Frontal Network Syndrome Testing: A hierarchical and time orientated approach

By

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Preface

This study represents original work by the author and has not been submitted in any form to another University. Where use was made of the work of others, it has been duly acknowledged in the text.

Signed: This 24th day of March 2014.....

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Abstract

Background

Research emanating from cognitive stroke and cognitive registries revealed that higher cortical function deficits (HCFD's), including frontal network syndromes (FNS) were common. The ubiquity of FNS involvement prompted the investigation of FNS diagnostic tests and utility of testing in the most common dementias.

Aims

1. To establish the importance of higher cortical function impairment in people with stroke.
2. To ascertain the frequency of FNS in stroke.
3. To develop a multidisciplinary diagnostic tool for FNS, that is both practical and valid.
4. To devise a system of cognitive and behavioral, tiered, diagnostic tools for the diagnosis of the three most common dementia syndromes; cognitive vascular disorders (CVD), Alzheimer's disease (AD) and frontotemporal lobe disorders (FTLD).

Methods

Two separate, prospective, cognitive registries were used for the evaluation of HCFD's and FNS. A third, specific cognitive stroke registry was used for the evaluation cognitive syndromes (CS) in stroke, the diagnostic tool and newer FNS entities such as emotional intelligence (EI) (retrospective components). A fourth cognitive registry tested a tiered, FNS based diagnostic tool in the diagnosis of common dementias (prospective component). Neuroimaging included multimodality magnetic resonance (MR) imaging and positron emission tomography (PET) brain scans.

Results

HCFD's were common in stroke, FNS frequent, no matter where in the brain the stroke occurred, the diagnostic COCONUT tool was found to be valid and practical and both CS and EI frequent in stroke. In the cognitive registry for dementias, the mean T-scores for the 3 principal frontal system syndromes for the AD group were all abnormal, save for disinhibition. For the CVD and FTLD groups, all four subcategory scores were abnormal. Disinhibition differed between the AD and FTLD groups (ANOVA, $p=0.02$) and there was a strong association between the memory for 5 words test and a significant difference in the WLT score among the 3 groups (ANOVA, $p=0.0233$). There was a strong association between the FDG-PET and the disease subtype ($p<0.0001$).

Conclusion

Both CS and FNS are frequent in stroke.

FNS subtests and neuroimaging revealed that disinhibition, word list generation, 5 word memory testing and PET brain imaging may help distinguish the three most common dementia subtypes.

Chapter 1. Introduction

Frontal lobe lesions and the consequent brain behavior relationship is a science that is at best only a few decades old, gaining momentum only by the 1980's. Two pivotal frontal lobe brain behavior studies were reported in the 19th century, within a few years of each other, one in the USA, the other one in France. Dr. John Harlow described the story of Phineas Gage's survival and profound behavioral impairment after a 3 ½ foot, 1 inch diameter iron tamping rod inadvertently passed through his frontal lobes in 1848 and reported in the Publications of the Massachusetts Medical Society in 1868 [1,2]. The second was Paul Broca's expressive aphasia pathological study, implicating the posterior, inferior frontal lobe in expressive speech [3]. Soon thereafter, other important contributions in the field such as Brodmann's cyto-architectonic brain studies and the emerging field of experimental psychology and Freud's writings prompted the American neurologist, Tilney in 1928 to suggest that the human evolutionary period should be called the age of the frontal lobes [4]. For several reasons these predictions did not materialize for most of the 20th century. Soon thereafter, psychiatry as a discipline, did not emphasize brain behavior relationships and neurology became relatively restricted to so-called elementary neurological syndromes of sensorimotor, visual and coordination systems. Penfield's contribution in the 1950's (intra-operative stimulation) was significant in that although he elicited a motor response to stimulation of the motor cortex, frontal lobe stimulation revealed no response at all [5]. Pick's disease was

described in 1892 and although it could have served as a very revealing pathology of differing frontal functions (as frontotemporal lobe dementia does today), it was largely ignored because of the fact that several different types of pathology, in addition to Pick bodies, can cause the so called frontotemporal lobe dementia (FTLD). Pick's is a very infrequent pathology, while FTLD is a common dementia. Hence, because of this pathology-clinical mismatch that occurred over the next century, the FTLD clinical syndrome received little attention [6]. Luria's unique and seminal contributions to frontal lobe function, gleaned largely from traumatic brain injury patients still profoundly influences neuropsychology today [7]. Similarly, Lhermitte's innovative style of frontal testing outside the usual office or hospital setting, illuminated how simple techniques may be very informative in discerning frontal brain behavior relationships. He described how field dependent behavior syndromes frequently emerge, consequent to disruptions of the mirror neuron network in the brain [8,9].

Other reasons why this has been so difficult, include the fact that patients with frontal lobe damage rarely initiate clinical evaluation and we test what we have tests for. Tests for many symptoms, syndromes and behaviors that cause someone to be irascible, facetious, puerile, profane, lacking curiosity, have aspontaneity and lack of foresight, do not exist. A number of researchers have devised metric tests that sample various components of frontal function. These include the Wisconsin Card Sorting test [10], Stroop test [11], Iowa Gambling Test [12], BRIEF [13], FRSBe [14], DKEFS [15], FAB [16], FBI [17], various trail

making tests such as the CTMT [18], Tower of London Test [19] and the EXIT [20].

Mesulam emphasized the frequent and surprising paucity of formal neuropsychological deficits associated with lesions of the frontal lobe lesions, some patients having normal scores in all tests. Behavioral tests however are more likely to elicit abnormalities [21]. He also proposed the term frontal network syndrome (as opposed to frontal lobe syndrome), in view of the most frequent causes including multifocal, subcortical processes such as cerebrovascular disease, multiple sclerosis and toxic metabolic encephalopathies, rather than lesions of the frontal lobes themselves [22-24].

With a single, landmark, case report launching clinical interest in frontal syndromes just over 100 years ago, the foregoing discussion has attempted to elucidate the problems encountered and their probable reasons why further testing, interest and the delineation of frontal syndromes has been lagging. Clinical experience with acute neurological patients such as stroke encephalopathy, multiple sclerosis, seizures and traumatic brain injury indicates that frontal syndromes are not only frequent, but likely the most common, not only neurological, but of cognitive syndromes. The presentation can be dramatic, and obvious, but often also subtle, covert and even frankly denied by the patient. A relatively frugal armamentarium for testing frontal syndromes is likely related to the limited understanding we have of the extent and nature of frontal syndromes.

Accordingly, a sequence of research questions were formulated, initially using the very common entity of stroke as the pathological domain. Isolated case reports or case series alone were inadequate in gaining insights as to the frequency of higher cortical function deficits (HCFD's), cognitive syndromes (CS) and frontal network syndromes (FNS). Hence a registry-based approach was considered and subsequently specific HCFD subtypes, including FNS were evaluated. The wealth of information concerning brain function and dysfunction from allied and overlapping disciplines such as psychiatry, psychology, speech and language, cognitive neuroscience and behavioral neurology was reviewed and the relative paucity of available tests for the vast panoply of human cognitive brain disorders was sobering. Therefore efforts to devise a comprehensive, yet practical test was researched and thereafter tested for its validity in the appropriate clinical contexts.

Aims and Objectives

1. To establish the importance of higher cortical function impairment in people with stroke.

2. To ascertain the frequency of FNS in stroke.

3. To develop a multidisciplinary diagnostic tool for FNS, that is both practical and valid.

4. To devise a system of cognitive and behavioral, tiered, diagnostic tools for diagnosis of the three most common dementia syndromes; cognitive vascular disorders (CVD), Alzheimer's disease (AD) and frontotemporal lobe disorders (FTLD).

Objective 1. To determine whether examination with frontal systems tests and neuroimaging, the most common dementia disorders may be distinguished.

Objective 2. Evaluate the utility of a context appropriate, tiered, FNS test battery, incorporating behavioral neurological, neuropsychiatric and neuropsychological components and compared to MRI brain (structural) and metabolic PET brain scanning (functional) to facilitate the diagnosis of the 3 most common dementia syndromes; AD, CVD and FTLD.

