only OA 2 (p=0.006).

Example 10.1c

Thus, by way of example, for the patient illustrated in figure 9.1, Q130, where OA 2 was 4.27, the model predicts a 99% chance that the patient has cortical stroke, while for a subsequent non-cortical stroke patient assessed (left brainstem stroke), Q132, where OA 2 was -3.71, there is a 3% chance that the patient has a cortical stroke.

10.0.1.3 Refinement of the stroke data set

Removal of the radiological and electrophysiological categorical data from the 1 leucotomy, 1 haemorrhagic and 5 previous ischaemic stroke patients (set 1) and from 14 patients with negative radiological results (set 2), resulted in all previous relationships being maintained, as did removal of both sets of data. These analyses were performed using the Fisher exact test (at the 0.05 level), as logistic regression was inappropriate due to the small numbers resulting from the restriction imposed by the exclusion criteria

10.0.1.4 Nominating variables in the multivariate analysis

Data used came from the total patient cohort for both studies, i.e., the first study within 48 hours of the stroke (n=51), and the subsequent study performed 4 - 15 days later (median: 7 days). As the CT is usually performed on acute stroke patients to determine whether the patient has had a haemorrhagic stroke, CT information is usually available. In this setting, if the CT variable is fixed in the model at step zero, a determination can also be made to assess whether the addition of qEEG would provide extra predictive power. Furthermore, before performing the qEEG, the information from the EEG would be available. Thus, to determine whether the qEEG would still be helpful (knowing the CT and EEG results), both CT and EEG were fixed in the model, before qEEG was entered. The same variables were found to be predictors.

10.0.2 Prediction of outcome using radiological and electrophysiological categorical data

10.0.2.1 Session 1

Univariate analysis

Initially the first Barthel Index, which was performed 1-15 days after the stroke (median 5 days), was used as an outcome variable, with a cut-off indicator of 'poor' functional outcome at ≤ 35 and a 'good' functional outcome at >35. The results of the univariate analyses (chi-square and logistic regression) using CT 1, EEG 1, qEEG 1, cSEP 1 and tSEP 1 (collected within the first 48 hours) are summarised in Table 10.4.

Table 10.4 **Univariate chi-square and logistic regression results of the first set of radiological and electrophysiological investigations using the first Barthel Index as the outcome variable.**

Test	Chi-square*	Chi-square* p-value	L.R. p-value	L.R. estimate	L.R. s.e.
CT 1	4.33	0.037	0.021	-1.609	0.543
EEG 1	1.97	0.160	0.094	-1.239	0.739
qEEG 1	0.09	0.768	0.538	-0.405	0.658
cSEP 1	9.90	0.002	0.001	-2.439	0.768
tSEP 1	8.59	0.003	0.003	-2.280	0.760

* Yates corrected/Fisher's exact test

Multivariate analysis

Multivariate analysis was then undertaken and all categorical variables with a univariate logistic regression $p \leq 0.15$ (i.e., CT 1, EEG 1, cSEP 1 and tSEP 1) were entered in the stepping procedure. In the univariate logistic regression analysis, both cSEP 1 and tSEP 1 tests showed strong association with the first Barthel Index. However, when placed in the multivariate logistic regression model, their individual statistical significance was reduced due to high correlation ($r=0.70$, $p \leq 0.05$), and neither was retained in the model ($p>0.05$). Multivariate analysis of the nominated variables cSEP 1 and CT 1 or tSEP 1 and CT 1 (as in 10.0.1.4), showed that each retained its predictive ability (cSEP 1: $p=0.001$ and tSEP 1: $p=0.003$), with a non-diagnostic cSEP 1 or tSEP 1 being an indicator of a 'good' functional outcome.

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Using the second Barthel Index, which was performed 77-155 days after the stroke (median 96 days), as an outcome variable for the CT and electro-physiological tests, also showed that each retained its predictive value (p=0.002 for cSEP 1 and p=0.008 for tSEP 1).

10.0.2.2 Session 2

Univariate analysis

The results of the univariate analyses (chi-square and L.R.) using CT 2, EEG 2, qEEG 2, cSEP 2 and tSEP 2 are summarised in Table 10.5. The second Barthel Index was used as a measure of outcome, with a cut-off indicator of 'poor' functional outcome at ≤ 60 and a 'good' functional outcome at >60.

Table 10.5 Univariate chi-square and logistic regression results of the second set of radiological and electrophysiological investigations using the second Barthel Index as the outcome variable.

Test	Chi-square*	Chi-square* p-value	L.R. p-value	L.R. estimate	L.R. s.e.
CT 2	0.30	0.586	0.358	-0.801	0.872
EEG 2	0.14	0.708	0.456	-0.560	0.751
qEEG 2	1.65	0.200	0.109	-1.264	0.788
cSEP 2	11.21	0.001	0.003	-3.332	1.134
tSEP 2	8.80	0.003	0.007	-3.035	1.124

* Yates corrected/Fisher's exact test

Multivariate analysis

Multivariate analysis was then undertaken by entering qEEG 2, cSEP 2 and tSEP 2 (univariate logistic regression $p \leq 0.15$) in the stepping procedure. The resultant model included only cSEP 2 as a predictor of 'poor' outcome (p=0.041), when using the second Barthel Index as an indicator of 'poor' functional outcome (≤ 60) and 'good' functional outcome (>60). Further breakdown of the conventional SEP data is shown in section 10.0.4.3, where the predictive model developed is shown.

10.0.3 Prediction of outcome using clinimetric data

10.0.3.1 Session 1

Univariate analysis

Univariate logistic regression results of the first set of clinimetric test investigations, using the early Barthel Index as the outcome variable, showed that the first modified Canadian Neurological Score showed significant positive association (p=0.001), as did the first Functional Independence Measure p=0.001).

Using the second Barthel Index as the outcome variable, significant positive association was seen for each test in session 1 (Barthel Index: p=0.008, Functional Independence Measure: p=0.004 and modified Canadian Neurological Score: p=0.002). Age and gender were found not to be statistically significant variables, however, as these variables (Barthel Index, Functional Independence Measure and modified Canadian Neurological Score) were highly correlated, multivariate modelling was not possible.

Multivariate analysis

Multivariate analysis was undertaken, and both the modified Canadian Neurological Score and the Functional Independence Measure were entered in the stepping procedure. The resultant model included only the Functional Independence Measure as a predictor of outcome (p=0.001).

10.0.3.2 Session 2

Univariate analysis

Univariate logistic regression results of the second set of clinimetric investigations, using the second Barthel Index as an indicator of outcome ('poor' when ≤ 60, and 'good' when >60), showed that the second modified Canadian Neurological Score showed significant positive association (p=0.004), as did the second Functional Independence Measure (p=0.005).

Multivariate analysis

Multivariate analysis was then undertaken by entering the second modified Canadian Neurological Score and the second Functional Independence Measure in the stepping procedure. The resultant model again included only FIM 2 as a predictor of 'poor' outcome (p=0.001).

Using multivariate logistic regression, age and gender, as well as age or gender, were tested for significant effects. There were no significant associations between age and gender, as well as age or gender, with either type and predictor variables, as well as type or predictor variables (p>0.05). Both Pearson's and Spearman's correlation was assessed and the correlation matrices showed that excessive colinearity was not present.

10.0.4 Analysis of conventional SEP metric data

10.0.4.1 Reference ranges on control subjects

22 healthy females and 32 healthy males with median age 64.2 years and range 40.4 to 95.8 years underwent the conventional SEP tests. Right and left arm temperature minima and maxima were the same, namely 30°C and 33°C respectively, with a median of 31°C. The right and left arm length minima and medians were the same, namely 58 cm and 68 cm respectively, with the right arm maximum being 75 cm, that of the left being 76 cm.

Not all amplitudes were provided for analysis, as in session 1, control Q229 had small dispersed P45 waves with troughs not fully defined bilaterally, as did control Q199 to left median nerve stimulation. In session 2, two controls, Q228 and Q229 were from interstate (Victoria) and returned home early; thus neither the right nor left sided SEPs were repeated. Control Q199 again had a small dispersed P45 wave with a trough not fully defined to left median nerve stimulation, as did control Q185.

The range statistics are shown in table 10.6 in appendix 10.1.

For the variable N9, using repeated measures ANOVA, age, arm length and side were found to be statistically significant factors at the 0.01 level. Age was also found to be a significant factor for N13 and N20, while arm length was also significant for N13, N20, P22 and P28. The remaining variables were not dependent on the factors described, and temperature and session (first or second) were not significant factors for any variable.

The models and expected values for those variables with significant factors (models 10.2 - 10.6 and examples 10.2 - 10.6) and expected values for variables unaffected by the factors tested (Table 10.7) for session 1 are as follows, where μ^*, s.e.(μ^*) and σ^* are the sample estimates of the corresponding population mean, standard error of the mean and standard deviation. The population 95% confidence interval about the predicted mean for the population is also shown, evaluated for a subject with a median age of 64 years, and for the other relevant significant factors as indicated by the equation.

Variable N9 (Erb's Point)
Using the data from session 1, a model was fitted to establish factor significance and determine the population 95% confidence interval.

Model 10.2   Prediction of mean value for N9.

Predicted mean value (μ^*) for N9

$$= 0.025(\text{age}) + 0.135(\text{arm length}) \begin{cases} + 0.085 \text{ (for the right side)} \\ - 0.085 \text{ (for the left side)} \end{cases}$$

Example 10. 2a

Using the median age 64 years and median arm length 68 cm from the control group, for right median stimulation:

$$\mu^* \quad = 0.025(64) + 0.135(68) + 0.085 = 10.87 \text{ msec}$$
$$\text{s.e.}(\mu^*) \quad = 0.72 \text{ msec}$$
$$\sigma^* \quad = 0.64 \text{ msec}$$

where μ^* = population mean

s.e.(μ^*) = standard error of the mean

σ^* = standard deviation

Thus the population 95% confidence interval for N9 is 9.0 - 12.8 msec, for the above specifications.

Example 10.2b

Using the median age 64 years and median arm length 68 cm from the control group, undergoing left median nerve stimulation:

$$\mu^* \quad = 0.025(64) + 0.135(68) - 0.085 = 10.70 \text{ msec}$$
$$\text{s.e.}(\mu^*) \quad = 0.72 \text{ msec}$$
$$\sigma^* \quad = 0.64 \text{ msec}$$

Thus the population 95% confidence interval for N9 is 8.8 - 12.6 msec, for the above specifications.

Variable N13

Using the data from session 1, a model was fitted to establish factor significance and determine the population 95% confidence interval.

Model 10.3   Prediction of mean value for N13.

> **Predicted mean value for N13 = 0.029(age) + 0.186(arm length)**

Example 10.3

Using the median age 64 years and median arm length 68 cm from the control group:

$$\mu^* \qquad = 0.029(64) + 0.186(68) = 14.50 \text{ msec}$$
$$\text{s.e.}(\mu^*) \qquad = 0.70 \text{ msec}$$
$$\sigma^* \qquad = 0.65 \text{ msec}$$

where μ^* = population mean

$\text{s.e.}(\mu^*)$ = standard error of the mean

σ^* = standard deviation

Thus the population 95% confidence interval for N13 is 12.6 - 16.4 msec, for the above specifications.

Variable N20

Using the data from session 1, a model was fitted to establish factor significance and determine the population 95% confidence interval.

Model 10.4   Prediction of mean value for N20.

Predicted mean value for N20 = 0.059(age) + 0.250(arm length)

Example 10.4

Using the median age 64 years and median arm length 68 cm from the control group:

$$\mu* \qquad = 0.059(64) + 0.25(68) = 20.78 \text{ msec}$$
$$\text{s.e.}(\mu*) \quad = 1.13 \text{ msec}$$
$$\sigma* \qquad = 1.00 \text{ msec}$$

where $\mu*$ = population mean

       $\text{s.e.}(\mu*)$ = standard error of the mean

       $\sigma*$ = standard deviation

Thus the population 95% confidence interval for N20 is 17.8 - 23.7 msec, for the above specifications.

Variable P22

Using the data from session 1, a model was fitted to establish factor significance and determine the population 95% confidence interval.

Model 10.5   Prediction of mean value for P22.

Predicted mean value for P22 = 0.337(arm length)

Example 10.5

Using the median arm length of 68 cm from the control group:

μ^* = 0.337(68) msec = 22.92 msec

s.e.(μ^*) = 0.23 msec

σ^* = 1.12 msec

where μ^* = population mean

s.e.(μ^*) = standard error of the mean

σ^* = standard deviation

Thus the population 95% confidence interval for P22 is 20.7 - 25.2 msec, for the above specifications.

Variable P28

Using the data described from session 1, a model was fitted to establish factor significance and determine the population 95% confidence interval.

Model 10.6   Prediction of mean value for P28.

Predicted mean value for P28 = 0.410(arm length)

Example 10.6

Using the median arm length of 68 cm from the control group:

$$\mu^* \qquad\qquad = 0.410(68)\ \text{msec} = 27.88\ \text{msec}$$
$$\text{s.e.}(\mu^*) \qquad = 0.35\ \text{msec}$$
$$\sigma^* \qquad\qquad = 1.89\ \text{msec}$$

where μ^* = population mean
  $\text{s.e.}(\mu^*)$ = standard error of the mean
  σ^* = standard deviation, assumed to remain constant

Thus the population 95% confidence interval for P28 is 24.1 - 31.7 msec, for the above specifications.

Variables independent of the factors tested for session 1 on control subjects are as follows:

Table 10.7 **Mean, standard error of the mean and standard deviation for variables independent of factors tested in the control group, session 1.**

SEP Variable	$\mu*$	s.e. $(\mu*)$	$\sigma*$	95% CI limits	
P25	26.04	0.32	1.81	22.4	29.6
N30	34.53	0.28	2.19	30.2	38.9
P45	44.42	0.47	3.58	37.3	51.5
ln(A1+1)	0.83	0.07	0.54	A1: $0.0^{1,2}$	5.7^2
ln(A2+1)	1.56	0.06	0.50	A2: 0.8^2	11.8^2
ln(A3+1)	2.58	0.06	0.49	A3: 4.0^2	33.7^2
N9 - N13	3.74	0.05	0.45	2.9	4.6
N13 - N20	6.27	0.10	0.78	4.7	7.8
N20 - N30	13.81	0.26	2.02	9.8	17.8
N20 - P45	23.74	0.48	3.71	16.4	31.1

[1] rounded to zero to reflect the positive nature of the variable

[2] amplitude scale in microvolts

where $\mu*$ = population mean

         s.e.$(\mu*)$ = standard error of the mean

         $\sigma*$ = standard deviation, assumed to remain constant

and   A1 is the amplitude: baseline-N20,

       A2 is the amplitude: N20-P22/25/28,

       A3 is the amplitude: N20-P22/25/28 plus P22/25/28-N30 plus N30-P45

10.0.4.2 Comparison of stroke and control subjects

The range statistics are shown in tables 10.8 - 10.13 in appendices 10.2 - 10.7.

Repeated measures ANOVA was performed on the patient and control groups to establish factor significance at the 0.01 level. The factors were group (patient-control), side, arm length, temperature and session, and in addition, for the patients, cortical versus non-cortical stroke patients. The SEP variables were the same as those listed for the controls.

The only significant group differences (patients versus controls) were for P28 latency and amplitudes, as shown in the table below, with none of the other factors tested found to be significant; interaction terms between group and side, and group and session were tested and found not to be significant. The direct comparison between patients and controls is displayed below.

Table 10.14   Mean, standard error of the mean, standard deviation and population 95% CI for P28 and amplitude in sessions 1 and 2, where the factor effect is patient or control.

Variable	$\mu*$	s.e.$(\mu*)$	$\sigma*$	95% CI	
P28: patients	30.24	0.48	2.72	24.8 - 35.7	
P28: controls	28.09	0.48	2.72	22.7 - 33.5	
ln(A1+1): patients	0.82	0.05	0.42	A1:	$0.0^1 - 4.2^2$
ln(A1+1): controls	1.21	0.05	0.42	A1:	$0.5^2 - 6.7^2$
ln(A2+1): patients	1.44	0.06	0.55	A2:	$0.4^2 - 11.5^2$
ln(A2+1): controls	1.76	0.06	0.55	A2:	$1.0^2 - 16.2^2$
ln(A3+1): patients	2.19	0.08	0.66	A3:	$1.4^2 - 31.9^2$
ln(A3+1): controls	2.65	0.08	0.66	A3:	$2.9^2 - 51.1^2$

[1] rounded to zero to reflect the positive nature of the variable

[2] amplitude scale in microvolts

where $\mu*$ = population mean

   s.e.$(\mu*)$ = standard error of the mean

      $\sigma*$ = standard deviation, assumed to remain constant

and   A1 is the amplitude: baseline-N20,

   A2 is the amplitude: N20-P22/25/28,

   A3 is the amplitude: N20-P22/25/28 plus P22/25/28-N30 plus N30-P45

10.0.4.3 Prediction of outcome using stroke data

Using the conventional SEP data from session 2, with a Barthel Index ≤ 60 indicating a 'poor' outcome and >60 indicating a 'good' outcome, logistic regression was performed to establish which of the SEP variables from the second session were predictors. The variables used were the SEP absolute latencies: N9, N13, N20, P22, P25, P28, N30, P45; the interpeak latencies: N9-N13, N13-N20, N20-N30, N30-P45, and amplitudes 1, 2 and 3 respectively, i.e., baseline-N20, N20-P22/25/28, N20-P22/25/28 plus P22/25/28-N30 plus N30-P45, as well as group (cortical/non-cortical), age, gender and arm length.

Most of the amplitude measurements showed a relationship to outcome, i.e., amplitudes 1 (right and left), 2 (right) and 3 (right and left); age was also a significant factor ($p<0.01$) in each case, as were group (cortical/non-cortical) and amplitudes 1 and 2 ($p<0.01$). Using amplitudes, logistic regression analysis showed that for this data set, the best predictive ability resided in a composite ($p<0.01$), as shown in model 10.7.

The model was developed as follows:

Model 10.7   Prediction of stroke outcome using SEP metric data.

$$\psi = -9.85 + 0.157(\text{age}) - 0.97(\text{LA 1}) - 0.68(\text{RA 2}) \begin{array}{l} + 1.34(\text{cortical}) \\ \\ - 1.34(\text{non-cortical}) \end{array}$$

LA 1 : SEP Amplitude 1 to left median nerve stimulation
RA 2 : SEP Amplitude 2 to right median nerve stimulation

Example 10.7a

Using the results of the first radiological confirmed cortical stroke patient that died (Q146), i.e., aged 80.2 years and amplitude 1 of 0.0 μV to left median nerve stimulation and amplitude 2 of 4.4 μV to right median nerve stimulation:

$$\psi = -9.85 + 0.157(80.2) - 0.97(0) - 0.68(4.4) + 1.34$$
$$= 1.12$$

Thus, using the model derived from the data in this experiment, a predicted 75% probability of a 'poor' outcome was predicted. The modified Canadian Neurological Score, Barthel Index and Functional Independence Measure measures were 2.0 and 2.0 when assessed seven days apart, 0 and 6 assessed ninety days apart and 22 and unmeasured due to death, respectively.

Example 10.7b

Using the results from the first radiologically confirmed lacunar infarction patient (Q144) aged 72.7 years and with a SEP amplitude 1 of 1.1 μV to left median nerve stimulation and amplitude 2 of 4.7 μV to right median nerve stimulation:

$$\psi = -9.85 + 0.157(72.7) - 0.97(1.1) - 0.68(4.7) - 1.34$$
$$= -4.05$$

Thus, using the model derived form the data in this experiment, this non-cortical stroke patient has a predicted 2% probability of a 'poor' outcome. The modified Canadian Neurological Score, Barthel Index and Functional Independence Measure measures were 9.5 to 10 when assessed six days apart, 89 to 100 one hundred and twenty-six days apart and 119 to 125 two hundred and ninety three days apart.

CHAPTER 11

CONVENTIONAL AND TOPOGRAPHIC qEEG AND SEP STUDIES IN STROKE PATIENTS AND CONTROL SUBJECTS -

DISCUSSION AND CONCLUSION

11.0 DISCUSSION

11.0.1 Diagnostic value

11.0.1.1 Sensitivity

Electrophysiological studies were more diagnostic (ipsilateral lateralisation) than CTs in the first 48 hours after the stroke (61%, 61% and 45% for qEEGs, EEGs and CTs respectively). On repeat assessment, 4 to 15 days later, CTs increased in sensitivity (68%), while EEGs and qEEGs showed decreased sensitivity (52% and 44%, respectively). The qEEG case study in Chapter 9, showing four qEEGs performed over a period of 13 days, illustrates the topographic changes that may be seen with time. Although the initial topographic qEEG abnormalities were small, they occurred when the CT was still considered negative. qEEG changes were noted also at the time of the second assessment, 2 days later, and remained fairly consistent when re-assessed 6 days after the event, at which time the CT provided structural evidence of infarction. Thirteen days later, only a little slow topographic qEEG asymmetry was seen.

Non-diagnostic findings consisted of studies with no abnormalities, as well as bilateral and contralateral abnormalities. Contralateral abnormalities may have been due to mass effects, previous cerebral events or diaschisis (the latter considered to be the effects of inhibition or loss of function in one region of the nervous system due to localised injury, for example stroke, in another region with which it is connected by fibre tracts (Meyer et al. 1970; Martin and Raichle 1983; Feeney and Baron 1986; Pantano et al. 1987; Ginsberg et al. 1989; Baron 1991; Kim et al. 1994; Miura et al. 1994; Infeld et al. 1995).

While inclusion of studies with bilateral and contralateral abnormalities would have increased the sensitivity, for example for EEG and topographic qEEG in the first session from 61% to 69%, the number of false positives would also have been increased (EEG: 14% to 40% and for qEEG: 2% to 8% for the first session, for example), and the relevant clinical question posed by the referring medical officer, i.e., the request for confirmation of abnormality on the affected side, would not have been addressed.

Sainio et al. (1983) recorded EEGs in 15 patients with cerebral infarction initially within 48 hours of the first symptoms, and found that visual analysis showed the correct side of the lesion in 54%, with spectral analysis having a sensitivity of 87%. Jonkman et al. (1985) considered the Neurometric method to be the most sensitive approach for detecting abnormalities in the EEGs of patients with unilateral cerebral ischaemia, reporting 90% sensitivity in 94 patients ranging from TIA to completed stroke. They cautioned, however, that the method did not seem very accurate for lateralisation or localisation when using multivariate asymmetry measures, as, even in their completed and partial non-progressive stroke subjects, the sensitivity for delta asymmetry was only 53% at zero to 312 days after one-sided ischaemic stroke (they reported no false positives). This sensitivity is midway between the 61% and 44% sensitivity in my study for assessments undertaken within the first 48 hours and between 4 and 15 days after the event respectively, although the multivariate measures were not used to calculate sensitivity in my study.

Nuwer et al. (1987) studied 20 consecutive mild stroke patients, most of whom were tested within days of symptom onset and 19 of whom underwent CT or MRI scans. They reported abnormal conventional EEGs in 6 of 20 cases (30%), but abnormal brain maps in 17 of 20 cases (85%); a normal CT was found in 8 of 16 cases (50%) in which topographic tests showed focal abnormalities.

In their discussion on the relatively low incidence of abnormal EEGs compared with topographic EEG tests, they identified the following : the greater number of electrodes employed in mapping allows small areas of abnormality to be seen : the ability of topographic EEG to separate the principal background activity from other frequencies with smaller amplitudes allows small increases or decreases in amplitude to be detected more readily : and the averaging of data for 10 minutes or more results in a quantified topographic display, allowing improved interpretation. They defined EEG focal abnormalities using a criterion of 50% asymmetry during more than 50% of the session at more than one adjacent electrode site. While they ascribe the low rate of abnormalities in their visually analysed EEGs to milder degrees of infarction, it is likely that the higher incidence of EEG abnormalities in my study is due to the use of the less exclusive definition of abnormality (i.e., consistent (more than 10%) delta activity approaching or above background alpha amplitude/episodic theta and alpha/asymmetrical theta). EEG mapping techniques, they considered, may represent true EEG features of the EEG trace that may have been overlooked, as subtle features were more apparent on quantification than on simple visual examination. This provided the electroencephalographer with some independent feedback regarding the record, however, while this could enhance skills, it could also increase the time taken to report the EEG (Nuwer 1990b).

Brigell et al. (1990) noted that their findings were similar to those of Nuwer et al. (1987), as 5 of 7 of their acute stroke patients (71%) had focal abnormalities on topographic EEG. When Jonkman et al. (1992a) used a slightly modified Neurometric method on EEGs performed within 48 hours of ischaemic stroke onset they showed abnormal qEEGs in 32 of 33 cases (97%) with middle cerebral artery infarcts with severe neurological deficit, verified by positive CT. However, when studies have included groups with less severe deficits or without this imaging confirmation, fewer abnormalities have been found. Examples include the moderate and reversible neurological deficit strokes studied by Jonkman et al. (1992a) within one week of the onset of the stroke (15 of 18 cases (83%) and 3 of 12 cases (25%), respectively (79% in total for these 3 groups)), the mild strokes in the Nuwer study (1987) (85%) and in the range of strokes in my study (61%).

Thus the lower qEEG sensitivity in my study may be due to the inclusion of patients with negative radiological tests and/or the exclusion of patients with multiple hemisphere lesions and/or due to the inclusion of non-cortical studies.

Conventional SEP sensitivity within the first 48 hours of the stroke and again 4 to 15 days after onset was lower and similar on both occasions (43% and 42%, respectively). This sensitivity is in keeping with that of the lower end of the range discussed in Chapter 4 (34% for Despland and Regli (1985) to 85% for Miyoshi et al. (1971)). Although Macdonell et al. (1991) considered that initial improvement was maximal in the first 6 weeks, Kovala et al. (1993) reported that median nerve SEP abnormalities were relatively permanent during a one-year period after cerebral infarct. Given the timing of my sessions and the range of stroke severity, while early change might have been detected at this time, the strokes may have been at different stages of evolution during this period, resulting in no overall change being detected.

Topographic SEP sensitivity was also low and similar to that of conventional SEPs (44% and 46% for the first and second sessions, respectively). However, the simplest form of data reduction was used for the SEP topographic traces, in this case visual analysis of all the traces, with subsequent reference to the maps. Methods of analysis that others have used include principal component and factor analysis. Duffy (1988) noted that principal component and related factor analysis were techniques considered to show great promise. This, he acknowledged, did not guarantee biologically meaningful factors. In 1989, John et al. reported principal component analysis of VEPs followed by Varimax rotation able to show clear abnormalities in the average maps of patients with senile dementia, non-medicated schizophrenia, alcoholism, unipolar and bipolar depression, with no significant abnormalities in the normal group average, while in 1993 John et al. reported that standardised quantitative descriptors of event related potentials, based on principal component Varimax analysis, were able to separate normal from abnormal subjects in psychiatric disorders, with high, replicable accuracy.

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In my study, although utilisation of statistical programs such as principal component or factor analysis may have increased the sensitivity (with a concomitant effect on specificity), the results from the Factor Analysis software were not readily interpretable and further analysis of this kind was not pursued. It may also be that the method of mapping did not provide efficient resolution. As noted by Spitzer et al. (1989), recordings of SEPs made in the region of the sensory strip with interelectrode distances greater than the Nyquist distances (3 cm distances), as is the case with Electrocaps using the 10-20 system (7 cm distances), may have significant errors. The improved spatial resolution offered by the spline Laplacian, for example, may have provided more information (Nunez et al. 1991; Law et al. 1993a, 1993b), however, the software available did not allow use of this derivation.

11.0.1.2 Specificity

Assessment of specificity (of ipsilateral lateralisation) showed that qEEG and conventional and topographic SEPs were the most specific tests in sessions one and two (99%, 96% and 94%, and 100%, 94% and 90% for the tests and sessions, respectively). EEG specificity was lowest, being 86% and 89%, respectively.

The qEEG specificities are similar to those of Jerrett and Corsak (1988) and Jonkman et al. (1992a). In the case of the former, there were no cases of false localisation by brain mapping in 46 patients with stroke and in the case of the latter, the number of false positives with respect to the multivariate measure overall all frequencies was 0% (28 normal controls). However, clinically relevant and visually evident brief background asymmetries or infrequent bursts of focal paroxysmal slowing may not be detected in spectral analysis, where only a small section of the EEG may be averaged. Even utilisation of statistical methods may not show abnormalities, for example, an increase in activity in one hemisphere and a decrease contralaterally may not fall outside the reference range selected. (Oken et al. 1989, Brigell et al. 1990; Nuwer 1990a; Duffy et al. 1994).

11.0.1.3 Predictive value

The positive predictive value is used to determine how likely it is that a person has the disease if the test is abnormal, and is best assessed in a population mimicking the one in which the test will be used. Thus a test with a high positive predictive value is useful to 'rule in' a disease. (Nuwer 1992a). The neurophysiological test with the highest positive predictive value in stroke is qEEG, i.e., 97% and 100% for the first and second sessions, respectively, the lowest being EEG for the first session (78%) and EEG and topographic SEPs in the second session (80% each); conventional SEPs were 92% and 86% for the first and second sessions, respectively. Thus, using this simplistic method on the neurophysiological tests, the test most able to confirm stroke (when positive) in both sessions is the qEEG.

The negative predictive value is used to determine how likely it is that a person is free from the disease if the test results are normal. Thus a test with a high negative predictive value is useful to 'rule out' a disease. (Nuwer 1992a). The highest negative predictive value is that of qEEG (76%) followed by EEG (74%) in session one; conventional and topographic SEPs having somewhat lower values, i.e., 64% and 65%, respectively. The values for EEG and qEEG decreased for the second session (68% and 67%, respectively), while there was little change for conventional or topographic SEPs (65% and 66%, respectively). Based on these figures using this method, the neurophysiological tests most able to exclude stroke (when negative) are EEG and qEEG. However, given the clinical diagnosis of stroke, the question of interest is whether the stroke is cortical or non-cortical. To answer this in a meaningful way, more complex analyses were undertaken to develop a predictive model.

11.0.2 Electrophysiological intersession stability in controls

11.0.2.1 qEEG intersession variability studies

The maximum number of significant differences in the Neurometric T-Score/difference z-score monopolar intersession measures in the 53 controls was seen in Absolute Power, the difference z-score assessment (Relative Power, Mean Frequency, Power Asymmetry and Coherence) showing fewer changes. Similar findings with respect to Absolute Power have also been reported by John et al. (1983) and Nagata et al. (1992).

It should be noted that clinical utilisation of this software package in a routine laboratory would be in testing individuals rather than groups, while the changes reported in my study were the maximum for any given parameter in the group, the purpose of this exercise being to assess the maximum difference in any parameter for each electrode in a group of subjects. Thus the conclusion drawn from the overall results of the older healthy volunteer group is similar to that from the initial younger healthy volunteer group (Chapters 6 and 7), namely that Absolute Power once again shows more variability than the other parameters. The reason for this increased variability of Absolute Power in my studies could be due to the selection of different epochs, use of the t-test for Absolute Power comparisons and difference z-score measures for comparison of Relative Power, Power Asymmetry and Coherence, diurnal variation or a variety of other factors, including genuine change (Cacot et al. 1995).

Clinical use would require reporting improvement, stability or deterioration of subsequent Neurometric T-Score/difference z-score assessment. This could be assessed with respect to the clinimetric scores or compared with change from the first to the second qEEG, using categorical data from reports as generated in my study, although the latter would be a test of variability rather than of improvement, deterioration or no change.

Alternatively, visual assessment of change in the Neurometric measures of interest could be made in order to issue a report of change. However, to further analyse the data, additional in-house software would need to be developed, but this was not relevant to this project, and, as such, has not been undertaken.

The clustering in the beta frequency in the frontopolar and temporal electrodes observed in the group intersession variability study using the t-test (SPSS) on the data from the younger controls (Chapter 7) did not re-occur, with comparison of the older controls by means of the t-test for the beta frequency showing a significant difference for one electrode position (O_2) only. As the method used was the same, this suggests that the clustering detected in the initial study on the younger controls may have been related to age or chance and emphasises the need to repeat studies at least once, using age-referenced normative databases. Intersession correlation was comparable with that of the initial study on the younger controls (Chapter 7) and that reported by John et al. (1983). However, this reflects a concomitant change in the data from one session to the next, rather than clinical usefulness. Thus the clinical application, other than to show consistency within my work and replicability with respect to that of John et al. (1983), is somewhat limited.

11.0.2.2 Conventional SEP metric data

No significant sessional effect was detected for absolute or interpeak latencies, or amplitudes at the 0.01 level. Shaw and Synek (1987) and Lim et al. (1995) considered that interpeak and absolute latencies were variable in intra- and intersession studies. Lim et al. (1995) reported N19-P22 amplitude variation as well, with the coefficient of variation ranging from 15% to 21% and 22% to 28% for intra- and intersession studies, respectively and considered that the differences noted between the two studies suggested intersession variability. Intrasession variability was not assessed as part of this thesis, but it would be anticipated to vary less than intersession amplitude and therefore would not be expected to differ significantly in this study (given that no significant differences were detected in the intersession study).

11.0.3 Predictive ability

11.0.3.1 Stroke type

Univariate analyses

Chi-square and logistic regression of radiological and neurophysiological investigations showed that individually the CT, EEG and qEEG were predictive of cortical stroke in the first session, as were CT, EEG, qEEG and conventional SEPs in the second session at the 0.05 level. Thus, with respect to differentiation of cortical from non-cortical stroke, if only one test is available, the CT, EEG and qEEG could be considered able to provide useful information independently within the first 48 hours, as would the CT, EEG, qEEG and conventional SEPs in the first 2 weeks. The ability of EEG to predict cortical stroke is in keeping with the findings of Macdonell et al. (1988), who concluded that the EEG was useful when the location of the infarct was difficult to determine clinically and the early CT was not helpful, as the EEG could distinguish between cortical and non-cortical stroke.

Multivariate analyses

Logistic regression showed that CTs and qEEGs were highly predictive of cortical stroke in the first session, as was qEEG, both in its categorical and metric form in the second session, at the 0.05 level. The three parameters with lateralising ability (Absolute Power, Relative Power and Power Asymmetry) and the three main frequencies (delta, theta and alpha) were used in the qEEG interpretation. The superiority of qEEG in distinguishing cortical from non-cortical stroke in this study may lie in the strict criteria utilising these parameters and frequencies, with Power Asymmetry (left/right differences) drawing out subtle asymmetries in the trace. The conventional and topographic SEP categorical data were found not to be capable of distinguishing the stroke types ($p > 0.05$), with repeated measures analysis of variance of the conventional SEP metric data confirming this finding. Thus if there is a choice of tests, the most useful predictors of cortical stroke would be qEEG and CT in the first 48 hours, as illustrated in the example from the first session (model 10.1).