Chapter 2: Review of the Literature

The long time reliance on autopsy studies to determine brain behavior relationships was finally over with the advent of increasingly sophisticated cerebral computerized tomography (CT) scanning. This was followed closely by more sophisticated neuroimaging including magnetic resonance imaging (MRI) for anatomical definition and positron emission computed tomographic (PET) studies for functional brain imaging starting in the 1980's. The convergence of clinical studies from neuropsychology, neurology and neuroimaging culminated in a long overdue surge in frontal lobe research. Endeavors to promote brain and mind research continued, with the next decade (1990's) being declared the decade of the brain [25] and the following decade beginning in 2000, led to the concept of the century of the mind, with Brain-Mind institutes forming at major universities that garner a multidisciplinary approach, for best results. Two examples include the McGovern Institute for Brain Research MIT, Massachusetts and Mind Brain Behavior Institute at Columbia University, New York, USA.

Approximately 90% of the brain is involved in cognition, based on cerebral cyto-architectonics [26]. The most important and pervasive cognitive processes, frontal network syndromes (FNS), are ubiquitous in neurological and psychiatric disease yet measurement remains poor with few available tests [27-29]. The most commonly clinically employed test, the Mini Mental State Examination (MMSE), does not even measure frontal systems [30]. Hence, there exists a

dilemma between the need for accurate clinical frontal network system assessment and the current battery of tests available for this purpose. Clinical cerebrovascular, neurological decision-making for example, is severely constrained by a 4.5 hour, so called thrombolytic therapy window [31]. In the setting of multiple concurrent tests including neuro-imaging, laboratory and cardiac investigations, this does not leave more than a few minutes for clinical assessment of the patient. During a typical stroke, approximately 2 million neurons and 14 billion synapses are lost each minute [32]. In this emergent setting, there is no place for formal neuropsychological assessment. It is also common experience in clinical practice that cognitive evaluation is challenging in the various stage of dementia. In some, the degree of cooperation or attention is limited to no more than a few minutes at best. Historically and philosophically, testing of the higher cortical brain functions has been approached differently by the three major disciplines (Neurology, Psychiatry, Neuropsychology) concerned with assessment of behavioral and cognitive effects of brain lesions and conditions. Each have different "cultures" and approaches to this clinical challenge but because each has unique contributions, they complement each other. These include i) behavioral neurological approach comprising of a myriad of syndromes that are best described in ordinal and nominal data terms, ii) neuropsychiatric approach with syndromes described in terms of pre-specified criteria (DSM-IV) and configured to nominal data and iii) neuropsychological battery approach, almost exclusively described according to numerical data and compared to normative data, less often ordinal and nominal data.

Time is brain (stroke) and time is limited (dementia for example). This necessitates a multi-tiered, time based, cognitive testing approach. To benefit from all the varying clinical neuroscience approaches, the FNS testing methodology should be cross-disciplinary while using a time based battery of tests that ranges from minutes to several hours. The special relevance to FNS testing is advocated because this expansive cognitive network may be viewed as a supervisory and wide ranging cognitive system (meta-cognition) that may be the most sensitive indicator of cognitive status.

To complicate matters however, cognitive reserve, may mask brain pathology until late, in certain brain disease processes. People with similar cognitive impairment may have markedly different Alzheimer disease pathology for example, depending on their degree of brain and cognitive reserve. Because of the cognitive reserve hypothesis, now well buttressed by clinico-radiologic studies, clinical examination alone cannot discern cognitive impairment [33]. The cognitive reserve hypothesis proposes that people with similar cognitive impairments or even no impairment at all, may nevertheless have rampant Alzheimer pathology [34]. Hence clinical psychometric testing is unlikely to reliably diagnose many people that may benefit from specific disease therapies. Metabolic testing with positron emission tomography (PET) brain scanning is known to improve diagnosis and extend the window of AD diagnosis into the mild clinical and even preclinical phase. In addition to psychometric features, it is

possible that certain behavioral neurological tests can diagnose disease earlier [35].

Another facet of complexity concerns the increasing number of classic dementia presentations being encountered, that are caused by other treatable and at times completely reversible medical and neurological diseases. Examples of masqueraders of Alzheimer's disease for example, include cognitive vascular disorders [36], cryptococcal meningitis [37,38], hepatic encephalopathy [39] and masqueraders of frontotemporal lobe disorders such as Whipple's disease [40] and multiple sclerosis [41]. This is underscored by the recent revisions to the diagnostic criteria for Alzheimer's disease released 2010 Alzheimer's Association International Conference on Alzheimer's Disease (AAICAD) [42].

Finally, Alzheimer's disease is today regarded as a vascular disease where clinically, there is a continuum from stroke only and to Alzheimer's disease only, with the vast majority of people having features of both neuronal degeneration and vascular cognitive impairment [43].

As FNS are common to all these disease entities and as the most pervasive cognitive function, in addition to its supervisory role, it makes sense to measure and monitor these, somewhat akin to fever and infection.

Dementia diagnosis and the various subtypes are challenging in the absence of biomarkers. Four different frontotemporal lobe degenerations subtypes are recognized and at least 4 different clinical Alzheimer disease subtypes known, with both entities having a frontal variant, with predominant behavioral presentation [44]. In addition the neuropathology is becoming more complex with a steadily increasing stream of new discoveries. However, treatment options and clinical trials depend on accurate diagnosis [45]. For example, anticholinergic therapy is of proven benefit in AD, serotonergic therapy has moderate scientific support in the treatment of FTLD [46] and cognitive vascular disorder (CVD) may benefit from dopaminergic, cholinergic as well as serotonergic therapies [47]. Importantly, all therapies are reliant on accurate diagnosis and incorrect treatment may lead to worsening [48]. It is a commonplace experience in clinical practice that cognitive evaluation is challenging in the various stages of dementia. In some, the degree of cooperation or attention is limited to no more than a few minutes at best. Research based and emanating from cognitive stroke registries for example, revealed that higher function abnormalities, including frontal network syndromes (FNS) were common in acute and sub-acute stroke [49,50]. In addition FNS may manifest no matter where the brain lesion, whether frontally located, sub-cortically, posteriorly or even sub-tentorially. An analysis of sub-tentorial stroke, found FNS in at least half of patients with this location of stroke. Many of these patients were unable to have comprehensive testing in these settings [51].

Even though much progress has been made, even brief reflection of other cognitive functions of the frontal networks such as emotional intelligence, creativity, savant abilities, artistic ability, artistic appreciation, spirituality, religiosity and the role of dreaming in maintaining optimum brain health, provides sobering prospects of what is still unchartered territory. Currently we are armed with the most popular, simple bedside tests (MMSE, MOCA) that provide helpful guidance for distinguishing our most common dementia syndromes, but these, as well as standard neuropsychological tests provide little, if any information, on the myriad of other frontal syndromes that have been documented [52-54]. Until now there has been a major focus on memory and subsequently executive function testing in common neurological conditions such as dementia, stroke, multiple sclerosis and traumatic brain injury with other FNS not formally tested [55]. For example, with frontotemporal lobe dementia or degeneration, it has been shown that an early presentation and useful way of monitoring the illness, may be through evaluation of artwork by the patient [56].

This brings us to consider the 'creative explosion' or 'big bang of human evolution' that occurred within the last 30 000 - 40 000 years ago [57]. Convergent evidence from archeology, genetics and evolutionary neuropsychology have forged a well supported hypothesis, that working memory (a core frontal systems function) was the so called 'cognitive missing link' that enabled a cognitive fluidity and networking of the various intelligence domains (social, technical, natural history) of the human mind, culminating in cross modal

connectivity and thence creativity. Although we do not have tests for a conundrum of frontal functions that we evolved with, we can at least test working memory, which is regarded as the 'engine' of cognitive connectivity and executive function [58].