When both the CT and the qEEG are non-diagnostic, the model predicts that there is only a 16% chance of the patient having a cortical stroke. By way of contrast, when the qEEG is positive and the CT negative, the model predicts a 94% chance of a cortical stroke. The findings of the second session emphasised the consistency of qEEG. As noted by Duffy (1990), the benefit of undertaking these tests more than once allows confirmation of the findings and affords protection against the criticism of chance finding. Furthermore, when nominated variables were included in the analysis, for example CT (a situation which could readily occur in routine practice where a second CT may be requested if the first was negative) and EEG (EEG information is also available before the qEEG analysis is performed), qEEG retained its predictive ability, thereby maintaining its utility.

The ability of qEEG topographic studies to distinguish cortical and non-cortical stroke, however, contrasts with that of Nagata et al. (1989) who reported no significant difference in qEEG data from patients with cortical and small subcortical infarctions (the results were only suggestive of the possibility that delta activity was associated with cortical ischaemic lesions when there was a reduction in cerebral blood flow and oxygen metabolism), despite mean cerebral blood flow and oxygen metabolism being significantly lower in patients with cortical infarctions. This, they considered, could be related to pathological factors. For example, despite the CT showing infarcts mainly involving cortical structures, nearby subcortical structures could also have been involved; furthermore, the results of the comparison between cortical and subcortical lesions could differ amongst patients, dependent on the nature of the lesions.

11.0.3.2 Stroke outcome

Univariate analyses

In the first session, CT and conventional and topographic SEPs were significantly associated with outcome (as measured by the Barthel Index), as were conventional SEPs and topographic SEPs in the second session at the 0.05 level. Thus, with respect to outcome predicted by radiological and electrophysiological tests, if only one test is available, each of the aforementioned could provide useful information, in the respective sessions.

The lack of predictive ability by electroencephalography agrees with the findings of Hossmann et al. (1980) and Schaul et al. (1986). The former reported lack of correlation between neurological scoring (rating of disturbance of consciousness and higher cortical function, motor dysfunction, cranial nerve abnormalities and sensation impairment) and qEEG, while the latter showed that EEG variables (focal slow wave features or lateralised background activity) did not correlate with clinical predictors of outcome. De Weerd et al. (1988) also reported that Neurometric parameters from 43 patients with unilateral supratentorial ischaemia had no predictive value, while Swart et al. (1997) reported no significant late changes in neurological deficit (assessed using the Canadian Neurological Score), EEG, Neurometric qEEG or volume of ischaemia (CT) three to twelve months after stroke.

These findings contrast with those of Sainio et al. (1983) and Gorbulev et al. (1994), where the first EEGs (recorded within 48 hours of the first symptoms) were considered to predict recovery outcome and cognitive decline, respectively. Sainio et al. (1983) concluded that the degree of background abnormality was important in visual analysis, while in spectral analysis a high proportion of delta or a low proportion of alpha power was a reliable indicator of poor outcome, with parameters from single derivations being superior to an average of all derivations within the first 48 hours. Similarly, Pool et al. (1990) reported a significant relationship between qEEG relative delta amplitudes and neurologic residua in patients with right middle cerebral artery infarction.

Multivariate analyses

In the first session, conventional and topographic SEPs were so predictive of outcome as to be mutually exclusive; in the second session however, only conventional SEPs were predictive of outcome at the 0.05 level. When the analysis was performed with the CT and conventional SEPs, or CT and topographic SEPs as nominated variables (both may be requested in routine practice), each retained predictive ability. Similarly, assessing the conventional and topographic SEPs using the second Barthel Index as an outcome measure, showed that each retained its predictive value. When a choice of electro-physiological tests exists, either conventional SEPs or topographic SEPs could be used within the first 48 hours or conventional SEPs from the second session - this test being the only test undertaken in the second session which retained predictive ability. Further analysis of the conventional SEP data from this second session showed that predictive ability with respect to outcome (Barthel Index ≤ 60 reflecting 'poor' outcome) resided in the amplitude measurements, in particular, the amplitude of the baseline to N20 peak after left median stimulation, together with that of the N20 to P22/25/28 after right median stimulation at the wrist, with group, i.e., cortical or non-cortical stroke, and age being additional significant factors. The examples showing how the model can be used indicated a 2% probability of a 'poor' outcome for the first patient in the study with a radiologically confirmed lacunar stroke, but a 75% chance of a 'poor' outcome for the first patient with a radiologically confirmed cortical stroke. The former recovered (final MCNS, BI and FIM measures were 10, 100 and 125 respectively), while the latter died after the second FIM was performed.

In a three-year follow-up study of stroke survival, Bonita et al. (1988) found that the strongest predictors of survival over 3 years were retention of consciousness, decreasing age and type of residence at the onset of stroke; other predictors included marital status, stroke history and ethnic group. Subsequently, in a study on survival prediction for 1 year among different subtypes of stroke, Anderson et al. (1994) reported that simple clinical measures reflecting the severity of the neurological deficit and associated cardiac disease at onset independently predicted death by one year.

My model has potential for further refinement by inclusion of clinical parameters, however, as this study was an assessment of electrophysiological utility in the prediction of stroke outcome, this has been the focus of the assessments.

Thus my work has shown that conventional SEPs have predictive ability with respect to outcome, confirming the reports of La Joie et al. (1982), Regli and Despland (1982), Pavot et al. (1986), de Weerd and Veldhuizen (1987a, 1987b), Zeman and Yiannikas (1989), Macdonell et al. (1989) and Kovala (1991), albeit for different outcome measures, follow-up times and SEP variables in some cases (an absent N20 in particular being associated with a 'poor' outcome).

Dependent on the number of channels and the montage setup, if SEP mapping is available, so is the conventional 3 channel SEP. As performance of the new test (SEP topography) involves increased time and cost, and as additional information is supplied by conventional SEPs when metric measures are used, the latter is the method of choice, with its timing dependent on clinical circumstances.

In his introduction to 'Research: the Validation of Clinical Practice', Payton (1988) observes that 'theories and models are better guides to knowledge than trial and error', while Gresham (1986) argues that research on stroke outcome is important as it monitors the impact of the disease and provides the basis for prognosis, as well as establishing a baseline to which controlled studies of interventions can be related.

Extension of knowledge in the field is by using the outcome data from my study both in a categorical (discrete) and metric (continuous) manner. Refinement of prediction is through examination of a set of variables simultaneously and developing a multivariate model incorporating the most useful measures. To be validated, the model still needs to be tested (particularly with its reliance on SEP amplitudes) by application to a different set of patients to those used in the development of the predictive model, preferably externally (Wasson et al. 1985; Jongbloed 1986).

11.0.3.3 Clinimetric tests predictive of stroke outcome

Univariate analyses

Both the MCNS and FIM were independently predictive of outcome in the first and second sessions respectively ($p \leq 0.05$). Thus, if only one test was available, either FIM or MCNS could be used.

Multivariate analyses

Only the FIM was predictive of outcome ($p \leq 0.05$) and is therefore the test of choice in either session.

11.0.3.4 Other medical conditions

Distinction of stroke types is highly dependent on the ongoing clinical assessment. While haemorrhagic strokes were excluded on the basis of the first CT which is considered to have a 90% sensitivity (Parsons 1993), ischaemic stroke may progress to haemorrhagic stroke or have a haemorrhagic component, as occurred in one patient in my project. When this patient's data were removed for re-analysis of the data from the second session (together with the data of other patients as detailed below), the outcome of the analyses remained unchanged.

The occurrence of previous 'silent' stroke (asymptomatic brain infarction) is also a potential limitation. Jørgensen et al. (1994) found a 29% prevalence in patients with first ever and recurrent stroke, while Ricci et al. (1993) reported 'silent' stroke in 38% of 209 patients with a first-ever stroke who underwent CT within 30 days of symptomatic stroke. Herderscheê et al. (1992) noted 'silent' stroke in 13% of 2329 patients with TIA or minor ischaemic stroke, while Chodosh et al. (1988) reported only 11% in 1203 patients without a stroke history, on first CT unrelated to the presenting stroke.

Some of the earlier findings are similar to the 10% detected by means of CT as having had an asymptomatic infarct in my study. Deletion of the data from these, as well as the one hemorrhagic and one leukotomy case did not alter the predictive relationships.

Other disorders that may have had an effect on the results include epilepsy and brachial plexus injuries. With respect to the former, Hornig et al. (1990) noted that the literature showed that epileptic seizures may occur in 4%-28% of ischaemic cerebrovascular disorders, Kovala (1990) detecting 25% in a one-year follow-up after cerebral infarct. Although it is conceivable that some lateralising electrophysiological abnormalities could have been due to undetected seizures, none of the patients were known to have epilepsy and during the study period seizures were not detected. With respect to brachial plexus and associated injuries, Kaplan et al. (1977) suggested that stroke patients with these would probably have a more arduous and prolonged course in upper limb rehabilitation, and, had any of the patients assessed in my study had such injuries, outcome could have been affected. In a study of the validity of median nerve somatosensory evoked potentials in the diagnosis of supraclavicular brachial plexus lesions by Synek (1986), median nerve SEPs were found to be abnormal in multiple trunk lesions and multiple root avulsions and on the basis of abnormal brachial plexus potentials indicating peripheral neuropathy, Zeman and Yiannikas (1989) identified and excluded 4 patients from a study of SEPs on 39 stroke patients.

A clear Erb's Point N9 response was not recorded bilaterally in 1 patient, being obscured by artefact. However, as the spinal and subsequent responses were present in each case, the other data were included in the analyses, none of the patients in my study being considered to have a brachial plexus injury on clinical grounds

None of the analyses of the categorical data were affected significantly by age or gender, or age and gender. Where age, arm length and side were found to be significant factors in the analysis of the metric data, they were factored into models for the reference ranges or outcome predictions.

11.0.4 Conventional SEP results

11.0.4.1 Controls

In my study, age and arm length affected most of the earlier absolute latencies. There were no gender, temperature or sessional effects on any absolute or interpeak latencies, or amplitudes. The remaining variables, as well as all amplitudes and interpeak latencies (N9-N13, N13-N20, N20-N30 and N30-P45) were unaffected by any of the factors.

Allison et al. (1983) considered that age-related increases in central latencies were secondary to peripheral increases, as most interpeak upper limits of normal were independent of age. They concluded in 1984 that age-related changes in the human sensory system were not uniform, but different in specific areas and at different life epochs, being more pronounced in males. This effect on the peripheral absolute latencies in my study is also in keeping with an earlier study on peripheral nerve conduction undertaken in my laboratory, where median nerve function showed a significant deterioration with age, but lack of uniformity in ageing effects in the peripheral system (Collins et al. 1991). More recently, Nuwer et al. (1994b) noted in the report of the IFCN Committee that in young children the N9 and N13 potentials occurred early and central conduction was relatively slow, while in older adults, particularly over 55 years of age, reference ranges for most latencies were 5-10% longer.

The effect of arm length on absolute latencies in my study is attributed to arm and shoulder dimensions, findings previously reported by Hume and Cant (1978), Allison et al. (1983) and Bergamaschi et al. (1993b). These findings are also in keeping with those reported for height by Hume and Cant (1978), Meervaala et al. (1988) and Akyüz et al. (1996). However, this may be due to the use of peak rather than onset latencies to calculate central conduction time. Takada et al. (1993) also noted that peak central conduction time did not correlate with height, which they attributed to variable duration of the N20. They considered that for clinical purposes the use of onset central conduction time was preferable, as it reflected the transit time of the somatosensory volley from spinal entry to parietal cortex reception. These findings have been detailed and developed further for the median and ulnar nerves by Ozaki et al. (1994, 1996). Tanosaki et al. (1997) have extended this work and concluded that peak central conduction time increased in older people, reflecting age-related changes in the N20-P20 profile, but not in the fastest central conduction.

Side (right or left) affected only the N9 in my study as seen in example 10.2, where the mean N9 to right median stimulation is slightly longer than that to the left (10.9 msec and 10.7 msec), the upper limit of normal also being 0.2 msec longer on the right than on the left (the mean arm lengths were 68.0 cm bilaterally, with the standard deviation on the right being 4.3 cm, that on the left being 4.4 cm). The significance of side as a factor could be due to slower peripheral conduction in the dominant arm or a systematic effect induced by the method, i.e., assessment of the right arm first in all cases, although all or most latencies would be expected to be affected. It may be, for example, that there is a minor temperature effect, which was not detected with the current method. While limb temperature was ensured to be at or above 30°C, changes were not recorded during the study and could not be related directly to latencies. Trying to relate outcome to temperature may be futile, although it may be that the right arm was marginally less warm and that side, in this instance, is a surrogate factor for temperature. In order to eliminate this possibility, in future studies the side of starting the investigation needs to be randomised, or, for practical purposes in a routine laboratory setting, it may be that sessions need to be randomised, with the same side being tested first in a session of several patients.

Allison et al. (1983) also detected slightly longer latencies to right median stimulation in both adults and children, these being of the order of 0.5% - 1.5%; however, they considered this to be near the limits of resolution when determining latencies, and therefore not significant.

If the statistically significant differences noted are considered important and if absolute latencies were used for interpretive work, significant factors would need to be taken into consideration. This could be achieved through the use of reference range tables derived from the models developed as part of my work, although the use of many tables in a routine laboratory would be cumbersome and impracticable, particularly when there are several significant factors.

Development of a software program for a personal computer to allow assessment of a patient's conventional SEP data and to calculate whether the results fall within or outside the reference range, taking all the appropriate significant factors into account, would improve utilisation.

11.0.4.2 Patients compared with controls

All 15 variables (absolute latencies: N9, N13, N20, P22, P25, P28, N30, P45; interpeak latencies: N9-N13, N13-N20, N20-N30, N30-P45, and amplitudes: baseline-N20, N20-P22/25/28, N20-P22/25/28 plus P22/25/28-N30 plus N30-P45) were assessed to determine differences between the groups.

Variables showing significant effects
Only the P28 absolute latency and the amplitude measures showed significant group (patient-volunteer) differences. However, considering the findings at the lower end of the range reported by some of the other researchers (34% - Despland and Regli 1985; 48% - Abbruzzese et al. 1989; 50% - de Weerd and Veldhuizen 1987a; 47% - Macdonell et al. 1989; 54% - Zeman and Yiannikas 1989; 44% - Gott et al. 1990; 48% - Kovala 1990; 45% - Kuntzer et al. 1991), my overall sensitivities are similar (43% and 42% for sessions 1 and 2, respectively).

Features which may have been contributory to a low sensitivity in my study need to be considered. With respect to stroke diagnosis, not all my patients had positive radiological confirmation of stroke and they may therefore have been less severely affected. Selection of controls was different to that of patients, the former by word of mouth and in-house advertisement, the latter by direct recruitment into my study. However, if healthy non-patient controls were used, this should not be a significant feature. Additionally, in this study strong evidence was considered necessary before significance was declared, and, as 15 variables were assessed, a significance level of 0.01 was used.

Factors showing no significant effects

Side, session, arm length, age and gender showed no significant effect in the patient-control comparison, although some of these factors were considered significant in the controls for some variables. This difference may be due to a dilution effect resulting from the large amount of extra data brought into the analysis by the addition of patient groups.

A contributor to the lack of sessional effect in the patient group may be that early electrophysiological sensory changes were maintained, as discussed earlier. It may also be that my patients were in different phases of stroke evolution or recovery, thereby showing no change for the group, although Britton and Roden (1985) reported that progression of stroke (ischaemic and haemorrhagic) occurred mostly within the first 24 hours. Macdonell et al. (1991) considered that the major effect of stroke on SEPs occurred acutely (maximal within the first 6 weeks), and Kovala et al. (1993) reported that median nerve SEP abnormalities were relatively permanent during a one-year period after cerebral infarct, as discussed earlier.

No significant difference was detected between SEPs recorded from patients with cortical and non-cortical stroke, confirming the findings from the logistic regression analyses of the categorical conventional SEP data.

11.0.4.3 Stroke outcome prediction

Multivariate logistic regression analysis of the radiological and electro-physiological categorical data identified conventional SEPs as the test most predictive of outcome in the second session. All 15 variables (absolute latencies: N9, N13, N20, P22, P25, P28, N30, P45; interpeak latencies: N9-N13, N13-N20, N20-N30, N30-P45, and amplitudes: baseline-N20, N20-P22/25/28, N20-P22/25/28 plus P22/25/28-N30 plus N30-P45) from the second session were therefore assessed to determine ability to predict outcome.

Stroke type, i.e., cortical or non-cortical was a significant factor, as was age - the latter possibly explained by a significant increase in infarct size with increasing age (Fotheringham et al. 1995). Age had not previously been found to be a significant factor in the analysis of the categorical data, however, using the metric data in a modelling situation is considered to be a more sensitive approach and may account for age being a significant factor in this method of stroke prediction. This work thus adds to the body of evidence showing the predictive ability of SEPs with respect to outcome in stroke (Larson et al. 1966; La Joie et al. 1982; Regli and Despland 1982; Pavot et al. 1986; de Weerd and Veldhuizen 1987a, 1987b; Chester and McLaren 1989; Gott et al. 1990; Zeman and Yiannikas 1989; Macdonell et al. 1989; Kovala 1991; Kuntzer et al. 1991; Liu et al. 1991; Lu and Yu 1993; Soors et al. 1994; Timmerhuis et al. 1996).

Only the three amplitude measurements, when examined separately had any relationship to the outcome variable. Amplitude is known to be quite variable and the predictive ability using probabilities developed as group characteristics could vary considerably, as seen in the outcome of the patients used in the examples. However, using the information available, this was the predictive model developed; this emphasises the need to verify the model both in-house and externally, as noted earlier. The data from the first session has not been tested on the model developed using the data from the second session or vice versa, as the data were not independent.

Future work needs to include verification by prospective determination, using the model to calculate probability, then, using the predictions of the model and the observed (real) outcome, performing a goodness of fit test to verify the model. If the evidence were to indicate that the model was not performing as intended, it would need to be re-examined and redeveloped. A multifactorial direction of research may prove fruitful, if factors found to show association with or to be predictive of outcome elsewhere were also considered, for example, the predictive ability of motor evoked potentials, magnetic evoked potentials, EEG, CT, SPECT, the effect of specific stroke types, clinical severity, neurological scales and scoring systems, recovery of motor function, age, diabetes and cardiac disease, interstitial oedema, erythrocyte sedimentation rate, serum creatinine, age, homonymous hemianopia and Mini-Mental State Score (Bonita et al. 1988; Chester and McLaren 1989; Flicker 1989; Macdonell et al. 1989; Lefkovits et al. 1992; Cillessen et al. 1994; Friedman 1994; Heinemann et al. 1994; Chamorro et al. 1995; Alexandrov et al. 1996; Muir et al. 1996; Timmerhuis et al. 1996; Toni et al. 1997).

11.0.5 LIMITATIONS

11.0.5.1 Stroke confirmation

The clinical diagnosis was made using the full clinical assessment and the radiology results. Fourteen patients had negative radiology test results (CT and MRI) and therefore probably had small strokes or RINDs. None were considered to have had TIAs, the distinction being based on symptom duration of less than 24 hours, not CT results. A few may have been part of that percentage of strokes that do not show positive radiological findings or are misclassifed or misdiagnosed. (Norris and Hachinski 1982; Chodosh et al. 1988; Dennis et al. 1990; Alberts et al. 1992; Herderscheê et al. 1992; Ricci et al. 1993; Jørgensen et al. 1994; Alfaro et al. 1995.) Norris and Hachinski (1982) found that the frequency of incorrect diagnosis was similar in 244 stroke patients who were investigated by means of CT as in 345 who were not (16% and 13% respectively).

CT is less sensitive than MRI in showing non-haemorrhagic stroke, as well as brainstem and cerebellar infarction and the focal lesions responsible for reversible TIA. However, it is commonly used for screening in the acute evaluation of stroke, because of ready availability, speed and comparative inexpense. Technically, MRI would be the neuroimaging method of choice, as it provides better anatomical and pathological definition, display in three dimensions, demonstration of blood/CSF flow and better visualisation of the posterior fossa, while there is a lack of ionising radiation. (Kertesz et al. 1987; Davis et al. 1989; Zappoli et al. 1989; Bryan et al. 1991; Chan et al. 1995). Thus utilisation of MRI may have provided further information and more hard evidence of stroke.

As this study was clinically orientated, it needed to show clinical purpose and relevance, and, at a time of severe budgetary constraint, to be of no extra cost to the department. Thus assessments were in keeping with routine laboratory practices, many as detailed by Duffy and Maurer (1989) and Nuwer (1992a). As recommended by the Task Forces on stroke impairment, stroke disability and stroke handicap (1990), whichever imaging technique is used for classification, the same technique should be employed for all patients, although additional studies could be described. Thus CTs were performed on all patients, MRIs only when requested by the patient's referring medical officer.

The difference between the blinded and unblinded CT results represents the difference between unblinded interpretation of CTs at the time of the CT scan by different radiologists together with staff in training, and blinded interpretation at the end of the project by a registrar at the end of training (45% and 35%, respectively). Shinar et al. (1987) noted that interobserver variability was found to range from substantial to excellent in their study conducted in a realistic environment (in offices, neurological and medical history provided and no time pressure) by 6 senior neurologists on 17 patients. A large difference was found by Alfaro et al. (1995), in a study of 555 patients undergoing CT scans during evaluation in emergency (cases reported unblinded). They reported non-concordance between emergency physicians and radiologists with 25 new infarctions in 79 cerebrovascular accident patients missed by the emergency physicians, and 12 reported abnormal by the emergency physician, but not by the radiologist. Stroke patients were, however, not considered to have been inappropriately managed by the department's continuous quality improvement committee.

11.0.5.2 Test assessment

All tests were performed unblinded at the time of the investigations. These included CT scanning, film development and reporting, as well as all neurophysiology recordings, selection of traces and epochs and printing of results, the results of these tests being made available as soon as possible for the clinical management of the patient. Subsequently, electrophysiology assessments were made by interpreters blinded to subjects' details. The results of the non-blinded CT interpretations were taken into account in the clinical diagnosis of cortical or non-cortical stroke and used in the comparison of the tests, while blinded CT results were also included in the analyses of the data from the first session.

Nonetheless, it could be argued that clinical information available at the time of the tests and prior to the blinded assessments may have been an influencing factor. However, if this were to have occurred inadvertently, it should be noted that this mis-interpretation could have resulted in diagnostic underinterpretation as well as overinterpretation, due to ambiguous clinical information provided to the laboratory initially about the type and location of the stroke in some cases. For example, when 'right CVA' was given in the clinical details section of the request form, this could have been interpreted as the right side of the body (face/arm/leg) being affected or the right side of the central nervous system being affected. Similarly, strokes initially identified in the diagnostic categories 'cortical/non-cortical', were only finally placed in that category by one experienced Neurologist (ABB) at the end of the study without knowledge of any of the electrophysiology test results.

Each neurophysiological test was assessed by only one person, who, in the case of equivocal results, had to decide whether the test was normal or abnormal. Thus interpreters made independent assessments - with only conventional and topographic SEPs being interpreted by the same person. Inter-interpreter agreement on EEG has been found by other researchers to vary considerably, from the 53% complete agreement between three electroencephalographers and 80% agreement between two of three (Woody 1968), 50-89% by Williams et al. (1990), 62% consensus (Spillane 1995), to 88% (Macdonell et al. 1988). Discriminant Analysis agreement in my qEEG interoperator study was shown to be 70% between our three operators (Chapter 6). Given the range of variation quoted, a useful in-house audit for the future would be both intra- and inter-operator assessment of EEG data such as that generated in this project.

Nuwer (1990b) stated that reading EEGs has been as much an art as a science for many years - the subjectivity of the reading making it difficult to replace the clinical reader with a computer. While I have attempted to identify and limit errors where possible in this project, as summarised earlier by Sir William Osler, 'Errors in judgement must occur in the practice of an art which consists largely in balancing probabilities' (cited in Norris and Hachinski 1982).

11.0.5.3 Clinical assessment

The final clinical diagnoses were made by one experienced neurologist taking into account all the information from the full clinical assessment and CT in the study. Although Norris and Hachinski (1982) stated that diagnostic accuracy for stroke varied from 38% to 89% depending on clinical skills, none of the patients in this project initially diagnosed as having had a stroke (by the admitting medical officer and consultant in charge) were excluded during the final assessment.

11.0.5.4 Artefact exclusion

In order to view and report the standard EEG subsequently and to analyse the EEG quantitatively, the entire EEG was recorded on optical disc. A judgement was therefore made at the time of the recording whether a recording should be extended to ensure sufficient 'artefact-free' trace for the selection of the proposed minimum 48 epochs. However, in some cases it was necessary for the Neurometric analyses to be performed on less than 48 epochs, the minimum number of 24 being achieved in all cases.

qEEG epoch selection was directed at being 'artefact-free' with automatic artefact rejection set to avoid ocular and muscle artefact in particular. Other exclusions, for example drowsiness and mu activity were dependent on the operator's judgement, unless they exceeded the amplitude of the electrical activity in the calibration epoch in several channels.

11.0.5.5 SEP methodology and analyses

All studies were performed at least twice and averages were used for illustrative and final analyses. Topographic SEPs were analysed visually from printed waveforms and topography, central interpeak and interside differences, as well as the more subjective morphology differences (particularly of the later waves), to evaluate results as diagnostic or non-diagnostic. Factors such as the asymmetry reported by Trotman and Hammond (1989) made this a somewhat complex undertaking, particularly for the topographic SEPs.

Although, as noted by Duffy in 1988, it was thought that factor analysis techniques were promising, the results of the Cadwell Factor Analysis package for topographic SEPs were not readily interpretable. No instructions or publications on exact interpretation of the quantitative results were made available and the study framework did not allow for extension into further statistical analyses of the raw data.

The conventional SEP study was performed with a cephalic reference electrode (Fz) and a stimulus rate of 4.86 Hz, that of the SEP topography with an earlobe reference and a stimulus rate of 9.8 Hz, as it was anticipated initially that the data would be assessed using Factor Analysis software, for which the protocol was preset. However, despite these differences, the outcomes were similar for the two tests in univariate and multivariate categorical data analyses in session 1 and univariate analysis in session 2, with only the multivariate analysis emphasising the better predictive ability of the conventional SEPs in the second session.

Anziska and Cracco (1981) indicated that useful information can be obtained by means of a combination of recording methods, for example, cephalic and non-cephalic reference electrodes. Inclusion of a range of further different recording and stimulation parameters in my testing protocol may well have provided extra information, as reported by García-Larrea et al. (1992), Fujii et al. (1994), Huttunen (1994) and Tinazzi et al. (1996). However, the studies undertaken were time-consuming and technically challenging, particularly the recordings undertaken soon after the stroke had occurred. Extension of the testing protocol would have resulted in an unmanageable project in a clinical environment.

In 1988(b) Nuwer stated that qEEG should be considered an adjunct to the traditional EEG and that the uses for quantitative EEG seemed clearest in cerebrovascular disease. He also concluded that much of the qEEG literature showed no direct clinical application, with many reports showing such application being 'flawed by blackbox-type methods, obtuse or exotic techniques'. A further failing in the general use of the method was that of not addressing important clinical issues such as sensitivity, specificity, reproducibility or comparative advantage over the conventional EEG or other common medical tests. In 1989, Hachinski noted that there appeared to be no studies demonstrating what brain mapping added to the diagnosis or whether the information was clinically better or worse than that obtained from the standard EEG.

This thesis has attempted to address some of the issues raised internationally. Some of the statements made by Nuwer (1988a) and the American Academy of Neurology (1989) have been confirmed, namely that electrophysiological tests can be quite abnormal even when the CT is still normal, for example in the first 2 to 3 days after the stroke or when the degree of ischaemia is mild enough to cause dysfunction without infarction. However, while they considered sensitivity high, the reverse was the case in my study. Furthermore, using logistic regression, qEEG localisation (cortical versus non-cortical) in this study was not inferior to CT, as they had indicated.

In an article on the 'cons' of brain mapping, also in 1989, the time at which this project was being considered, Fisch and Pedley asked: 'Have we reached the point where stand-alone computer analysis of EEG and evoked potential data can be used routinely in the diagnosis and management of neurological and psychiatric disorders?' Nuwer et al. stated in 1994(a) that the field was not sufficiently mature to allow clinical interpretation by itself. In answer to the question posed by John (1989), 'How do we decide when an experimental tool is ready to become a clinical method?', this thesis has shown the effectiveness of qEEG with respect to stroke subtype prediction and of conventional and topographic SEP with respect to outcome prediction (Hamilton-Bruce et al. 1997b, 1997c (appendices 11.5 and 11.6, respectively)). As such, they are available for clinical use in my laboratory. Independently, it has also shown that the Functional Independence Measure is predictive of outcome (Hamilton-Bruce et al. 1996b, 1996c, 1997d (appendices 11.7, 11.8 and 11.9, respectively)).

How does one know if a method is accepted clinically by the practising medical fraternity? It could be assumed to be so if:

a) it is accepted as such in the literature, as seen by the reporting of retrospectively and prospectively conducted audits, rather than research studies

b) it is considered to provide additive information to that provided by the standard EEG by accepted medical associations, as, for example, by the American Medical EEG Association (Duffy et al. 1994) and the American Clinical Neurophysiology Society (Nuwer 1997b)

c) there is acknowledgment by Public Health Ministries (Valdés et al. 1992) for the payment of rebates, and

d) it is used in clinical practice for diagnosis and monitoring of and prognosis for individual patients with the referring medical officer and participating laboratory staff taking responsibility for the consequences of its use and being held responsible legally for its misuse, as should apply to all procedures performed on patients.

With respect to current status in Australia, it is noted that the 1997 Medicare Benefit Schedule Book (Commonwealth Department of Health and Family Services 1997) states that EEG and central nervous system evoked responses (sic) are covered by Medicare benefits when 'not being a service ... involving quantitative topographic mapping using neurometrics or similar devices' in the case of the former, or 'not being a service ... involving quantitative topographic mapping of event-related potentials' in the case of the latter.

While qEEG has been shown to have diagnostic ability, conventional SEPs and, in the first session, topographic SEPs, have been shown to have prognostic ability. Predictive models have been developed for cortical/non-cortical stroke differentiation and stroke outcome using qEEG and conventional SEPs, respectively. Algorithms which would help quick identification of those who would benefit from intervention are anticipated to become increasingly important with the development of new stroke treatments (Goldstein and Matcher 1994).

However, models remain such until proven reasonable, although it is accepted that it is impossible to design a mathematical model able to predict each individual stroke patient's outcome accurately (Barer and Mitchell 1989; Chua et al. 1995), particularly with the difficulty in assessing the influence of emotional and social factors (Allen 1984). As the models may produce valuable information, validation is necessary (Wasson et al. 1985; Jongbloed 1986); the benefits of prognostic information in individual stroke patients, as noted by Lefkovits et al. (1992), being the influence on the use of specific therapies and rehabilitation planning.

Development of new modalities of treatment has raised the need for more precise knowledge of the pathophysiology of acute ischaemic stroke and early pathophysiological studies are considered to augment the clinical diagnosis of stroke (Fiesche et al. 1989). As noted by Dvorák et al. (1991), there is still a large gap between the analysis of signals from the brain and interpretation. Discrepancies between EEG topography and other functional assessments may contain key information in the evaluation of brain pathophysiology and function (Macdonell et al. 1988; Nagata 1993; Alper 1993).

In 1926, Pavlov wrote: 'If one could observe the activity of the brain through the skull, one would see a continuously changing light-spot whisking over the hemispheres and surrounded by darker shadows arrested sometimes here, sometime there and then again jumping to other regions' (cited in Petsche 1989). Since this statement, the field has matured substantially and evidence of development and clinical maturation through the decades has been described in this thesis. It is thus proposed that, more than a century after seminal work by Caton (1895), Berger (1929), Motokawa (1944) (cited in Brazier (1992), Gloor (1969c) and Petsche (1989), respectively), Dawson (1947a, 1947b) and others (albeit not all in topography), the topographic/quantitative method be utilised clinically, as clear evidence of clinical application of the topographic investigations has been demonstrated during the century. Considering the results of this study and others mentioned previously, I propose that these electrophysiological tests be added to the investigations for stroke assessment, for use as needed. However, it may be in these times of amalgamation and financial restraint, that further savings could be made if electrophysiological technology, including brain mapping, became part of the battery of tests offered by organ imaging departments.

Thus comparison and/or combination of electrophysiological brain mapping with techniques such as SPECT, functional MRI and CT, all of which are now more readily accessible, may assist in eliciting such information, as well as possibly providing evidence of neuroplasticity (Graf von Keyserlingk et al. 1989; Yang et al. 1993; Buchner et al. 1994; Gevins et al. 1994; Maclin et al. 1994; Renault et al. 1995; Robb 1995c; Warach et al. 1996; Zifko et al. 1996; Fuchs et al. 1997; Kristeva-Feige 1997; Soufflet et al. 1997; Towle 1997; Wagner at al. 1997; Wong 1997; Yoo et al. 1997). As a result of the advances in neuroimaging techniques, a better understanding of stroke pathogenesis is evolving and current diagnostic labels may well change in some cases in the near future (Loeb 1991; Donnan et al. 1994). As stated by Swanson (1995), the future of brain mapping is in computer science, with applications such as interactive 3D reconstructions and utilisation of warping algorithms to solve distortion problems. Electronic publishing will allow increased access to these peer-reviewed complex, interactive maps with increased refinement of databases, by means of sophisticated discovery engines. As summarised by Mazziotta (1997), in a period of approximately 100 years, brain imaging has progressed from 'crude radiographs to startling images of neuroanatomy and brain function'. The ability to integrate information across subjects, laboratories, modalities, temporal domains and disease states, he anticipates, will provide extraordinary insights into healthy and diseased brain function, thereby maximising every clinical and research dollar spent.

11.1 CONCLUSION

The purpose of this section of the thesis has been to address issues crucial to the interpretation of topographic qEEG and topographic SEP in stroke, for application in a routine clinical laboratory under standard monitoring conditions. This has been achieved by the assessment of the clinical usefulness, i.e., the diagnostic and prognostic applications of brain mapping, with respect to a 'gold-standard' and other accepted tests utilised for these purposes, as well as the establishment of normative databases, in an independent laboratory considering introducing these techniques.