Sometimes we find simple tests that may discern and diagnose complex processes. The mirror neuron system (MNS) for example, evolved at some stage in our primate history about 60 million years ago and can be affected by cerebral lesions. We can test for the MNS by documenting syndromes such as echopraxia, utilization behavior and environmental dependency syndromes. These are not commonly employed tests, yet they offer an important opportunity of how we can improve neurological evaluation and monitoring of complex FNS [59]. Together, the working memory circuit and the mirror neuron circuitry, both extensive frontoparietal cerebral circuits, are arguably the key circuits that made us human and both are core frontal systems circuits that can be assessed clinically, by relatively simple bedsides tests.

Another important area of active research today is the role of sleep and particularly dreaming, in FNS. Dreaming has been shown to improve memory, executive function, attention, depression and creativity. Current hypotheses regard dreaming as a critical survival attribute, particularly with regards to optimizing our polyadic relationships in society, seen by some as our biggest challenge as humans [60]. The adage; 'we test for what we have tests for' is

particularly pertinent in this discussion and serves as a reminder of the vast opportunities in cognitive neuroscience that await discovery. At the present time, with the tsunami of dementing illness upon us, coupled by the expense of cerebral assessments such as brain scans, any help we can muster from simple, quick and reliable tools currently available, serves as the conceptual approach in this study.

Chapter 3. Methodology

General Methodological Approaches in the included studies

Participants

Consecutive stroke and cognitive impairment patients, aged 18-90 years, were accrued through prospectively coded, dedicated stroke and cognitive disorders registries in tertiary referral centers. These were approved by the relevant University Institutional Review Boards and the latter two registries were also in compliance with HIPAA (Health Insurance Portability and Accountability Act) regulations when this was enacted.

1. The NIH-NINDS Stroke Data Bank (New York)

Under the following contracts;

N01-NS 2-2302, N01-NS-2-2384, N01-NS-2-2398, N01-NS-2-2399, N01-NS-6-2305

Status of stroke research fellow (1990-1991)

2. The Durban Stroke Data Bank. IRB approval University of Natal, Durban, South Africa (memorandum dated signed)

Status: Principal Investigator (1992-1998)

3. The USF-TGH Stroke Registry. IRB # 102354 (University of South Florida)

Status: Principal Investigator (2002-2006)

4. The USF-Cognitive Stroke Registry. IRB # 106113 (University of South Florida)

Status: Principal Investigator (2007-2010)

Consent

All patients signed informed consent for the evaluation and the collection of the their neurological, medical and neuro-cognitive data.

Ethics

This thesis and registry #4 was approved by the Ethics Board of the University of Kwa-Zulu Natal in conjunction with the University of South Florida IRB application # 106113 (Appendix 2).

Diagnosis of dementias

Analysis of the dementia subtypes was performed retrospectively. The DSM-IV criteria were used for Alzheimer's disease (AD) and cognitive vascular disorder (CVD) diagnosis [61]. For the Frontotemporal lobe disorders (FTLD), the core diagnostic criteria by Neary et al were used [62]. In brief these included insidious onset and gradual progression, early decline in social interpersonal conduct,

early impairment in regulation of personal conduct, early emotional blunting and early loss of insight.

Neuropsychological Testing used in the registries included semi-quantitative bedside and metric neuropsychological tests

Semi-quantitative bedside tests

Frontal Systems Behavioral Scale (FRSBE) [63]

Mini-Mental State Examination (MMSE) [64]

Montreal Cognitive Assessment Test (MOCA) [65]

Orientation for 5 items

Serial 7's x 5

Memory for 5 words at 5 minutes

Word list generation test (WLT) using the letter "F" [66]

Luria Motor Sequence test [67].

Metric Neuropsychological, behavioral and language tests

Computerized Wisconsin Card Sorting Test [68]

Tower of London Test [69]

Behavioral Rating Inventory for Executive Function (BRIEF) [70]

Frontal System Behavioral Scale (FRSBE) [63]

Emotional Intelligence Quotient (Bar-On) [71]

Computerized Iowa Gambling Test [72]

Stroop Test [73]

Comprehensive Trail Making Test [74]

Letter/category fluency tests [75].

Neuroradiology

1. Anatomical structural brain scanning

All patients (unless contraindications existed) had multimodality MR imaging, MRI T1 and T2, fluid attenuation inversion recovery (FLAIR), diffusion weighted imaging (DWI), magnetic resonance angiography (MRA) to exclude secondary dementia causes such as brain tumor, stroke, multiple sclerosis as well as assessing for leukoaraoisis and degree of generalized and focal atrophy.

2. Functional brain scanning

Positron emission tomography (PET) ^{18}F Fluorodeoxyglucose (FDG-PET) brain scans were performed if any uncertainty existed with respect to dementia subtype in accordance with FDA regulations. In addition, PET scans provided an indication of cognitive reserve pertaining to a particular individual. Following intravenous injection of ^{18}F fluorodeoxyglucose, with a dose of 15 milli Curies (mCi), the patient was kept in a quiet, darkened room for 60 minutes during the uptake phase. Standard acquisition time was 15 minutes. A single bed PET and

co-acquired, low dose CT scan of the same areas was performed. Attenuation corrected PET images of the brain were created in sagittal, coronal and transverse projections and reviewed on a computer work-station. Using GE cortex ID software, with comparison to aged matched normal, z-scores of regional hypometabolism were obtained in 10 regions of interest and a z-score of 2.0 or greater regarded as statistically significant. A General Electric Brilliance LS camera was used.

Chapter 4. Results

Overview and synthesis of results relating to the studies

A. Results from specific research and previous publications focusing on cognition and stroke

The two initial clinical registries established that higher function abnormalities, including FNS, were common in acute and sub-acute stroke period [49]. The initial registry was the first computerized registry spanning four major academic institutions in the USA (New York, Boston, Baltimore, Chicago), but did not have a predefined category for diagnosis of frontal lobe lesions, frontal network systems syndromes or executive dysfunction. This was therefore one of the aims of the stroke data bank developed in Durban, South Africa, with the notable finding, that at least by relatively crude methods, FNS occurred in approximately 9.2% of patients with stroke [50].

Subsequent clinically based research registries revealed that FNS may manifest no matter where the brain lesion, whether frontally located, subcortically, posteriorly or even subtentorially [51]. In a separate analysis of subtentorial stroke, both isolated cerebellar lesions and brainstem strokes, in the largest series of its kind to date, revealed that FNS occurred in almost half (47%) of the patients, who showed impairment on frontal tasks and 40% had significant

impairment on delayed recall with sparing of immediate memory and visuospatial skills [76]. Retrospectively, this is not surprising as the frontal lobes and their networks connect to all other regions of the brain. Further research into the neurobiological substrates of FNS being caused by brainstem or cerebellar stroke, revealed that a neuroimaging correlate was found in the supratentorial region, that is, within the cerebral cortex consequent to the isolated brainstem or cerebellar stroke by SPECT brain scanning, suggesting that a neurotransmitter perturbation was a likely candidate [77]. This was corroborated by another clinical study that revealed minimal or no long tract signs as measured by the NIH stroke scale in the setting of FNS, caused by isolated brainstem or cerebellar stroke [78].

More recent studies (2009-2012) addressing the key problems of clinical FNS measurement and its most important subcomponents

1. A new test was devised that incorporated cognitive, behavioral neurological and neuropsychiatric syndromes

Several notable findings emanating from this research included; the relative paucity of both bedside and metric tests to measure frontal cognitive or executive type function, even less behavioral neurological tests and the very infrequent inclusion of so called neuropsychiatric syndrome assessments in studies of cognitive assessment in stroke. A semi-quantitative bedside test was devised incorporating cognitive, neuropsychiatric and behavioral syndromes that enables

assessment within approximately 20 minutes (COCONUTS). During the conduction of this research it was also appreciated that many patients were unable to have comprehensive testing in these settings, let alone extensive testing traditionally performed by neuropsychologists. By incorporating the much more extensive testing of syndromes that are germane to behavioral neurology and neuropsychiatry, a more accurate appraisal of true FNS is accomplished [79].

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ACTA NEUROLOGICA
SCANDINAVICA

Comprehensive cognitive neurological assessment in stroke

Hoffmann M, Schmitt F, Bromley E. Comprehensive cognitive neurological assessment in stroke.
Acta Neurol Scand 2009: 119: 162–171.