Given that a CT (or MRI) will usually be performed to differentiate haemorrhagic from ischaemic stroke, qEEG has been shown nonetheless to be able to differentiate cortical from non-cortical ischaemic stroke, both at the acute stage (within 48 hours) and 4 to 15 days later, having both the highest positive and negative predictive values of the electrophysiological tests. Both qEEG and CT were included in the multivariate model predictive of cortical stroke at the acute stage, but only qEEG was retained in the model developed using data collected 4 to 15 days after the event. Conventional and topographic SEPs have provided information that can be used for prognostic purposes with respect to stroke outcome at the acute stage, and within 4 to 15 days in the case of conventional SEPs. Most the diagnostic, differentiation and prognostic effects were thus sustained. These relationships were maintained when patients with previous 'silent' strokes (as evidenced on CT), haemorrhagic stroke development and other disorders which could have affected the results, as well as those with negative radiology, were excluded, and, independently, when nominated studies (CT and EEG) were included in the model.

A reference database for conventional SEPs was also established, with population 95% confidence intervals for absolute and interpeak latencies and amplitude measures. Where factors such as age, arm length and side of stimulation were found to have a significant effect, they were incorporated in the mathematical model. Only the P28 latency and amplitude measures showed a significant difference when patients with stroke were compared with healthy controls. There was no significant intersession effect and no significant differences between the cortical and non-cortical groups. T-Score/difference z-score qEEG measures testing on the older controls showed consistency with earlier findings on younger controls.

Further analysis, using the conventional SEP data generated during the second session, identified amplitude as the variable with predictive ability; a model was generated allowing the incorporation of amplitude and other significant factors (age and stroke type, i.e., cortical or non-cortical). FIM was assessed as having good predictive value, while MCNS was rejected during multivariate modelling, using BI as an outcome measure, for both the acute and later studies.

Thus the aims, as originally determined, have been achieved. The findings have been used to generate predictive models for stroke type (cortical/non-cortical) and outcome. The results add to the growing body of evidence that there is additional clinical utility to be found in brain mapping, as well as emphasising the value of the conventional studies. These findings can be used as a baseline for further development in clinical neurophysiology with the approach of the 21st century.

CHAPTER 12

SUMMARY AND CONCLUSION

12.0 SUMMARY

12.0.1 Background

Computerised electrophysiological brain mapping allows visualisation of functional electrophysiological abnormalities in diseases such as stroke, traditionally diagnosed by clinical assessment, computerised tomography and, where available, magnetic resonance imaging, methods which do not always agree. With the clinical application of electrophysiological brain mapping still considered to be in its infancy, its usefulness needs to be demonstrated in laboratories independent of those where it was developed.

12.0.2 Purpose

The purpose of this thesis, therefore, is to evaluate conventional and topographic quantitative EEGs and conventional and topographic SEPs in patients with early ischaemic stroke, as well as in normal subjects, to determine diagnostic and prognostic value. In order to undertake this assessment, equipment and qEEG variability needed to be assessed first.

12.0.3 Equipment assessment

Amplitude accuracy and consistency of voltage mapping were assessed using an external calibration signal for qEEG and EP. Although some EP amplitudes fell well outside the $\pm4\%$ machine limits, this was not detected by the machine's internal check; a customised software upgrade was used to rectify the problem. Voltage mapping showed that, with the scale set to $\pm15\mu V$ for EEGs and $\pm10\mu V$ for SEPs, a single colour change could represent variation of 1-25% in plotted voltage.

Thus newly acquired equipment should be tested comprehensively with an independent signal generator in the laboratory in which it is used. As upgrades may affect relevant software, equipment should be checked at regular intervals and after upgrades. Mapping should not be used as the sole basis of interpretation of the tests. Such checks enhance awareness of amplitude, timing, scaling and resolution issues, allowing better interpretation of topographic and other results.

12.0.4 qEEG operator variability

Intraoperator and interoperator qEEG variability studies were undertaken on 10 young healthy volunteers (mean age 33.8 years, SD 9.4).

12.0.4.1 qEEG intra-operator study

Using the Cadwell T-Score Analysis software, most differences at the 0.05 level occurred in the Absolute Power Mono- and Bipolar measures, whereas Relative Power, Power Asymmetry and Coherence, measured as z-score differences rather than by T-Score, showed fewer and mostly no significant differences. The minimal variability in Relative Power, Power Asymmetry and Coherence results may have reflected the stability of these measures or been due to a lack of independence of the measures when using z-score differences.

12.0.4.2 qEEG interoperator study

More differences in Absolute Power than in the other parameters were also detected when using the T-Score Analysis software to compare 2 operators at a time at the 0.05 level, reflecting the findings of the intra-operator study. This may be due to the selection of different epochs by the different operators and/or the increased number of abnormalities found when using the t-test to compare more than 2 variables. However, when comparing results from the 3 operators by analysis of variance, no significant differences were detected for the Absolute Power or discriminant analysis reports.

On the basis of the analysis of variance findings, qEEG can be used interchangeably by the different operators in the laboratory where it was tested, although it is accepted that any additional variable could increase the number of differences detected when comparing records.

12.0.5 qEEG intersession variability

Intersession qEEG variability studies were undertaken on a group of 20 young healthy volunteers of mean age 33.9 years (SD 10.9) 10.3 days (SD 4.2) apart, as well as 51 older healthy volunteers (controls for the stroke patients) of mean age 64.2 years (SD 10.3) 9.8 days (SD 3.6) apart.

T-Score/difference z-score changes in young healthy volunteers were also maximal for each subject for Absolute Power at the 0.05 level. A few intra-individual changes were also seen in parameters considered to be more reliable, i.e., Relative Power, Power Asymmetry and Coherence, reflecting changes in the EEG (confirmed by independent visual inspection). Thus with larger EEG changes, difference z-score measures reached statistical significance. The use of different probability cut-offs (0.01 or 0.005) did not greatly affect the number of Absolute Power parameters declared significant; similarly, few changes were noted in the other parameters. To check these findings, T-Score/difference z-score intersession variability was also assessed in the older volunteers at the 0.05 level. Absolute Power again showed more variability than the other parameters. This could reflect different epoch selection, diurnal variation or a variety of other factors, including genuine change.

Different methods used by two operators for reporting EEGs (visual versus discriminant analysis) from the younger volunteers were not comparable at the 0.05 level (kappa: -0.04 for the initial study and 0.19 for the second study). However, significant association was obtained within methods (kappa: 0.32 and kappa: 0.45 for visual and discriminant analysis, respectively).

Intersession group studies (t-test using SPSS, 0.05 level) on the younger volunteers showed differences mainly in frequencies and electrodes likely to be contaminated with artefact (beta frequency range in frontal and temporal electrodes) or where measures were small (delta in healthy non-patient volunteers). However, the comparable t-test assessment on the older volunteers showed none of the beta clustering in the frontopolar and temporal electrodes observed in the group intersession variability study. As the recording technique was the same, this suggests that the clustering detected initially on the younger volunteers may have been due to age differences (younger subjects being less relaxed than older subjects) or chance and emphasises the need for age-related databases and repetition of studies on at least one occasion. Intersession correlation was also comparable with that of the initial study on the younger volunteers.

Thusly, qEEG variability studies have been extended to show intra-individual as well as group and method differences, allowing use of this information for quality assurance purposes.

12.0.6 Clinical study

Fifty-one unselected acute ischaemic stroke patients (mean age 70.2 years, SD 10) were assessed clinically. All underwent non-contrast CT, conventional and topographic qEEG and conventional and topographic SEP testing within 48 hours of the stroke. Forty-five (mean age 70.5 years, SD 10.1) underwent all tests 4 to 15 days later (CT: mean 7.5 days, SD 2.0; EEG and topographic qEEG: mean 7.0 days, SD 1.9; SEPs: mean 6.9 days, SD 1.9). Final diagnostic classification was based on the full clinical assessment, including the later CT. Clinimetric evaluation included comparing the modified Canadian Neurological Score and the Functional Independence Measure with the Barthel Index. A control group of sixty-five healthy volunteers (mean age: 64.3 years, SD 9.6) was screened clinically and underwent electrophysiological assessment. Fifty-one (mean age: 64.2 years, SD 10.3) were reassessed 5-16 days later (mean: 9.8 days, SD 3.6 for EEG and qEEG; mean: 9.6 days, SD 3.3 for EEG and qEEG).

Forty-five percent of the CTs were positive in the first session and this increased to 68% in the second session. qEEG had the highest positive predictive value (97%) for the first session, followed by conventional SEPs (92%), this order being retained for the second session. Thus the test most able to confirm stroke when positive was the qEEG followed by conventional SEPs. In the first session, qEEG also had the highest negative predictive value (76%) followed by EEG (74%), while in the second session, this order reversed. With the highest negative predictive value in the first session, therefore, a qEEG when negative would be considered the test best able to eliminate stroke as a possibility, as is the case for EEG in the second session. However, with the higher positive predictive value, more confidence would be placed in stroke confirmation than in the lack of confirmation.

While these assessments provided useful information, where the diagnosis of stroke remains clinical, the question of real interest is whether the stroke is cortical or non-cortical. To answer this and allow development of a predictive model, more complex analyses were undertaken.

12.0.6.1 Cortical stroke prediction

Using logistic regression on the studies assessed, qEEG and CT were assessed best able to detect cortical stroke in the first session at the 0.05 level. As these findings may have been limited by patients having other conditions not detected or documented during the clinical assessment, the analyses were repeated after exclusion of such patients. This group consisted of 5 patients who showed changes on CT indicative of previous ischaemia, one who developed hemorrhagic stroke subsequent to the first CT and one who had previously undergone a leukotomy. Exclusion did not significantly affect the results; neither did exclusion of the 14 subjects with negative radiological findings, nor did exclusion of both groups. In the second session, multivariate analyses resulted in only the qEEG measure estimating the abnormality of the entire Neurometric evaluation of the EEG, being retained in the model. A predictive model for cortical stroke was developed for both sessions. Furthermore, qEEG was retained in the model when nominated variables CT and EEG were included, indicating that the test provided further information, even when information from more conventional tests was included. Potential clinical application of qEEG, therefore, lies in its superior ability to predict stroke type.

12.0.6.2 Stroke outcome prediction

The prognostic value of CT, EEG, topographic qEEG, conventional and topographic SEPs (categorical data) was then assessed by means of logistic regression, using the Barthel Index as an indicator of outcome, at the 0.05 level. In the first session, both conventional and topographic SEPs, independently, were strongly associated with the Barthel Index, however, they were highly correlated and neither was retained in the multivariate model. In the second session, multivariate analysis resulted in a model with only conventional SEPs strongly associated with the second Barthel Index.

The conventional SEP metric measures providing a model for indicating stroke outcome were identified by means of further logistic regression analysis, using conventional SEP absolute and interpeak latencies and amplitudes from the second session. A model was developed for the prediction of stroke outcome; it included amplitude, the conventional SEP variable found to be most useful. The model also incorporated significant factors, namely age and group (cortical or non-cortical); side and gender were not found to be significant factors.

12.0.6.3 Prediction of outcome using clinimetric data

The association of the first and second modified Canadian Neurological Score and first and second Functional Independence Measure assessments with the first and second Barthel Index, respectively, was also assessed by means of logistic regression at the 0.05 level. For both sessions, univariate analysis showed that the modified Canadian Neurological Score and Functional Independence Measure were associated with outcome as measured by the Barthel Index, but multivariate analysis identified only the Functional Independence Measure for outcome prediction. Thus the Functional Independence Measure was a better predictor of the Barthel Index than the modified Canadian Neurological Score. Using the second Barthel Index as the outcome measure, significant positive association was seen for all three tests (Barthel Index, Functional Independence Measure and modified Canadian Neurological Score) from the first session, however, as these were all highly correlated, multivariate modelling was not possible.

12.0.6.4 SEP reference ranges on control subjects

Development of conventional SEP reference ranges on healthy non-patient volunteers was by assessment of conventional SEP absolute and interpeak latencies and amplitudes, using repeated measures analysis of variance to identify significant factors at the 0.01 level.

There was no evidence that arm temperature, which ranged from 30° C to 33° C, had any significant effect. No sessional effect was detected, thus the reference range from the first session could be used for subjects undergoing a test on more than one occasion. Age affected only the shorter latencies, i.e., N9, N13 and N20. As anticipated, arm length did not affect interpeak latencies or amplitudes, however, it affected most of the absolute latencies, i.e., N9, N13, N20, P22 and P28. Side of stimulation affected only the N9. This could be due to chance or a systematic effect, the latter as right arms were always tested first. The side of starting will be randomised in future studies to eliminate possible systematic effects. Mathematical models were generated to take the significant factors into account when utilising the aforementioned variables to generate the population 95% confidence interval for the reference range.

12.0.6.5 Comparison of conventional SEP studies on stroke and control subjects

Conventional SEP results from patients were also compared with those of the healthy older volunteers by means of repeated measures analysis of variance. In the assessment of the cortical and non-cortical patient groups, no significant difference was detected at the 0.01 level, reflecting the findings from the analyses of the categorical data. In the assessment of stroke patients and controls, the only significant differences detected between the groups were all the amplitude measurements and the P28 absolute latency, with the population 95% confidence intervals generated for the patient and control groups showing considerable overlap

12.1   CONCLUSION

Important brain mapping issues have been addressed, including equipment assessment, qEEG variability, and the diagnostic and prognostic ability of topographic qEEG and topographic SEPs in early ischaemic stroke.

Newly acquired equipment should be assessed and calibration-checked at regular intervals, using an independent signal generator in the laboratory in which the equipment is to be used. Such assessment also enhances awareness of amplitude, timing, scaling and resolution issues, allowing better interpretation of topographic and other results. qEEG variability studies have been extended to show intra-individual as well as group and method differences, allowing use of this information for quality assurance purposes.

Topographic qEEG has provided a new perspective in stroke diagnosis, being the most sensitive of the methods used and providing early information of altered function after stroke, at a time when the CT is frequently negative. It distinguished cortical from non-cortical stroke, which may be important in determining new treatment strategies in selected cases. This may apply, for example, to the selection of cases for clinical trials of experimental treatments, and may assist in determining the kind of treatment likely to produce optimal benefit in individual cases. In these circumstances, topographic qEEG could find a clinically relevant place as a non-invasive electrophysiological assessment, providing useful evidence of early response to interventional treatment for stroke. Conventional and topographic SEPs were associated with functional outcome of ischaemic stroke and a predictive model has been developed. Although topographic SEPs have not provided additional information beyond that provided by conventional SEPs, it is anticipated that additional quantitative analysis may increase the sensitivity by enhancing subtle differences. This may assist further with early diagnosis and prognosis, and consequently have a role to play in therapeutic intervention.

In conclusion, topographic qEEG and conventional SEPs have provided the most clinically applicable information. They are thus deserving of inclusion in the range of tests offered for diagnosis and prognosis in ischaemic stroke. Acknowledgment of this is by the clinical application of these tests to assist in determining the diagnosis, type and prognosis of ischaemic stroke, for the benefit of stroke patients.

APPENDICES

11.6   Hamilton-Bruce MA, Yiannikas C, Black AB. Clinical application
of somatosensory evoked potential (SEP) studies in ischaemic stroke. North
Western Adelaide Health Service Research Day 1997 programme and
abstracts 1997:#17.   kk

11.7   Hamilton-Bruce MA, George S, Archer C, Lee R, Luke CG, Black AB.
Functional outcome prediction in ischaemic stroke. Stroke Society of
Australasia 1996 Annual Scientific Meeting programme and abstract
book 1996:36.   ll

11.8   Hamilton-Bruce MA, George S, Archer C, Lee R, Luke CG, Black AB.
Functional outcome prediction in ischaemic stroke. NWAHS Research Day
'96 programme & abstracts 1996:#12.   mm

11.9   Hamilton-Bruce MA, George S, Archer C, Lee R, Luke CG, Black AB.
Functional outcome prediction in ischaemic stroke. J Clin Neuroscience
1997;4(3):415.   nn

APPENDIX 5.1   Information on the Cadwell Spectrum.

Cadwell Spectrum

Hardware

The Cadwell Spectrum AT 386 has provided the features required for our Neurophysiology Laboratory since its purchase in 1989.

The central processing unit has an Intel® 80386 20-MHz processor, 4 megabytes of RAM, a 80387 Math Coprocessor and three Motorola® 68010 coprocessors to provide graphics, data acquisition and stimulus control functions. The system has a 70 megabyte hard disk drive, two 1.2 megabyte 5.25 inch floppy disk drives and a 650 megabyte Pioneer optical recording/playback disk drive. The floppy drives allow optional program loading, data storage, hard disk backup and program updates or new application installation. The hard disk is used for operation, patient data storage or as a data buffer and the optical disk provides EEG storage for recording and playback of up to 32 channels of data.

It has a high resolution colour and separate monochrome monitor. The user interface is the ASCII keyboard (IBM-AT configuration) and Microsoft® mouse, most control being by cursoring the appropriate screen command with the mouse. Thirty-two data input channels are provided on the headboard and hardcopy in our department is by means of a Hewlett Packard Paintjet colour printer or a Canon LBP-8MarkIII monochrome laser printer. The former allows printout of data, traces and maps utilising colour, printouts from the latter being monochrome (black).

Software

Spectrum Test software allows system checks (Cadwell Laboratories Inc., 1989) and calibration is built in, however, external calibration can be performed. Electrode impedance can be measured for all electrodes, including the ground. Montage switching is electronic.

Filter settings are independent and changeable, other than in the qEEG and Factor Analysis programs. Lowcut filters range from 0.016 Hz to 10 Hz in the EEG mode and 0.016 Hz to 300 Hz in the EP mode. Highcut filters range from 15 Hz to 100 Hz in the EEG mode and 70 Hz to 10K Hz in the EP mode. A 50 Hz notch filter can be selected for each channel. The timebase is 5 to 1000 msec/division in the 32-channel mode, and 1 to 1000 msec/division in the 8-channel mode.

The averager allows 1 to 32,000 averages, with an amplitude sensitive reject window for rejecting all or any channels simultaneously. The electrical stimulus is from a constant current isolated output and pulse widths may range from 50 μsec to 3 msec. Operating parameters are stored on disk for automatic customised recall, with manual control over parameters during individual test situations, other than for preset software analysis montages, as described above. (Cadwell Laboratories Inc., n.d. (b)).

A variety of clinical protocols may be purchased and the Spectrum at The Queen Elizabeth Hospital runs Neurometric Analysis (qEEG) - providing mono- and bipolar raw, z-score, normative and multivariate z-score data, and up to 16 monopolar topographic maps of EEG data. Voltage and frequency maps are also offered as options. EP protocols allow 3-channel programs providing EP traces for routine work, as well as 21-channel programs which produce traces and brainmaps. Maps are constructed from a four point linear interpolation program (Shuttlesworth 1987).

Manufacturer warranties and backup are provided on condition that users do not install non-Cadwell software on the hard drive, other than in the F partition. As this partition is also used for temporary storage, software problems may occur after use and additional computing hardware and software are required to undertake further analyses.

Neurometrics

While up to 32 channels of EEG can be recorded in user selected montages, for Neurometric Analysis, only 21 channels referenced to linked ears are used. Neurometrics, as provided with the Spectrum, quantitates a series of selected EEG epochs and compares the resulting measures with those of a database of subjects aged 6 to 90 years of age. Subject measures are age-matched to normative measures and statistical deviation is expressed as z-scores. These indices of score deviation from the mean, in standard deviation units, allow estimation of the probability that quantitative features reflect dysfunction (Cadwell Laboratories Inc., 1990a; Shuttlesworth 1987). The Neurometric analysis can be performed using the live option, i.e., while recording from the subject, or using the review option allowing analysis of the EEG files stored on the optical disk.

Additional EEG software

Additional software includes Discriminant Analysis which provides a quantitative estimate of similarity between a subject profile and the characteristic patterns of groups of patients with a variety of disorders. The classification is a multivariate statistical summary of Neurometric evaluation, serving as an adjunct to clinical evaluation (Cadwell Laboratories Inc., 1990b).

Comparisons can be made by means of the:

> Correlated T Score Analysis - a statistical comparison of two subject files with the same number of epochs and some common features
>
> or
>
> Independent T Score Analysis - a statistical comparison with a different but comparable numbers of epochs (Cadwell Laboratories Inc., 1990c).

Somatosensory Evoked Potentials

Somatosensory Evoked Potential protocols include user defined montages, for example 3-channel SEPs for standard evoked potential tests, 21-channel SEPs for mapped evoked potential tests displayed as 21 trace waveforms in the shape of head, standard mapped SEPs, a waveform display of channels in numerical order together with 4 maps displayed at selected latencies (in milliseconds) (Cadwell Laboratories Inc., 1990d); and sequence mapped SEPs, where maps are produced at 12 latencies of interest, at user specified time intervals (Cadwell Laboratories Inc., 1990e).

"Grand averaging" obtains an average of stored EP files and stores the result as a new file (Cadwell Laboratories Inc., 1990f). Peak latency/amplitude scoring allows peaks and troughs to be cursored by the operator and performs automatic amplitude calculations (Cadwell Laboratories Inc., 1990g).

An additional option is that of Factor Analysis of SEPs. This software allows analysis of the principal components of the EP. Results are compared with normative reference groups and displayed as brain maps to assist in evaluation and diagnosis of a variety of psychiatric and neurological disorders, with deviation from normal expressed as z-scores (Cadwell Laboratories Inc., 1990h).

APPENDIX 5.2   Richards A, Hamilton-Bruce MA. Brainmapping - equipment
                 consistency. International OSET Congress Abstract of Papers
                 1991:10.

INTERNATIONAL OSET CONGRESS 1991

Melbourne Australia

Abstract of Papers
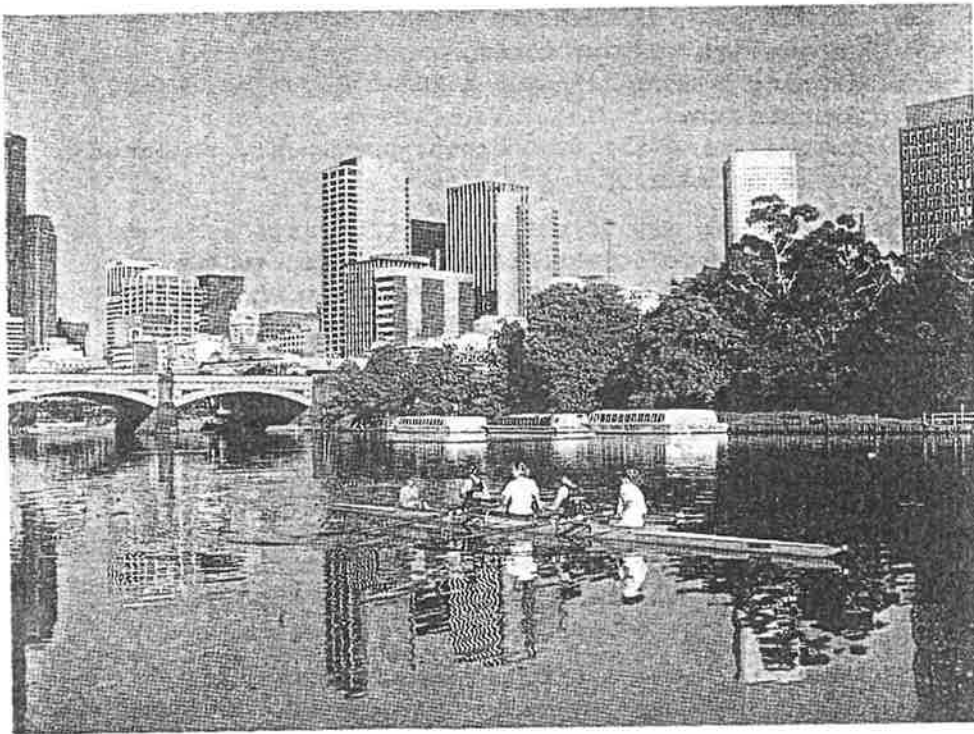
Photo courtesy Melbourne Tourism Authority.

"International Organisation of Societies
for Electrophysiological Technology"

Richards, A. and Hamilton-Bruce, M.A. (1991) Brainmapping - equipment consistency.
International OSET Congress Abstract of Papers, no. 10, 1991

APPENDIX 5.3   Richards AK, Hamilton-Bruce MA. Calibration assessment in quantitative electroencephalographic brainmapping and evoked potential studies. Australas Phys Eng Sci Med 1994;17(3):150-154.

Richards, A. and Hamilton-Bruce, M.A. (1994) Calibration assessment in quantitative electroencephalographic brainmapping and evoked potential studies.
Australasian Physical and Engineering Sciences in Medicine, v. 17 (3), pp. 150-154, 1994

APPENDIX 6.1   **Control information sheet.**

THE
QUEEN ELIZABETH
HOSPITAL

INFORMATION FOR NEUROPHYSIOLOGY TESTS

We are conducting trials on healthy volunteers (men and women) over 60 years of age, to obtain results on normal nervous system function, in order to assess the results from patients with disease or injury of the nervous system eg. stroke, epilepsy etc. We place electrodes on the head and/or body and perform one or more of the following tests on our neurophysiology equipment.

An Electroencephalographic Study: This is a painless recording of the brain's function. We place a cap of electrodes on the head and record the electrical activity of the brain on the electroencephalography machine.

A Somatosensory Evoked Potential Study: This is a test of sensation (feeling). We place a cap of electrodes on the head then we stimulate a nerve using brief electrical impulses and record the responses on the Evoked Potential machine. This may be a little uncomfortable initially, but there are no short- or long-term side effects. If you will find the test unpleasant, we will not proceed.

The tests are not dangerous, are not a form of treatment and do not involve the use of needles. They will not make you drowsy or cause any reactions, and they do not interfere with pacemakers or your ability to drive home. As some drugs may interfere with the tests, we would like to know what drugs you are on at the time of the test.

Each test takes up to an hour to complete and we repeat the study 1-2 weeks later to determine normal variability. No special preparation is necessary, however, washing your hair the night before testing and keeping it free of hair oil or lacquer would facilitate the electrode application. At the end of our project we will let volunteers know the outcome of our trial.

If you would like to volunteer or if you have any questions, please contact:

Anne Hamilton-Bruce
Principal Hospital Scientist
Neurophysiology Laboratory
Neurology - 5C
Telephone: extension 6411
pager 3459

AHBFORMS.DOC

PLEASE HELP US TO HELP OUR PATIENTS

APPENDIX 6.2   Control consent form.

CONSENT FORM FOR NEUROPHYSIOLOGY VOLUNTEERS

Researcher: M. Anne Hamilton-Bruce

1. The nature and purpose of the trial have been explained to me. I understand both and agree to take part.

2. I understand that the test(s) may be of no benefit to me.

3. I understand that, while the information gained in the study may be published and/or presented at a scientific meeting, I will not be identified.

4. I understand that I may withdraw from the study at any stage, and that this will not affect my medical care.

5. I have had an opportunity to discuss my participation in the trial with a friend or family member.

NAME: ....

ADDRESS: ....

....

TELEPHONE: ....

SIGNED: ....

DATE: ....

I certify that I have explained the study to the above and that s/he understands what is involved.

Signed: ....
M. Anne Hamilton-Bruce
Principal Hospital Scientist

Date: ....

APPENDIX 6.3   Control questionnaire and clinical examination form.

THE
QUEEN ELIZABETH
HOSPITAL

NEUROPHYSIOLOGY LABORATORY

LABORATORY SCREEN FOR QEEG AND SEP FA.

NAME: ....

TELEPHONE: ....

1.   TELEPHONE SCREEN:

a.   Do you have any medical, neurological or psychiatric illnesses?
Y/N.   **If YES, elaborate.**

b.   Have you visited a doctor for anything serious in the last 5 years?
Y/N   **If YES, elaborate.**

c.   Have you had an EEG previously and/or visited a neurologist?
Y/N   **If YES, elaborate.**

d.   Do you have migraines, severe or periodic headaches?
Y/N   **If YES, elaborate**   (vascular H/A to be excluded, tension not)

e.   Have you ever had any of the following: **Y/N**
head injury or operation
loss of consciousness
amnesia
stroke
hypertension

f.   Do you have epilepsy, diabetes, renal failure or cancer   **Y/N**

g.   Do you take alcohol or drugs (recreational or therapeutic)?
Y/N   **If YES: Have you taken anything within the last 24 hours?**

i.   Are you left/right handed?

DATE: ....   SCIENTIST: ....

anne.doc

28 WOODVILLE ROAD, WOODVILLE SOUTH, SOUTH AUSTRALIA 5011
TELEPHONE (08) 345 0222   INTERNATIONAL +618 345 0222
FACSIMILE (08) 243 6806

VOLUNTEER NAME: ....

2. VERBAL LABORATORY SCREEN:

    a.   Confirm the above.

    b.   Exclude:

Drug abuse	:
Encephalitis	:
Myocardial infarction	:
Abnormal audition	:
Mental retardation	:
Genetic abnormality	:
Clinical depression	:
Hypertension	:
Coma	:
Abnormal pulmonary function	:
Abnormal hepatic function	:
Abnormal vision	:
Recognised learning disability	:
Psychiatric hospitalisation	:
Schizophrenia (thought disorder)	:
Alcoholism	:
Meningitis	:

    DATE: ....   SCIENTIST: ....

3. MEDICAL AND NEUROLOGICAL SCREEN:

    a.   History (also see screen above)
            MMSE: /30.

    b.   Examination:
          i)   Cranial nerves (1-12):

          ii)   Motor system: power
                                            tone
                                            co-ordination
                                            reflexes

          iii)   Sensory system: joint position sense
                                              vibration sense
                                            pain
                                            light touch
                                            temperature

          iv)   Gait: walking
                                            heel-toe testing
                                            Romberg testing

    c.   Comment:

    DATE: ....   MEDICAL OFFICER: ....

APPENDIX 6.4   Hamilton-Bruce MA. Intraoperator variability in quantitative electroencephalography on normal volunteers. International OSET Congress Abstract of Papers 1991:11.

Hamilton-Bruce, M.A. (1991) Intraoperator variability in quantitative electroencephalography on normal volunteers.
International OSET Congress Abstract of Papers, no. 11, 1991

INTERNATIONAL OSET CONGRESS 1991

Melbourne Australia

Abstract of Papers
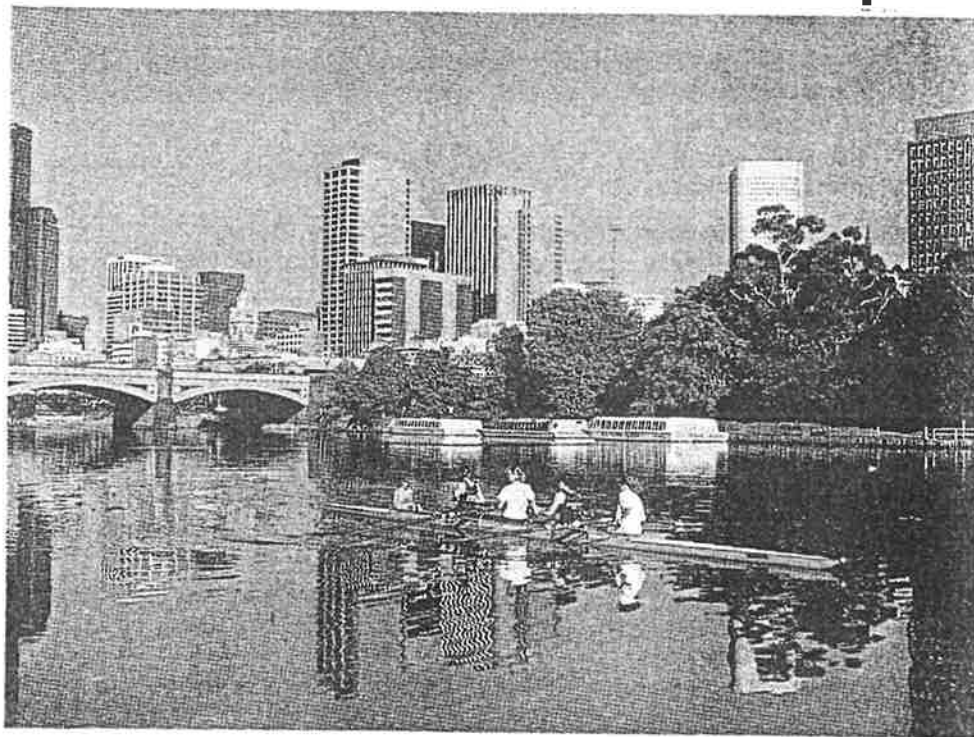
"International Organisation of Societies for Electrophysiological Technology"

APPENDIX 6.5 Hamilton-Bruce MA, Boundy KL, Purdie GH. Interoperator variability in quantitative electroencephalography. Clin Exp Neurol 1991;28:219-224.

Hamilton-Bruce, M.A., Boundy, K.L. and Purdie, G.H. (1991) Interoperator variability in quantitative electroencephalography.
Clinical and experimental neurology, v. 28, pp. 219-24, 1991

Clinical and Experimental Neurology

Proceedings of the Australian Association
of Neurologists, Volume 28, 1991

Edited by
Mervyn J. Eadie, Cecilie Lander and Michael P. Pender

Supplement to

The Royal Australasian College of Physicians

Volume 21, Number 4

Supplement 2

The Australian and New Zealand Journal of Medicine

Proceedings of Meetings of the College and Special Societies

CONTENTS

APPENDIX 7.1   Hamilton-Bruce MA, Majedi PM, Dennis S, Black AB.
Determination of a normative neurophysiological brainmapping
database and intersession variability. Proceedings of the Annual
Scientific Meeting of the Australian Society for Medical
Research, South Australian Division, 1992:Abstract 20.

q

Hamilton-Bruce M.A., Majedi, P.M., Dennis S. and Black, A.B. (1992)
Determination of a normative neurophysiological brainmapping database and
intersession variability.
*Proceedings of the Annual Scientific Meeting of the Australian Society for Medical
Research, South Australian Division, Friday 29th May 1992, Abstract 20*

PROCEEDINGS

ANNUAL SCIENTIFIC MEETING

FRIDAY 29TH MAY 1992

THE AUSTRALIAN SOCIETY
FOR MEDICAL RESEARCH

SOUTH AUSTRALIAN DIVISION

APPENDIX 7.2   Hamilton-Bruce MA, Black AB, Majedi PM, Dennis S.

qEEG reference data collection and intersession variability.