Background – Cognitive syndromes (CS) after stroke may be important to measure and monitor for management and emerging therapies. *Aim* – To incorporate known behavioral neurological and neuropsychiatric syndromes into a bedside cognitive assessment in patients with stroke. *Methods* – A validated cognitive examination (comprehensive cognitive neurological test in stroke, Coconuts) was administered during the first month of stroke presentation and analyzed according to five large-scale networks for cognition and correlated with neuropsychological tests. Validity testing of the test was performed for overall sensitivity, specificity, positive predictive value and negative predictive value to stroke in comparison with MRI diagnosis of stroke as well as discriminant validity, construct validity and inter-rater reliability. *Results* – Overall the sensitivity of the Coconuts scale was 91% and specificity 35%. PPV 88% and NPV 41% vs stroke lesions using MRI. Cognitive syndrome frequencies: frontal network syndrome frequency was 908/1796 (51%), left hemisphere network syndrome frequency was 646/1796 (36%), right hemisphere network included 275/1796 (15.3%), occipitotemporal network for complex visual processing 107/1796 (6%), the hippocampal limbic network for amnesias and emotional disorders 397/1796 (22%) and miscellaneous network syndromes 481/1796 (27%). *Conclusion* – The Coconuts is a valid and practical test of a comprehensive array of known behavioral neurological and neuropsychiatric syndromes in patients with stroke.

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Key words: cognitive syndromes; stroke

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Background

Cerebrovascular disease and neuropsychiatric disorders are the leading causes of disability worldwide (1, 2). Cognitive impairment is present in the majority of patients with stroke (3–5), transient ischemia attack (6) and even in patients without stroke who have cerebrovascular risk factors (7). Cognitive syndromes were undervalued in the stroke assessment literature, yet may be important to measure and monitor neurological outcome, management and assessment of current and emerging therapies (8–20). Behavioral neurology and neuropsychiatry are replete with numerous and intriguing syndromes that occur in association with stroke. The rich diversity of some of these syndromes hint at the complexity of the underlying neural networks and at the same time remind us that simple mental status or rating scales are resoundingly inadequate for documenting these sequelae. Furthermore, neuropsychological procedures do not capture the majority of behavioral neurological syndromes in either a syndromic or metric fashion, nor is this form of evaluation practical in the acute and subacute stroke phases.

A growing body of literature identified frontal network syndromes reflecting discreet lesions outside the anatomical boundary of the frontal lobe, such as subcortical gray matter (21, 22), subcortical white matter (23–25) and with isolated lesions of the brainstem and cerebellum (25–27). Localization of a lesion may be less important than

identification of the type and extent of a cognitive syndrome. With respect to the clinical neurological dictum of 'localize the lesion', a paradigm shift may be needed in order to study the broad range of post-stroke sequelae. With the accuracy of lesion localization using multimodality magnetic resonance imaging (MRI) not in question, precise neurological deficit ascertainment is critical to monitoring improvement, deterioration or therapeutic efficacy. In addition, there has been an almost universal failure of acute stroke neuroprotective agents despite extensive success in animal models (28). This may be due in part to the reliance of most studies on oversimplistic stroke rating scales to guide evaluation of thrombolytic therapy outcomes. Another factor may be reflected in the use of brief mental status scales that under-represent frontal syndromes as well as other syndromes related to secondary and tertiary association cortex.

Although the term vascular dementia was reported for several decades, it was redefined recently to encompass the more realistic spectrum and behavior of cognitive disorders after stroke. The spectrum of vascular cognitive impairment includes the brain at risk stage, strategic infarct dementia, single and multiple stroke with cognitive impairment, leukoaraiosis-related subcortical impairment and vascular dementia (10). Most patients with cognitive disorders post-stroke recover and the entity of mild cognitive impairment of the vascular type (MCI-V) akin to the MCI of neurodegenerative disease is likely to be common (29). Some patients with stroke deteriorate in a stepwise fashion, the latter with an overall prognosis similar to Alzheimer's dementia. Many post-stroke cognitive deficits are evanescent, but some are pervasive. For example, the specific individual import for a person with post-stroke amusia might be devastating to a musician but of no consequence to some non-musicians. No studies have tested for the reported range of cognitive impairment syndromes known to behavioral neurology in a stroke population. The challenge therefore is to devise a measure that captures the wide range of impairments yet can be administered post-stroke when existing measures are impractical and/or inadequate.

Aim

With this background in mind, the aims of the present research were to devise a comprehensive and practical method of assessing the spectrum and frequency of cognitive disorders in the first month after stroke.

Methods

Subjects

Consecutive patients with stroke aged 18–90 years, were accrued through a prospectively coded dedicated cognitive stroke registry as part of a tertiary care Joint Commission on Accreditation of Healthcare Organizations (JCAHO) primary and Comprehensive Agency for Health Care Administration (AHCA) Stroke Center (Florida). Patients with coma (n = 216) and encephalopathy (n = 144) were excluded from the analyses of the 2389 stroke registry patients except for the 11 who recovered from coma and the 65 (total subtracted from 2389 – 284 = 2105) who recovered from encephalopathy sufficiently within the first month to allow cognitive testing. The 309 transient ischemic attacks (TIA) patients were not included in the analysis yielding the study number of 1796 (Fig. 1).

All patients were examined and managed by board-certified neurologists. The cognitive bedside tests were administered by trained stroke team members comprising of residents and stroke research nurses who also tested the normal volunteers, and graded stroke severity. The Stroke registry was approved by the University Institutional Review Board and in compliance with HIPAA (Health Insurance Portability and Accountability Act) regulations. All patients signed informed consent for the evaluation and collection of their neurological, medical and neurocognitive data.

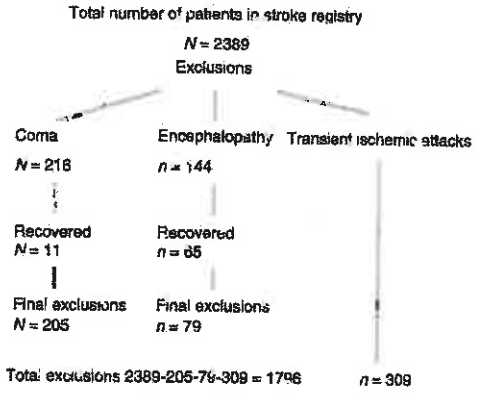

Figure 1. Cascade diagram of patients in the study and specific exclusions.

Specific exclusions

Stroke victims were excluded from the study due to persistent obtundation, metabolic derangement, encephalopathy or coma (usually due to transient ventilator dependency), history of dementia or other neurodegenerative disease, moderate and severe depression screened using the Carroll Depression Scale (30), inability to complete all the subtests, less than 8 years educational level. Moderate and severe depression but not mild were exclusions because of their effect on cognitive testing.

Cognitive testing

The cognitive examination (Coconuts: comprehensive cognitive neurological test in stroke) (Appendix 1) was administered during the first month of stroke presentation recording a cognitive deficit score and number of cognitive syndromes. The cognitive syndromes were grouped into five principal categories to reflect the five major large-scale networks for cognition and one miscellaneous group (31). Aside from the general attentional systems which needed to be intact for any further testing, these included a: (i) left hemisphere network (aphasias, Gerstmann's and angular gyrus syndrome), (ii) hippocampal limbic network (memory and emotional disorders); (iii) frontal subcortical network for executive function; (iv) right hemisphere (anosognosias, neglect, visuospatial and aprosodias); (v) complex visual processing group (occipitotemporal network) including alexias, simultanagnosia, achromatopsias, prosopagnosia, simultanagnosia, object agnosias, visual hallucinations, illusions and delusions and (vi) a group with ill-defined networks and a miscellaneous group such as dyscalculias, apraxias, delusional misidentification syndromes and disconnection syndromes. Neuropsychiatric syndromes incorporated in these networks included emotional disorders such as Involuntary Emotional Expression Disorder (IEED), delusional misidentification syndromes, apathy, disinhibition, delusions and Geschwind Gastaut syndrome.