Electroencephalogr Clin Neurophysiol 1995;94(4):64p.

APPENDIX 8.1   **Patient information sheet.**

INFORMATION ON STROKE TRIAL TESTS.

AIM : To find an improved, non-invasive
inexpensive method of diagnosing
ischemic stroke early on, in order
to allow improved diagnosis and
treatment of stroke.

THE FOLLOWING TESTS WILL BE PERFORMED :

An Electroencephalograph. This a painless recording of the brain's
function. We place a cap of electrodes on the head and record the
electrical activity of the brain on the electroencephalography
machine.

A Somatosensory Evoked Potential study. This is a test of sensation
(feeling). We stimulate a nerve in the arm or leg with brief
electrical impulses, and record the responses of the nervous system
on an Evoked Potential machine from electrodes on the head and
body. The test may initially be a little uncomfortable, but there
are no short- or long-term side effects. If you find the test
unpleasant, we will not proceed.

A Computerised Tomography scan. This is an X-Ray examination of the
head, done on a specialised machine which takes pictures of the
brain at specific levels.

The tests **are not** dangerous, **are not** a form of treatment and **do not**
involve the use of needles. They **will not** make you drowsy, or cause
any reactions. As some drugs may interfere with the test,
we would like to know what drugs you are on at the time of the
test.

We perform these tests on admission and after one week. We will
organise the appointments, if they have not already been organised
by your doctor (some of these tests are routinely performed in this
condition). Each test takes approximately an hour to complete. No
special preparation is necessary, however, washing your hair the
night before the neurophysiology tests and keeping it free of hair
oil or laquer would facilitate the electrode application.

Should you have any questions, please contact :

Anne Hamilton-Bruce
Principal Hospital Scientist
Neurophysiology Laboratory.
Tel. : ext 6411/pager 3459.

APPENDIX 8.2   **Patient consent form.**

t

CONSENT FORM FOR STROKE TRIAL TESTS

Researcher : M. Anne Hamilton-Bruce

1. The nature and purpose of the trial have been explained to me. I understand both and agree to take part.

2. I understand that the tests may be of no benefit to me.

3. I understand that, while the information gained in the study may be published and/or presented at a scientific meeting, I will not be identified.

4. I understand that I may withdraw from the study at any stage, and that this will not affect my medical care.

5. I have had an opportunity to discuss my participation in the trial with a friend, family member or someone not associated with the trial.

NAME   : ....   TQEH U/NO : ....

SIGNED : ....   WARD/TEL : ....

DATE   : ....

OR   : I, the undersigned (being the above-mentioned patient's relative/legal guardian) give permission for these tests to be performed.

NAME   : ....   TEL NO.   : ....

SIGNED : ....   DATE   : ....

ADDRESS : ....

I certify that I have explained the study to the above and that s/he understands what is involved.

SIGNED : ....   DATE   : ....

M. Anne Hamilton-Bruce
Principal Hospital Scientist
Neurophysiology Laboratory
The Queen Elizabeth Hospital
Woodville 5011.

APPENDIX 8.3   Example of advertisement for controls.

The Editor
AFUW-SA Inc News
Mailroom Box 6
University of Adelaide
GPO BOX 498
Adelaide SA 5001.

THE
QUEEN ELIZABETH
HOSPITAL

Dear Madam,

Subsequent to my letter to and discussion with Mrs Brenda Nettle, I write to ask for help
with my PhD project. I am studying electrophysiological brain mapping in stroke and
need healthy volunteers aged 50 and over in order toe establish a reference database. The
following is our standard advertisement for recruiting volunteers, and I would be most
grateful if this could be placed in the AFUW-SA Inc News.

A RARE OPPORTUNITY

One of the latest neurophysiological techniques is that of mapping the brain's electrical
activity. If you are healthy, over 50, interested in seeing your brain in action and would
like to help, please contact :

> Anne Hamilton-Bruce
> Principal Hospital Scientist
> The Queen Elizabeth Hospital
> Woodville SA 5011.
> Tel 345 0222 ext 6411, pager 3459.

Should you need any further information, please do not hesitate to contact me.

Yours sincerely

M Anne Hamilton-Bruce
MSc CBiol MIBiol FIMLS
Principal Hospital Scientist

APPENDIX 8.4   **Letter of thanks to control subjects.**

AHB:LT

THE
QUEEN ELIZABETH
HOSPITAL

Brainmapping Laboratory, Neurophysiology, 5B

Dear

Just a short note of appreciation to thank you very much for your help with our brainmapping studies.

We need as many volunteers as possible, as it is very important for us to be able to establish extensive control reference ranges, in order to be able to interpret our patients' results. Your data will be added to the database and, as such, is a valuable contribution to our work.

Once again, many thanks.

Yours sincerely,

Anne Hamilton-Bruce
MSc, CBiol, MIBiol, FIMLS
Principal Hospital Scientist

APPENDIX 8.5   Patient clinical screen form.

W

NEUROLOGY DEPARTMENT 5C
NEUROLOGICAL SCREEN FOR TYPING STROKE PATIENTS
Please return to A. Hamilton-Bruce

Screen for stroke patients at start and end of hospitalisation/trial.

NAME: UR: WARD: DOB:

ASSESSMENT NUMBER AND DATE	1	2
1. CORTICAL SIGNS: YES/NO		
Left Cortical		
Dysphasia (Type, Gerstman's Syndrome)		
Neglect (Visual/Sensory/Motor)		
Eye deviation		
Visual field defect		
Right Cortical		
Constructional apraxia		
Neglect (Visual/Sensory/Motor)		
Eye deviation		
Visual field defect		
Motor Response		
2. BRAINSTEM/CEREBELLAR SIGNS		
Yes / No / (If Yes, What?)		
Dysarthria		
3. OTHER SIGNS		
4. CT RESULTS		
5. WORKING DIAGNOSIS (inc CT info)		
a. TIA/RIND/CVA		
b. B/Stem/Subcort (Lac)/Cortical		
Site uncertain		
c. Improved/deteriorated?		
6. FINAL DIAGNOSIS		
(inc CT & all other information)		
PATHOPHYSIOLOGY		
Embolic?		
Thrombotic?		
c. Hemorrhagic?		
TYPE: TIA/RIND/STROKE?		
VASCULAR TERRITORY		
ACA, MCA, PCA?		
WATERSHED?		
VBI?		
SIDE: Right/Left?		
If diagnosis is incomplete, does		
patient need to be recalled?		

MEDICAL OFFICER: DATE: MEDICAL OFFICER   DATE:

PLEASE COMPLETE MODIFIED CANADIAN NEUROLOGICAL SCORE ON THE OTHER SIDE
Please return to Anne Hamilton-Bruce, 5C-EMG, Extension 6411/Pager 3459

APPENDIX 8.6   Modified Canadian Neurological Score form.

MODIFIED CANADIAN NEUROLOGICAL SCORE

			Date						
			Time						
M	Level of Consciousness	Alert	3.0						
E	(if less than drowsy refer to GCS)	Drowsy	1.5						
N									
T	Orientation	Orientated	1.0						
A		Disoriented or non-applicable	0.0						
T									
I	Speech	Normal	1.0						
O		Expressive deficit	0.5						
N		Receptive deficit	0.0						
S N	MOTOR FUNCTIONS: WEAKNESS:								
E O	Face	None	0.5						
C		Present	0.0						
T									
I C	Arm: Proximal	None	1.5						
O O		Mild	1.0						
N M		Significant	0.5						
P		Total	0.0						
A R									
1 E	Arm: Distal	None	1.5						
H		Mild	1.0						
E		Significant	0.5						
N		Total	0.0						
S									
I	Leg: Proximal	None	1.5						
O		Mild	1.0						
N		Significant	0.5						
		Total	0.0						
D									
E	Leg: Distal	None	1.5						
F		Mild	1.0						
E		Significant	0.5						
C		Total	0.0						
T									
S	MOTOR RESPONSE:								
E Compre-	Face	Symmetrical	0.5						
C hension		Aysmmetrical	0.0						
T									
I Defect	Arms	Equal	1.5						
O		Unequal	0.0						
N									
	Legs	Equal	1.5						
A2		Unequal	0.0						
		MAX:	15						

Maximum score on the MCNS is 11.5

Section A1 refers to side affected by paresis
If patient's conscious state is less than drowsy, recorded 1.5 on the MCNS then also use the Glasgow Coma Scale (GCS)
Patient must be assessed on both scales on all subsequent examination if GCS is used

APPENDIX 8.7   **Barthel Index form.**

y

BARTHELS INDEX

Scoring for each task and each level of independence is shown on the graph. Add the scores to give the total BI score (maximum = 100). Record the total in the relevant box.

PATIENT'S NAME: _____   **UR NUMBER**: _____

ITEMS	1	2	3	4	5
1. Personal Hygiene	(0)	(1)	(3)	(4)	(5)
2. Bathing Self	(0)	(1)	(3)	(4)	(5)
3. Feeding	(0)	(2)	(5)	(8)	(10)
4. On and Off Toilet	(0)	(2)	(5)	(8)	(10)
5. Stairs	(0)	(2)	(5)	(8)	(10)
6. Dressing	(0)	(2)	(5)	(8)	(10)
7. Bowels	(0)	(2)	(5)	(8)	(10)
8. Bladder	(0)	(2)	(5)	(8)	(10)
9. Chair / Bed Transfers	(0)	(3)	(8)	(12)	(15)
10. Ambulation or	(0)	(3)	(8)	(12)	(15)
11. Wheelchair	(0)	(1)	(3)	(4)	(5)

TOTAL BI SCORE:

Pre-Admission: ☐☐☐

Initial OT Assessment: ☐☐☐   Date _____

At Discharge: ☐☐☐   Date _____

COMMENTS:

_____
_____
_____
_____
_____
_____

July 1992

APPENDIX 8.8   Functional Independence Measure form.

UNIFORM DATA SYSTEM FOR MEDICAL REHABILITATION
INPATIENT CODING SHEET   SIDE 2

COMPLETE BOTH SIDES

Patient Number __ __ __ / __ __ / __ __ __ __

16. Impairment Group (complete on discharge)
See Impairment Group Code at bottom of page

17. Date of Onset
month | day | year

18. Principal Diagnosis (complete on discharge)
ICD 9 Code

19. Other Diagnoses

DISCHARGE
1
2
3
4
5
6
7

FOLLOWUP
1
2
3
4
5
6
7
ICD 9 Code

20. Payment Source
a. Primary
b. Secondary
(complete on discharge)

01- Blue Cross 02- Medicare 03- Medicaid/Welfare
04- Commercial Insurance 05- HMO 06- Work Comp
07- Crippled Child Serv 08- Regional Ctr Devel Disab
09- State Voc Rehab 10- Private Pay 11- Employee
Courtesy 12- Free 13- Champus 14- Other
15- None

21. Charges (Dollars only)
a. Total Rehab Hospital $
b. Include Physician?   1- Yes   2- No

22. Functional Independence Measure (FII

LEVELS		NO
7 Complete Independence (Timely, Safely)		NO
6 Modified Independence (Device)		HEL
Modified Dependence		
5 Supervision		
4 Minimal Assist (Subject = 75%+)		
3 Moderate Assist (Subject = 50%+)		HEL
Complete Dependence		
2 Maximal Assist (Subject = 25%+)		
1 Total Assist (Subject = 0%+)		

	ADMIT	DISCHG	FOL-
Self Care			
A. Feeding			
B. Grooming			
C. Bathing			
D. Dressing—Upper Body			
E. Dressing—Lower Body			
F. Toileting			
Sphincter Control			
G. Bladder Management			
H. Bowel Management			
Mobility			
Transfer:			
I. Bed, Chair, W/Chair			
J. Toilet			
K. Tub, Shower			
Locomotion			
L. Walk/Wheel Chair	W C	W C	W C
M. Stairs			
Communication			
N. Comprehension	a v n	a v n	a v n
O. Expression	a v n	a v n	a v n
Social Cognition			
P. Social Interaction			
Q. Problem Solving			
R. Memory			
Total			

Impairment Group Code:

01 Stroke
01.1 Left Body Involvement
01.2 Right Body Involvement
01.3 Bilateral Involvement
01.4 No Paresis

02 Brain Dysfunction
02.1 Non-Traumatic
02.2 Traumatic
02.21 Open Injury
02.22 Closed Injury

03 Neurologic Conditions
    -Other

UDS CODE-2   8/31/87

04 Spinal Cord Dysfunction
04.1 Non-Traumatic
04.2 Traumatic
04.-1 Paraplegia
04.-2 Quadriplegia
04.--1 Incomplete
04.--2 Complete

05 Amputee
05.1 Single Upper AE
05.2 Single Upper BE
05.3 Single Lower AK
05.4 Single Lower BK
05.5 Double AK/AK
05.6 Double AK/BK
05.7 Double BK/BK
05.8 Other Combinations

06 Arthritis
06.1 Rheumatoid
06.2 Osteoarthritis
06.3 Other

07 Pain Syndromes
07.1 Neck Pain
07.2 Back Pain
07.3 Extremity Pain
07.4 Abdominal Pain
07.5 Pelvic Pain
07.6 Facial Pain
07.7 Headache
07.8 Other Pain

08 Orthopaedic Conditi
09 Cardiac
10 Pulmonary
11 Burns
12 Congenital Deformit
13 Other Disabling Impairments

COMPLETE
BOTH SIDES

IF DATA ON THIS FORM
ARE REVISED, WRITE DATE
HERE: ___|___|___ , AND
CIRCLE NEW DATA.

Rehab Facility Code [ ][ ][ ]

Patient Number [ ][ ][ ][ ][ ][ ][ ][ ]

Admission Date [ ][ ][ ]
(month) (day) (year)

1. Discharge Date [ ][ ][ ]
(month) (day) (year)

5. Program Interrupted [ ] 1- Yes
2- No

1st Interruption

a. Transfer Date [ ][ ][ ]

b. Return Date [ ][ ][ ]

2nd Interruption

c. Transfer Date [ ][ ][ ]

d. Return Date [ ][ ][ ]

3rd Interruption

e. Transfer Date [ ][ ][ ]

f. Return Date [ ][ ][ ]

6. Admission Class [ ]

1- First Rehab   2- Evaluation   3- Readmission

7. Zip Code [ ][ ][ ][ ][ ][ ]
(Home)

8. Birthdate [ ][ ][ ]
(month) (day) (year)

9. Sex [ ]
1- Male   2- Female

10. Race/Ethnicity [ ]
1- White   2- Black   3- Asian
4- American Indian   5- Other   6- Hispanic

11. English Language [ ]
1- Yes   2- No   3- Partial

12. Marital Status [ ]
1- Single   2- Married   3- Widowed
4- Separated   5- Divorced

13. Living Arrangement
a. Setting
PRE HOSPITAL   ADMIT FROM   DISCHARGE   FOLLOWUP
[ ][ ]   [ ][ ]   [ ][ ]   [ ][ ]
01- Home   02- Board and Care
03- Transitional Living   04- Intermediate Care
05- Skilled Nursing   06- Acute Unit-your own facility
07- Acute Unit-another facility   08- Chronic Hospital
09- Rehab Facility-other   10- Other   11- Expired

b. Living With
PRE HOSPITAL   DISCHARGE   FOLLOWUP
[ ]   [ ]   [ ]
1- Alone   2- Family/Relatives
3- Friends   4- Attendant   5- Other

14. Vocational Status
a. Category
ADMISSION   FOLLOWUP
[ ]   [ ]
1- Employed   2- Sheltered   3- Student
4- Homemaker   5- Not working
6- Retired-age   7- Retired-disability

b. Effort
ADMISSION   FOLLOWUP
[ ]   [ ]
1- Full   2- Part   3- Adjusted
time   time   workload

15. Followup
a. Date [ ][ ][ ]
(month) (day) (year)

b. Information Source [ ]
1- Patient   2- Family   3- Other

c. Method [ ]
1- In person   2- Telephone   3- Mail

d. Health Maintenance [ ]   [ ]
primary   secondary
1- Own Care   2- Unpaid Helper
3- Paid Attendant   4- Paid Professional

e. Therapy [ ]
1- None   2- Outpatient Therapy
3- Home Based Paid Therapy   4- Both

COPY FREELY
DON'T CHANGE   UDS CODE-1   8/31/87

APPENDIX 10.1

Table 10.6 Conventional SEP data range statistics for healthy controls.