Admittedly, the use of ordinal, nominal as well as mean values to yield a numeric score can at best be described as a semiquantitative battery similar to the Mini Mental Score. This gives an approximation of not only the nature of cognitive impairment but some measure of severity.

Validity testing of the Coconuts was evaluated along several lines including overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to stroke. The test was compared with magnetic resonance (DWI and FLAIR) imaging for the presence or absence of stroke lesion. All MRI scans were interpreted by board-certified radiologists.

Discriminant validity

In order to evaluate the scale's ability to discriminate between normal control subjects and patients with stroke; the Coconuts scale was administered to 27 normal individuals stratified for age, gender and educational level in comparison with the stroke population (n = 27).

Construct (correlational) validity

The validity of the Coconuts (how well the battery evaluates the existence of a cognitive deficit) was analyzed by comparing the Coconuts subscores association (correlation coefficients) with neuropsychological tests considered to be sensitive to the five principal domains. There is no 'gold standard' that determines the existence and severity of a cognitive syndrome. The derived scale was compared with neuropsychological tests that survey at least part of the five principal network systems. These included the Wisconsin Card Sorting Test (WCST) (32) and Frontal Systems Behavioral Inventory (FRSBE) (33) for the frontal network, the Western Aphasia Battery (WAB) (34) coefficient for the left hemisphere language network, the Rey Complex Figure Test (RCFT) (35) for the right hemisphere network, the Visual Object and Space Perception Battery (VOSP) (36) progressive silhouette subtest for the occipitotemporal network and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (37) memory subscales for the memory and limbic network. Stroke team members schooled in neuropsychological tests and neuropsychologists administered these metric tests, different to the bedside administrative personnel.

Reliability

Inter-rater reliability was determined by comparing the scores of two independent raters derived from the stroke team. Each rater was blind to the ratings made by the other. Inter-rater reliability was conducted in 27 patients and determined by calculating the Pearson r-value.

Stroke protocol

All patients had a standardized stroke protocol evaluation incorporating complete blood count,

electrolytes, blood urea nitrogen, creatinine, lipid panel, homocysteine, C-reactive protein, chest radiograph, electrocardiogram, multimodality (GE 1.5 T) MRI (T1 and T2), fluid attenuation inversion recovery (FLAIR), diffusion-weighted imaging (DWI) magnetic resonance angiography (MRA) (intracranial and cervicocephalic), echocardiography (transthoracic or transesophageal) and duplex Doppler sonography. Standardized qualitative stroke scores included the National Institute of Health Stroke Score (NIHSS) (38) and Rankin scores (17).

Stroke severity and etiology

Lesion severity was graded with the NIHSS and stroke etiology was evaluated according to the TOAST classification (Trial of Org 10172 in Acute Stroke Trial) (19) by one of the two stroke neurologists (MH and AM). An expanded version of the category 'other' was used: cerebral venous thrombosis, vasculitis, prothrombotic disorders, dissection and other vasculopathy such as posterior reversible encephalopathy syndrome (PRES), eclampsia, cerebral vasospasm, dolichoectasia and migraine-related stroke (39).

Neuroimaging

Lesion location and cerebral localization using MRI was performed according to the 3D co-planar stereotaxic digital human brain atlas, Cerefy Clinical Brain atlas version 2.0 (2004) (40).

Statistical analysis

Descriptive analysis, including mean values, 95% confidence intervals and standard deviations for continuous variables and frequency distributions for categorical variables, were obtained for all study parameters. *T*-tests were used to compare mean values and a value of $P = 0.05$ was regarded as statistically significant. Associations between continuous variables were analyzed using Pearson's product moment correlation (in particular NIHSS and to the Coconuts score). ANOVA was used to analyze differences in mean Coconuts score by lesion location and the Tukey test used to compare intergroup differences. All analyses were run in SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

The overall mean age of the patient cohort ($n = 2389$) was 62.4 years (SD 16.38), women 1187 (49.7%), race ethnicity included white 1717 (71.9%), African American 352 (14.7%), Hispanic 157 (6.6%) and other 163 (6.8%). Handedness included right 1664 (69.7%), left 45 (1.9%), ambidextrous 12 (0.5%) and uncertain in 668 (27.9%).

After the exclusion of the patients with persisting coma ($n = 216$) and encephalopathy ($n = 144$) from the analyses of the 2389 stroke registry patients and adding back 11 who recovered from coma and the 65 who recovered from encephalopathy sufficiently within the first month to allow cognitive testing yielded 2389 – 284 = 2105 patients. The 309 TIA patients were also excluded to leave a final number of 2105 – 309 = 1796 patients (Fig. 1). One or more cognitive disorders were present in 1569 of 1796 (87%). As and overall comparison, cognitive disorder frequency among stroke (1569/1796; 87%) and TIA (112/309; 36%) patients was different ($P = < 0.001$) was different. For the purposes of the remainder of the study, TIA patients were excluded.

Sensitivity, specificity, positive and negative predictive values

Overall, the sensitivity of the Coconuts scale was 91% and specificity 35%, PPV 88% and NPV 41% of the cognitive test vs stroke lesions using MRI (DWI or FLAIR) (Fig. 2).

Discriminate validity

Separate from the stroke group study, a group of 27 normal volunteers were tested and a normal Coconuts score of 1.9 (SD 1.6) was determined; hence, a score of > 3.5 was regarded as abnormal. For the Coconuts subtests, the mean memory score was 0.6 (SD 0.67), frontal 0.8 (SD 1.1), attention and concentration 0.13 (SD 0.43), visuospatial 0.3 (SD 0.5) and complex visual processing 0.1 (SD 0.3). For these subscales, abnormal scores were defined as mean + 1 SD. For subscales rating orientation, language, praxis, emotion, neglect, anosognosia, prosody and delusional misidentification syndrome, the score was 0. Therefore, any error was regarded as abnormal (Table 1).

	MRI abnormal	MRI normal	Subtotals
Coconut test abnormal	1376	183	1559
Coconut test normal	140	97	237
Subtotals	1516	280	1796

Figure 2 Magnetic resonance imaging brain vs Coconut testing results: sensitivity, specificity, positive and negative predictive values in 1796 patients.

Table 1 Coconut normal subtest mean values and SD

	Mean	SD	Mean + 2 SD
Total	1.97	1.58	5.0
Memory	0.6	0.67	2.0
Frontal	0.9	1.1	3.0
Attention (serial 7's)	0.13	0.43	1.0
Visuospatial	0.3	0.5	1.3
CVP	0.1	0.3	0.7

The count was rounded up or down to the nearest whole number. For the entities of orientation, language, praxis, emotion, neglect, anosognosia, prosody and DMS, the score was 0 thus any point was regarded as abnormal. CVP, complex visual processing; SD, Standard deviation.

In order to assess for differences between the normal and stroke groups, total score performances on the Coconuts were compared using independent *t*-tests. The mean score of an age-, gender- and education-matched group of 27 stroke patients sampling five regions of interest (frontal, parieto-occipital, temporal, subcortical, subtentorial) yielded a mean score of 18.7 (SD 10.5, *t*-test = −8.1, $P \leq 0.0001$). For the frontal stroke group, the score was 22.0 ± 13.8, the subcortical gray matter was 20.4 ± 7.2, subcortical white matter 18.6 ± 15.1, parieto-occpito-temporal 16.8 ± 7.7 and subtentorial 12. 6 ± 3.8 and normal group 2.1 ± 1.6. Comparisons for each pair revealed that the normal group differed significantly from all the stroke topographical groups. Within the stroke group, the frontal group differed significantly from all other stroke entities as well as the normal group (Fig. 3).

Construct (correlational) validity

Coconuts subscales were developed to assist the clinician in describing the neurocognitive sequelae of strokes in different regions of the brain. Therefore, total scores as well as ROI scores were evaluated between MRI-identified strokes as well as other measures of cognition and ratings of patient functioning.

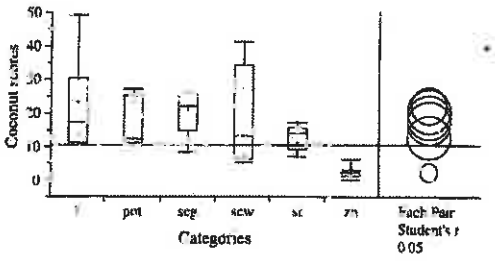

Figure 3. Analysis of variance: Coconut scores by categories. Legend: F, frontal; Par, parieto-occipitotemporal; Scg, subcortical gray matter; Scw, subcortical white matter; St, subtentorial; N, normals.

Frontal networks

The Coconut frontal network scores vs FRSBE (total family rating) Spearman correlation 0.7214 ($P = 0.085$).

The Coconut frontal network vs WCST error percentage *T* score was Pearson $r = 0.59$ (F ratio 2.9, $P = 0.04$ (quartic polynomial fit).

Left hemisphere networks

The Coconut left hemisphere network scores vs WAB, Spearman correlation: 0.9747 ($P = 0.0048$).

Right hemisphere networks

The Coconut visuospatial scores vs RCFT, Spearman correlation 0.9485 ($P = 0.0138$).

Complex visual processing networks

The Coconut complex visual processing score vs VOSP progressive silhouette subtest: Spearman correlation: 0.9177 ($P = 0.028$).

Hippocampal limbic networks

Coconut memory score vs RBANS subtests, Spearman correlation: −0.9515 ($P = 0.0001$).

Examination timing

In normal volunteers, the examination timing 13.4 min (SD 2.4).

Inter-rater reliability

Two examiners with kappa value of 0.94 indicating excellent agreement.

Cognitive syndrome frequencies

1. The left hemisphere network syndrome frequency was 646/1796 (36%) including aphasias (625/1796, 34.8%), with subtypes Broca's aphasia ($n = 225$), anomic aphasia ($n = 193$), global aphasia ($n = 151$), subcortical aphasia ($n = 85$), transcortical aphasia ($n = 15$), Wernicke's aphasia ($n = 12$), conduction aphasia ($n = 7$), aphemia ($n = 3$), pure word deafness ($n = 2$), Gerstmann's syndrome ($n = 10$) and the angular gyrus syndrome ($n = 11$).

2. The hippocampal limbic network for amnesias and emotional disorders. $n = 397$ (22%) including dysmemory ($n = 379$) emotional disorders, IEED ($n = 12$) and Geschwind Gastaut syndrome ($n = 6$).
3. Frontal (including prefrontal) network syndrome frequency was 908/1796 (51%) and only prefrontal was 581/1796 (32.3%).
4. The right hemisphere network included $n = 275$ (15.3%) instances with components of neglect ($n = 173$), anosognosia ($n = 115$), visuospatial dysfunction ($n = 70$) and aprosodia ($n = 43$).
5. The occipitotemporal network for complex visual processing ($n = 107$, 6%) included instances of alexias ($n = 45$), simultanagnosia ($n = 22$), achromatopsias ($n = 15$), prosopagnosia ($n = 18$), object agnosias ($n = 25$), Anton's syndrome ($n = 4$), cortical blindness ($n = 5$), simple visual hallucinations ($n = 10$) complex visual hallucinations (autoscopy, peduncular and palinopsias) ($n = 9$) and visual illusions ($n = 9$) (upside down vision, micropsia, polyopia, astereopsis and akinetopsia).
6. The miscellaneous network syndromes ($n = 481$, 27%) with less well-defined localization included apraxias ($n = 139$), acalculias ($n = 292$), delusional misidentification syndromes ($n = 33$), disconnection syndromes ($n = 4$), including alien hand syndrome ($n = 1$), tactile allesthesias ($n = 3$), geographical disorientation or planotopagnosia ($n = 10$).

Discussion

This study attempted to embrace the wide array of neurocognitive and principal neuropsychiatric conditions found in stroke conditions by employing a scale that is practical with good validity. As brain lesion localization today is accurately depicted using multimodality MR or CT imaging, a more pertinent challenge is to ascertain the degree and nature of neurological deficit and the likely etiology to enable appropriate measurement, monitoring and treatment. However, this requires interdisciplinary collaboration with behavioral neurology, neuropsychiatry and neuropsychology for optimum representation of brain-mind syndromes known to us.

The relatively good sensitivity but low specificity of the Coconuts test may be explained using MR imaging being oversensitive and that some silent brain lesions may not be associated with significant cognitive impairment. Alternatively, all brain lesions are supposedly associated with some degree of cognitive impairment but our testing is rudimentary. The sole deficit of isolated right temporal lobe stroke may be a complex cognitive syndrome such as Geschwind Gastaut syndrome. Rather than be localization obsessed, perhaps more useful information is the nature and extent of cognitive disturbance as a function of stroke etiology or mechanism. MR imaging is a superb modality for depicting the localization of a lesion or lesions well beyond the capabilities of clinical and cognitive examination. However, revealing non-relevant other lesions and clinically silent lesions is a potential pitfall. In addition, advanced neuroimaging may not even show the lesion at all despite a clear-cut clinical syndrome.

The high frequency of frontal disorders (51%) is a relatively novel finding in this study that warrants more precise measurement in a stroke population as a form of measurable neurological deficit that requires monitoring. The relatively higher left hemisphere network syndromes (36%) as opposed to right hemisphere networks (15.3%) might be a reflection of the increased likelihood of right hemisphere syndromes to be clinically 'silent' which in turn may be due to our paucity of appropriate tests. Moreover, the left hemisphere language network is more easily diagnosed because of speech impairment. The 22% hippocampal limbic network frequency is largely contributed to by memory disorders. This in itself is a controversial area with memory components being widely distributed in the cortical networks. However, the clinical rationale is that the hippocampus is an important orchestrator of memory processes and at least for now this understanding remains clinically useful. The relative paucity of occipitotemporal network representation (6%) is best explained by the posterior circulation receiving only one quarter of cerebral blood flow with consequently lower incidence of central embolgenic potential as well as a lower likelihood to be involved in large- and small-vessel cerebrovascular disease. A distinct difference though is the predediction for vasospastic cerebrovascular disease (PRES syndrome and eclampsia) to involve the posterior circulation with ensuing cognitive syndromes such as visual agnosia, simultanagnosia and Balint's syndrome. The relatively large proportion of miscellaneous syndromes (27%) reflects our nascent and incomplete understanding of cerebral networks and their relation to cognitive syndromes.

Behavioral neurology and neuropsychiatry share many cognitive syndromes. The syndromes

regarded as neuropsychiatric in this study include apathy (abulia), disinhibition of the frontal network syndromes, delusional misidentification syndromes, anosognosias of right hemisphere origin, Geschwind Gastaut syndrome, IEED of temporal lobe origin and sensory hallucinations, illusions and delusions seen with posterior circulation ischemic events. This study emphasizes the importance of a cross disciplinary (behavioral neurology, neuropsychiatry and neuropsychology) approach to cognitive syndromes seen in stroke.

A potential criticism of the study is the compilation of ordinal and nominal values into a total score, in that this presents methodological problems when viewed from a mathematical point of view. However, similar to other tests that do this most notably the MMSE, FAB (Frontal Assessment Battery) and the NIH stroke score, the total score or individual domain scores serve more to alert the clinician or investigator to a problem at hand (much like the ESR does for us in internal medicine) rather being specific about what it is. The total score is less important than what it signifies. At the very least, we know that a cognitive domain (or the overall score) spells impending cognitive impairment of some kind, which then necessitates more in-depth neuropsychological testing. The Coconut examination is able to discern with much greater clarity the nature of the cognitive deficit (when compared with MMSE for example) that requires further attention. It is true that one point for the diagnosis of an Anton's syndrome for example might not have the same import as one missed word on five-word memory testing. However, what is more important is that the vast array of cognitive syndromes known to us has at least been tapped into a more comprehensive manner than any other screening test currently does.