Variable	S		Right arm				Left arm		
		n	Min.	Max.	Median	n	Min.	Max.	Median
N9	1	54	9.02	13.32	10.62	54	8.67	13.32	10.47
N9	2	52	9.07	13.56	10.70	52	8.67	13.38	10.59
N13	1	54	11.98	16.70	14.49	54	11.93	17.11	14.40
N13	2	52	11.93	16.99	14.43	52	11.87	16.99	14.55
N20	1	54	17.92	24.38	20.46	54	17.46	24.97	20.63
N20	2	52	18.33	24.85	20.63	52	18.10	24.15	20.44
P22	1	20	20.31	25.18	22.72	23	20.13	25.31	23.04
P22	2	21	20.60	24.91	22.81	22	20.42	26.13	23.10
P25	1	29	23.45	30.09	25.72	26	23.28	29.97	25.61
P25	2	24	23.57	30.15	25.71	27	23.39	29.10	25.37
P28	1	25	25.31	32.24	27.64	28	24.73	33.06	27.59
P28	2	24	24.79	32.75	27.47	25	24.55	32.71	27.64
N30	1	54	29.56	40.22	34.57	53	28.28	38.53	34.10
N30	2	52	29.33	41.90	34.48	52	29.91	40.97	34.19
P45	1	53	37.54	51.80	44.23	52	37.36	50.34	44.20
P45	2	52	36.26	51.86	43.92	50	36.20	49.59	44.76
N9-N13	1	54	2.91	5.06	3.72	54	2.68	4.48	3.79
N9-N13	2	52	2.73	5.00	3.66	52	2.50	4.78	3.70
N13-N20	1	54	4.71	8.15	6.17	54	5.18	9.14	6.14
N13-N20	2	52	4.77	8.68	6.29	52	5.18	9.67	6.26
N20-N30	1	54	9.25	19.73	13.68	53	8.21	18.28	13.85
N20-N30	2	52	8.21	20.19	13.62	52	8.15	19.50	13.42
N20-P45	1	53	16.01	31.20	23.11	52	16.24	32.48	23.72
N20-P45	2	52	14.79	30.15	22.41	50	16.24	30.56	23.23
A1	1	54	0.94	7.38	2.56	54	0.44	6.56	2.49
A1	2	52	0.31	5.75	2.77	52	0.31	5.63	2.19
A2	1	54	1.37	13.63	4.89	54	0.94	13.44	4.59
A2	2	52	1.37	13.81	5.07	52	1.15	15.09	3.85
A3	1	53	4.48	32.56	14.69	52	4.19	29.47	13.46
A3	2	52	5.58	37.72	14.77	50	4.66	31.16	12.14

S: Session 1 or 2

APPENDIX 10.2

Table 10.8   **Conventional SEP temperature and arm length range statistics for all stroke patients, session 1.**

		Right arm				Left arm		
Variable	n	Min.	Max.	Median	n	Min.	Max.	Median
Temp. °C	51	30	34	31	51	30	34	31
Arm (cm)	48*	59	75	68	48*	59	75	68

*Some measures were not recorded

Min.   :   Minimum

Max.   :   Maximum

Temp. °C: Temperature in degrees Celsius

Arm (cm):   Arm length measured in centimetres.

APPENDIX 10.3

Table 10.9   **Conventional SEP temperature and arm length range statistics for cortical stroke patients, session 1.**

		Right arm				Left arm		
Variable	n	Min.	Max.	Median	n	Min.	Max.	Median
Temp. °C	37	30	34	31	37	30	34	31
Arm (cm)	34*	59	74	68	34*	59	74	68

APPENDIX 10.4

Table 10.10:   **Conventional SEP temperature and arm length range statistics for non-cortical stroke patients, session 1.**

		Right arm				Left arm		
Variable	n	Min.	Max.	Median	n	Min.	Max.	Median
Temp. °C	14	30	33	31.5	14	31	33	31.5
Arm (cm)	14	59	75	66.5	14	59	75	66.5

APPENDIX 10.5

Table 10.11   Conventional SEP data range statistics for all stroke patients.

| Variable | S | | Right arm | | | | Left arm | | |
		n	Min.	Max.	Median	n	Min.	Max.	Median
N9	1	50	9.19	13.61	11.17	50	8.96	13.73	10.77
N9	2	44	9.13	13.97	11.13	44	8.96	14.08	10.92
N13	1	51	12.28	17.88	14.66	51	11.87	18.15	14.43
N13	2	44	12.74	18.45	14.98	44	12.22	18.15	14.78
N20	1	46	17.86	26.68	20.98	46	17.75	24.31	20.89
N20	2	42	17.25	24.59	21.07	41	18.16	24.73	21.12
P22	1	24	20.60	29.97	23.51	22	20.89	29.97	23.40
P22	2	21	21.24	26.48	23.74	20	21.36	28.40	24.42
P25	1	22	21.86	39.64	26.76	23	21.23	30.18	25.84
P25	2	22	21.79	31.13	26.45	20	21.72	29.27	25.57
P28	1	21	25.50	37.54	29.16	21	26.13	37.72	29.51
P28	2	20	27.41	37.79	29.80	18	27.18	38.76	29.74
N30	1	44	28.70	50.36	34.98	44	30.15	48.19	35.24
N30	2	41	30.38	46.79	34.92	36	29.06	48.25	33.95
P45	1	30	36.90	52.74	46.01	35	37.07	52.21	46.09
P45	2	31	38.18	52.21	44.73	32	34.22	53.14	44.12
N9-N13	1	50	2.38	4.77	3.49	50	2.33	4.89	3.58
N9-N13	2	43	2.51	4.88	3.56	43	2.61	4.60	3.66
N13-N20	1	46	4.19	8.80	6.14	46	4.47	7.18	6.14
N13-N20	2	41	3.63	7.97	6.12	40	4.75	8.21	6.20
N20-N30	1	44	7.11	30.31	13.62	44	10.59	25.79	14.42
N20-N30	2	41	9.20	25.32	13.45	36	7.06	27.07	12.71
N20-P45	1	30	16.71	29.97	24.28	35	15.19	31.09	25.35
N20-P45	2	31	17.57	30.74	22.94	32	12.28	30.87	23.83
A1	1	51	0.00	5.63	1.25	51	0.00	4.38	1.57
A1	2	45	0.00	4.75	1.88	45	0.00	5.06	1.84
A2	1	51	0.00	16.75	4.52	51	0.00	11.41	3.75
A2	2	45	0.00	15.59	3.64	45	0.00	10.91	3.47
A3	1	38	0.00	30.66	8.12	38	0.00	27.03	10.63
A3	2	38	0.00	48.63	10.63	36	0.00	27.53	9.55

S: Session 1 or 2

APPENDIX 10.6

Table 10.12   Conventional SEP data range statistics for cortical stroke patients.

Variable	S		Right arm				Left arm		
		n	Min.	Max.	Median	n	Min.	Max.	Median
N9	1	37	9.31	13.61	11.17	37	9.13	13.50	10.83
N9	2	31	10.01	13.97	11.00	31	9.60	13.44	10.94
N13	1	37	12.28	17.88	14.72	37	11.87	17.60	14.46
N13	2	30	13.21	17.74	14.95	30	12.68	17.60	14.86
N20	1	32	17.86	26.68	21.10	32	17.75	22.64	21.01
N20	2	28	19.09	24.59	21.13	27	18.50	23.26	21.18
P22	1	17	20.60	29.10	23.28	17	20.90	25.90	23.16
P22	2	15	21.24	25.49	23.74	14	21.36	27.41	23.75
P25	1	15	23.26	39.64	27.00	15	23.16	30.18	25.84
P25	2	14	24.91	31.13	26.69	12	23.75	29.27	26.01
P28	1	14	25.50	35.91	28.66	15	26.59	36.02	29.39
P28	2	14	27.41	37.79	29.71	12	27.18	38.47	29.85
N30	1	30	28.70	50.36	35.12	31	30.15	46.73	35.27
N30	2	27	30.38	46.79	34.80	22	30.49	48.25	33.70
P45	1	19	36.90	50.98	44.87	23	37.07	52.21	46.09
P45	2	19	38.18	52.21	44.12	19	34.22	53.14	43.69
N9-N13	1	37	2.38	4.77	3.37	37	2.33	4.89	3.49
N9-N13	2	30	2.51	4.88	3.32	30	2.61	4.53	3.67
N13-N20	1	32	4.68	8.80	6.17	32	4.96	7.18	6.14
N13-N20	2	27	5.00	7.97	6.17	26	5.10	8.03	6.26
N20-N30	1	30	7.11	30.31	13.79	31	10.59	25.72	14.46
N20-N30	2	27	9.20	25.32	13.45	22	9.72	27.07	12.40
N20-P45	1	19	16.71	29.97	23.46	23	15.19	31.09	25.21
N20-P45	2	19	17.57	30.74	22.81	19	12.28	30.87	22.64
A1	1	37	0.00	5.63	1.28	37	0.00	4.38	1.69
A1	2	31	0.00	4.75	1.69	31	0.00	5.06	1.60
A2	1	37	0.00	16.75	4.16	37	0.00	11.41	3.63
A2	2	31	0.00	15.59	3.00	31	0.00	10.91	3.43
A3	1	27	0.00	30.66	7.39	28	0.00	27.03	11.47
A3	2	26	0.00	33.63	6.68	23	7.73	27.53	8.13

S: Session 1 or 2

Table 10.13   **Conventional SEP data range statistics for non-cortical stroke patients.**

Variable	S		Right arm				Left arm		
		n	Min.	Max.	Median	n	Min.	Max.	Median
N9	1	13	9.19	13.13	10.90	13	8.96	13.73	10.68
N9	2	13	9.13	13.67	11.34	13	8.96	14.08	10.90
N13	1	14	12.68	16.82	14.45	14	12.51	18.15	14.17
N13	2	14	12.74	18.45	15.05	14	12.22	18.15	14.53
N20	1	14	18.30	23.63	20.72	14	17.88	24.32	20.28
N20	2	14	17.25	24.27	20.98	14	18.16	24.73	20.80
P22	1	7	21.53	29.97	24.94	5	21.01	29.97	25.72
P22	2	6	22.11	26.48	24.27	6	22.11	28.40	25.32
P25	1	7	21.86	28.50	25.02	8	21.23	27.24	25.92
P25	2	8	21.79	29.04	24.70	8	21.72	28.84	25.19
P28	1	7	27.02	37.54	29.16	6	26.13	37.72	31.31
P28	2	6	28.17	31.19	30.15	6	27.93	38.76	29.39
N30	1	14	31.01	46.44	34.98	13	30.24	48.19	35.15
N30	2	14	30.52	40.27	35.05	14	29.06	43.30	33.95
P45	1	11	39.34	52.74	46.73	12	41.44	49.99	46.01
P45	2	12	38.49	51.70	45.61	13	36.67	49.99	44.63
N9-N13	1	13	3.02	4.65	3.67	13	3.14	4.83	3.96
N9-N13	2	13	2.98	4.78	3.63	13	2.98	4.60	3.66
N13-N20	1	14	4.19	8.48	6.08	14	4.47	6.85	6.06
N13-N20	2	14	3.63	7.40	6.09	14	4.75	8.21	6.08
N20-N30	1	14	10.82	23.98	13.38	13	10.75	25.79	14.26
N20-N30	2	14	10.89	19.03	13.54	14	7.06	20.90	13.21
N20-P45	1	11	20.95	29.94	25.96	12	19.90	30.21	25.97
N20-P45	2	12	20.95	28.90	24.79	13	17.04	28.81	25.09
A1	1	14	0.00	3.16	1.04	14	0.20	3.38	1.47
A1	2	14	0.00	4.03	1.33	14	0.00	2.81	1.08
A2	1	14	1.00	7.47	4.71	14	1.40	6.41	4.28
A2	2	14	0.97	14.44	4.48	14	0.60	6.84	4.39
A3	1	11	3.75	26.04	15.06	13	4.60	24.75	9.25
A3	2	12	4.72	48.63	12.85	13	3.53	21.81	13.48

S: Session 1 or 2

APPENDIX 11.1   Hamilton-Bruce MA, Black AB. EEG brainmapping in
                 stroke. Brain Topogr 1994;7(1):92-93.

Proceedings

Second Pan Pacific Conference
Sydney, Australia, February 10, 11 and 12, 1994

Organizers: Evian Gordon & Richard B. Silberstein

APPENDIX 11.2   Hamilton-Bruce MA, Black AB. Electroencephalographic brainmapping in stroke. Research Day '95 programme and abstracts 1995:#12.

Hamilton-Bruce M.A. and Black, A.B. (1995) Electroencephalographic brainmapping in stroke.
Research Day '95 programme and abstracts held 19th October, 1995. Number 12

RESEARCH DAY '95

PROGRAMME
&
ABSTRACTS

19th October, 1995.

Main Lecture Theatre
(2nd level, TQEH)

APPENDIX 11.3   Hamilton-Bruce MA, Black AB, Yiannikas C.
Electrophysiological brain mapping in stroke. Journal of the
Association of Neurophysiology Technicians of Australia
1996.,

Hamilton-Bruce M.A., Black, A.B. and Yiannikas, C. (1996) Electrophysiological brain mapping in stroke.
Journal of the Association of Neurophysiolory Technicians of Australia, 1996

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

ASSOCIATION OF

NEUROPHYSIOLOGY

TECHNICIANS OF

AUSTRALIA

JOURNAL OF THE ASSOCIATION

1996

APPENDIX 11.4   Hamilton-Bruce MA, Black AB, Yiannikas C, Luke CG.
Conventional and topographic quantitative electro-
encephalography and somatosensory evoked potentials in
ischaemic stroke. Seventh Australasian Psychophysiology
Conference - abstracts 1997.

Hamilton-Bruce, M.A., Black, A.B., Yiannikas C. and Luke C.G. (1997)
Conventional and topographic quantitative electroencephalography and
somatosensory evoked potentials in ischaemic stroke.
*Seventh Australasian Psychophysiology Conference and Annual General Meeting of
the Australasian Society for Psychophysiology Inc. held at Swinburne University of
Technology, Melbourne, 6-8 December 1997.*

SEVENTH AUSTRALASIAN PSYCHOPHYSIOLOGY CONFERENCE

And

Annual General Meeting of the Australasian Society for Psychophysiology Inc.

Swinburne University of Technology
Melbourne

6 – 8 December 1997

APPENDIX 11.5   Hamilton-Bruce MA, Yiannikas C, Black AB. Clinical application of somatosensory evoked potential (SEP) studies in ischaemic stroke. PERM-IT '97. 1997 Combined Annual Conference of the Australasian Radiation Protection Society Inc., Australasian College of Physical Scientists and Engineers in Medicine, The Institution of Engineers Australia, College of Biomedical Engineers, The Society for Medical and Biological Engineering (SA) Inc. conference proceedings 1997:9C-5.

Hamilton-Bruce, M.A., Yiannikas, C. and Black, A.B. (1997) Clinical
application of somatosensory evoked potential (SEP) studies in
ischaemic stroke.
*Combined Annual Conference of the Australasian Radiation Protection Society Inc.,
Australasian College of Physical Scientists and Engineers in Medicine, The
Institution of Engineers Australia, College of Biomedical Engineers, The Society for
Medical and Biological Engineering (SA) Inc. Conference Proceedings. PERM-IT '97
held 8-11 September 1997. pp. 9C-5*

PERM-IT '97
ADELAIDE South Australia
8-11 September

CONFERENCE PROCEEDINGS

• PHYSICS • ENGINEERING •
• RADIATION • MEDICINE •
with a special emphasis on
INFORMATION TECHNOLOGY

1997 Combined Annual Conference of

Australasian Radiation
Protection Society Inc

Australasian College of
Physical Scientists and
Engineers in Medicine

The Institution of Engineers
Australia, College of
Biomedical Engineers

S   M.B.E.
The Society for Medical
and Biological Engineering (SA) Inc

APPENDIX 11.6   Hamilton-Bruce MA, Yiannikas C, Black AB. Clinical application of somatosensory evoked potential (SEP) studies in ischaemic stroke. North Western Adelaide Health Service Research Day 1997 programme & abstracts 1997:#17.

kk

Hamilton-Bruce M.A. Yiannikas, C. and Black, A.B. (1997) Clinical application of somatosensory evoked potential (SEP) studies in ischaemic stroke.
Research Day 1997 programme and abstracts held 16th October, 1997. Number 17

NORTH WESTERN ADELAIDE HEALTH SERVICE

RESEARCH DAY 1997

PROGRAMME
&
ABSTRACTS

16th October, 1997.

Main Lecture Theatre
(2nd level, TQEH)

APPENDIX 11.7 Hamilton-Bruce MA, George S, Archer C, Lee R, Luke CG, Black AB. Functional outcome prediction in ischaemic stroke. Stroke Society of Australasia 1996 Annual Scientific Meeting programme and abstract book 1996:36.

Hamilton-Bruce, M.A., George, S., Archer, C., Lee, R., Luke, C.G. and Black A.B. (1996) Functional outcome prediction in ischaemic stroke.
Stroke Society of Australasia. Annual Scientific Meeting programme and abstract book 1996, pp. 36

Stroke Society of Australasia

1996 Annual Scientific Meeting

The Stamford Grand Hotel
Glenelg, SA

2 - 4 October 1996

PROGRAMME
and
ABSTRACT BOOK

APPENDIX 11.8   Hamilton-Bruce MA, George S, Archer C, Lee R, Luke CG, Black AB. Functional outcome prediction in ischaemic stroke. NWAHS Research Day '96 programme and abstracts. 1996:#12.

mm

Hamilton-Bruce, M.A., George, S., Archer, C., Lee, R., Luke, C.G. and Black A.B. (1996) Functional outcome prediction in ischaemic stroke.
NWAHS Research Day '96 programme and abstracts held at The Stamford Grand Hotel, Glenelg, SA 2-4 October, 1996. Number 12.

NWAHS

RESEARCH DAY '96

PROGRAMME
&
ABSTRACTS

24th October, 1996.

Main Lecture Theatre
(2nd level, TQEH)

APPENDIX 11.9   Hamilton-Bruce MA, George S, Archer C, Lee R, Luke CG, Black AB. Functional outcome prediction in ischaemic stroke. J Clin Neuroscience 1997;4(3):415.

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