Cognitive impairment was determined to be the most frequent, the earliest and the subtlest presentation of cerebrovascular disease (10). In addition, it was showed that approximately one in six patients had cognitive impairment before stroke onset (41). With cognitive competence (or cognitive fitness) and quality of life closely tied and cognitive well-being regarded as the most important factor for institutionalization and a more powerful predictor than age and physical impairment (42). Alzheimer's disease and stroke share many risk factors such as hypertension, hyperlipidemia, smoking and homocysteine. For every person with Alzheimer's or stroke, two have vascular cognitive impairment, because of the preclinical nature of onset of cerebrovascular disease (43). In Hachinski's words, the opportunity for intervention is unprecedented (43). However, the identification of the subclinical cognitive impairment is all the more important and this study has focused on a method of elucidation of the fascinating panoply of presentation of the limping brain. Continued advances in our understanding of frontal network syndromes and their frequency in stroke augur for renewed interest in neuropharmacological treatments (44).

In conclusion, cognitive syndromes are present in the vast majority of patients with stroke. Clinical stroke scale evaluations that ignore the many and varied behavioral neurological or neuropsychiatric syndromes are not representative of the patient's neurological status.

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Appendix

Coconut Comprehensive Cognitive Neurological Test

Name	Gender	
Education years (schooling, college, other)		
Handedness (Epworth Scale). Circle		Right/Left/
Cognitive Risk Factors: Family history of Alzheimer's, head trauma		
Vascular Risk Factors: Hypertension, diabetes mellitus, dyslipidaemia, smoking, ethanol abuse homocysteine elevation, cardiac: atrial fibrillation, coronary arte valvular heart disease, patent foramen ovale, dilated cardiac chamber, leukoaraiosis, BMI >30.		
Neuropsychiatric (DSM IV):		
Depression, anxiety, obsessive compulsive disorder, substance abuse		
A. General attentional systems		
1. Orientation 5 items – score 1 for each error; 0 is normal		
Date (3 for day, month, year), day of week (1), place hospital (or clinic) (1)		
2. Attention and calculation – score 1 for each error; 0 is normal 5 serial 7's, if unable double to 128		

Appendix (Continued)

Name	Gender	Age
B. Left hemisphere network for language, Gerstmann's, Angular gyrus syndrome		
3. Speech and language – score 1 for each error, 0 is normal Naming: Name 3 objects (pen, watch, ID card) and name 3 colors.		/6
Fluency: grade as fluent (0), non-fluent (1), mute (2)		/2
Comprehension: Close your eyes, squeeze my hand. Score 1 for each failure		/2
Repetition: "Today is a sunny and windy day". No word repeated (2), partial (1), all (0)		/2
Write a sentence: What is your job ? Must contain subject and verb and make sense		/3
Reading: "close your eyes". No words read (2), partial (1) or all words (0)		/2
4. Motor speech		
Dysarthria: During interview are words slurred? No (0), mild slurring 1, marked slurring (2)		/2
Hypophonia (normal 0, voice softer than normal (1), very low volume, barely audible (2)		/2
5. Praxis		
Rating scale: Impaired 1, unable 2, smooth execution 0		
Melokinetic: Thumb – finger opposition test: Compare R + L (only if < 4/5 power)		/2
Buccolingual: Lick your lips, blow up your cheeks		/2
Ideomotor apraxia (clumsy action with pen or eating utensils).		/2
Ideational: Fold piece of paper in half, write your name and place inside a file or book		/2
6. right, left and body part orientation,		
Left pointing finger on right ear (one point for each error)		/2
C. Hippocampal limbic network for memory and emotion		
7. Memory – score 1 for each error, 0 is normal		
Short term memory: Register five words (orange, ocean, courage, rapid, building)		
Test recall at 5 min. Score one for each omission		/5
Remote memory: Recite last 3 presidents or 3 important personal dates (graduations)		/3
8. Emotions		
Lability – laughs or cries easily, out of context. Rarely (1), sometimes (2), frequently (3), never (0).		/3
Geschwind Gastaut Syndrome: Stroke or new lesion induced new evidence of viscous personality, metaphysical pre-occupation and altered physiological drives		
i) Viscous personality: One or more of the following: Circumstantiality in speech, over inclusive verbal discourse, excessive detail or information, stickiness of thought processes, interpersonal adhesiveness, prolongation of interpersonal encounters and hypergraphia		
ii) Metaphysical pre-occupation. One or more of the following: Overly philosophical pre-occupation, nascent and excessive intellectual interests in religion, philosophy and moral issues		
iii) Altered physiological drives: One or more of the following: Hyposexuality, aggression and fear		/3
Scoring: Two out of 3 components required for diagnosis		
Score as 3 components (3), 2 components (2), 1 component (1), nil (0)		
D. Prefrontal network, subcortical network for executive function and comportment		
9. Serial motor programming: Luria motor sequence test (fist-palm-hand). Demonstrate		
Sequence until patient able to replicate. Then no 5 cycles.		
Score 1 for each error in sequence		/5
10. Word fluency. Say as many words starting with S in one minute (no names or places)		
Grading: >15 (0), 13–15 (1), 10–12 (2), 7–9 (3), 4–6 (4), 0–3 (5)		/5
11. Environmental autonomy (imitation and utilization behavior).		
Imitation behavior: Maintaining eye contact, examiner pats side of face and then claps the hands without suggesting patient to follow suit		/2
Scoring: copies all actions spontaneously (2,) copies some (1), nil (0),		
Utilization behavior: Place three objects in front of patient (key, cell phone and pen. Scoring: unsolicited manipulation of 1 or 2 objects (1) or all (2)		/2
12. Interference and inhibitory control (Go/No Go paradigm)		
If examiner taps once raise your finger, if examiner taps twice do not raise finger		/3
Do three cycles: 1-1-2, 1-2-1, 2-2-1. Score 1 for each incorrect response		
13. Abulia: Poverty of action and speech. Grade as marked 2, somewhat 1, nil 0		/2
14. Disinhibition: comments or actions during interview. Occasional 1, frequent 2, nil 0		/2
15. Inpersistance: Discontinues Luria's sequences, despite repeated coaching		/1
16. Perseveration: During Luria sequence test, dominates same hand position		/1
E. Dorsal right parietofrontal network for visuospatial function, attention, emotion and prosody		
17. Visuospatial		
Copy a 2 D image of examiner's drawn flower. Impaired 1, marked 2, nil 0		/2
Copy a 3 D image representation of examiner's cube. Impaired 1, marked 2, nil 0		/2

Appendix (Continued)

Name	Gender	Age
18. Neglect syndromes		
Tactile. Simultaneous stimulation of both arms. Omission of one side score 1		/1
Auditory. Simultaneous stimulation of both ears. Omission of one side score 1		/1
Visual. Simultaneous stimulation of both fields. Omission of one side score 1		/1
Motor Neglect. Bisect10 cm line. More than 1/4 (2.5 cm) distance from midline, score 1)		/1
19. Anosognosia		
Recognizes weakness 0, underestimation 1 or complete denial of deficit or illness 2		/2
20. Prosody		
As per family, speech has become flat or monotone, then score1 if not score 0		/1
Cannot comprehend different intonations (happy/sad) (then score1 if not score 0		/1
Cannot repeat altered intonation (happy/sad), then score1 if not score 0		/1
F. Ventral occipitotemporal network for object and face recognition		
21. Complex visual processing		
Object agnosia. Cannot name 3 objects by visual inspection, but can by touch or sound		/3
Achromatopsia (cannot distinguish 2 different hues or colors). Score 1 for each error		/2
Simultanagnosia: CTPT, identify all 3 persons (score 3) or analog time telling (m/h/sec)		/3
Optic ataxia. Touch examiners finger under visual guidance. Score 1 for a miss		/1
Optic apraxia. Look left, right, up or down to command. Score 1 for any error		/1
Prosopagnosia. Does not recognize family or friends by visual appearance, score 1		/1
Line orientation. Draw 45 degree and 30 degree lines. Match 2 lines to figure. Score one for each error		/2
Subjective report of impaired motion perception (akinetopsia). Score 1 if present		/1
Subjective report of depth perception impairment (astereopsis). Score 1 if present		/1
Hallucinations. Simple (colors, shapes), complex (scenes, people, animals) or experiential (out of body experience or autoscopy). Score 1 if present		/1
Illusions of shape or size. Score one if present. Example macropsia or micropsia		/1
Denial of cortical blindness (Anton's syndrome). Score 1 if present		/1
G. Syndromes with ill defined neural networks		
22. Disconnection syndromes – Score 1 if present, 0 if absent.		
Alien hand syndrome. The one hand interferes with the other during routine tasks		/1
Alexia without agraphia. Can write but cannot read		/1
Pure word deafness. Hears environmental sounds but not spoken speech.		/1
23. Delusional misidentification syndromes (incorrect ID of people or place). If present 1		
Reduplicative paramnesia (person thinks that are lying or geographically elsewhere)		/1
Capgras or Fregoli's syndrome. Familiar people appear strange or vice versa		/1
H. Miscellaneous syndromes		
Amusia – may be receptive (poor appreciation of music or expressive where no longer able to play or sing. Score 1 if either is present		/1
Allesthesia. During neurological examination, transfers perceived tactile stimuli from left to the right		/1
Autoscopy. During interview reports out of body experience		/1
Synesthesia. Activation of one sensory system induces perceived sensation in another		/1
Geographical disorientation or phenotopagnosia		/1
Cognitive Score Total		–

Chapter 5. Discussion of Results

Critique of Coconuts

Apart from very good sensitivity, specificity, positive and negative predictive values of this test, the most significant clinical finding was a 51% frequency of FNS, diagnosed by this tool. This is in marked contradistinction to the initial New York based HCFD study and of 9.2% frequency in the Durban Stroke Data Bank Study, but perhaps not surprising in view of the extensive frontal tests employed and spanning at lest 3 clinical brain disciplines.

2. A paradigm shift proposal was studied, in which, rather than focus on lesion localization, the lesion seen on a brain scan was evaluated for associated cognitive deficits

As brain lesion localization is very accurately depicted by MRI brain scans, a more important diagnostic process that impacts management and prognosis is the associated nature and extent of cognitive (and elementary neurological) deficits, given a particular lesion. The diagnosis of certain signature presentations helps to create a type of cognitive compass for focused testing. In this respect, brain scanning can assist by directing the testing procedure [26]. FNS in particular, are most important in this regard, as the frontal circuitry is most expansive and a lesion almost anywhere in the brain can cause a FNS. Hence they are the most important to measure no matter where the brain lesion. In this regard, FNS may be viewed as a kind of "ESR" (erythrocyte sedimentation rate). The ESR is a laboratory test frequently used in general medicine, as a general alerting measure of detecting a problem in the organism, mostly that of inflammation of some kind. The signature syndromes and associated etiologies were summarized in the attached manuscript [80].

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Vascular cognitive syndromes: relation to stroke etiology and topography

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Background – Cognitive syndromes (CS) after stroke may be important to measure and monitor for management and emerging therapies. *Aim* – To describe the spectrum and frequency of CSs in the first month after stroke and to relate these to stroke etiology and topography. *Methods* – A validated cognitive examination was administered during the first month of stroke presentation and analyzed according to five large-scale networks for cognition and correlated with neuropsychological tests. A multivariate analysis was performed to determine association of CSs with etiology (TOAST classification), topography and neurological deficit by National Institute of Health Stroke Score (NIHSS). *Results* – Of a total of 2105 patients, one or more patients with CS was present in 1569/1796 (87%) stroke patients vs 112/309 (36%, $P \leq 0.001$) transient ischemic attack (TIA) patients. The frequency of frontal network syndromes (FNS) was 908/1796 (51%), left hemisphere network (LH) syndromes 646/1796 (36%), right hemisphere (RH) network syndromes 275/1796 (15.3%), occipitotemporal network (OT) syndromes 107/1796 (6%), hippocampal limbic (HL) network syndromes 397/1796 (22%) and miscellaneous (M) syndromes 481/1796 (27%). Stroke etiology and their signature CS by multivariate analyses revealed significant associations for LH with cardioembolism (OR 1.61, $P = 0.0029$), FNS and 'other' etiology (OR 1.96, $P \leq 0.0001$) and HL also for 'other' etiology (OR 1.57, $P = 0.0026$). Coma (OR 2.95, $P \leq 0.0001$) and encephalopathy (OR 2.82, $P \leq 0.0001$) were both associated significantly with hemorrhage. A left hemisphere lesion was associated with LH CSs (OR 9.26, $P \leq 0.0001$). An FNS was associated with frontal lesions (OR 5.19, $P \leq 0.0001$) as well as subcortical lesions (OR 1.91, $P \leq 0.0001$). The M group of CS was associated with subtentorial (OR 1.86, $P = 0.0283$) and right hemisphere lesions (OR 2.47, $P \leq 0.0001$). The LH and RH syndromes had the highest NIHSS and differed significantly from all others. *Conclusions* – (1) CSs are present in the vast majority of stroke patients. (2) Particular stroke etiological subtypes are associated with specific CS. (3) Certain signature CS results from lesions that relate to the major anatomical cognitive networks.

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Key words: cognitive syndromes; stroke etiology; topography

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Background and aim

Cognitive impairment is present in the majority of stroke (1–3), transient ischemia attack patients (4) and non-stroke patients who have cerebrovascular risk factors (5), corroborated by animal models (6, 7). Cognitive syndromes (CS) have been undervalued in the stroke assessment literature (8–17), despite the conundrum of behavioral neurology and neuropsychiatric syndromes that have been described in association with stroke. Nowadays, with excellent lesion localization by multimodality magnetic resonance imaging not in question, the nature and degree of cognitive/

neurological deficit become all the more important with the so-called silent brain lesions requiring a clinical correlate. A paradigm shift has also occurred in cognitive cerebrovascular medicine in that the term vascular dementia has been redefined. Vascular cognitive disorder is the modern umbrella term which includes a number of entities such as strategic infarct dementia, single and multiple stroke with cognitive impairment, leukoaraiosis-related subcortical impairment and vascular dementia (8). A newly coined entity, mild cognitive impairment of the vascular type (MCI-V) and the brain at risk stage are even more recently appreciated concepts that are likely to be common (18). These developments in our understanding necessitate a fresh look at the spectrum of cognitive disorders in stroke. We sought to study these cognitive vascular syndromes in a large stroke population and related them to stroke etiology, topopgraphy and stroke severity scores to facilitate clinical identification and monitoring of overall neurological deficit.

Methods

Consecutive stroke patients, aged 18–90 years were accrued through a prospectively coded, dedicated cognitive stroke registry, as part of a tertiary care JCAHO primary and Comprehensive (AHCA) Stroke Center (Florida). All patients were examined and managed by board certified neurologists. The Stroke registry was approved by the University Institutional Review Board and in compliance with HIPAA regulations. All patients signed informed consent for the evaluation and the collection of their neurological, medical and neurocognitive data.

Exclusions

Stroke victims were excluded from the study if there was a history of dementia or other neurodegenerative disease, moderate and severe depression screened by the Carroll Depression Scale (19), inability to complete all the subtests and less than 8 years of educational. Moderate and severe depression were exclusions because of its effect on cognitive testing. Persistent obtundation, metabolic derangement, encephalopathy or coma was recorded but cognitive testing was performed only in those recovering sufficiently within a month.

Cognitive testing

The cognitive examination (COCONUTS: Comprehensive Cognitive Neurological Test in Stroke) (Appendix 1) was administered during the first month of stroke presentation recording a cognitive deficit score and the number of CSs (20). The CSs were grouped into five principal categories to reflect the five major large-scale networks for cognition and one miscellaneous group (21). These included a (1) prefrontal subcortical network for executive function, (2) left hemisphere network (aphasias, Gerstmann's and angular gyrus syndrome), (3) right hemisphere (anosognosias, neglect syndomes, visuospatial and aprosodias), (4) hippocampal limbic network (memory and emotional disorders), (5) occipitotemporal network for complex visual processing (alexias, simultanagnosia, achromatopsias, prosopagnosia, simultanagnosia, object agnosias, visual hallucinations, illusions and delusions) and (6) a miscellaneous group for less well defined network associations such as dyscalculias, apraxias, delusional misidentification syndromes and disconnection syndromes. Neuropsychiatric syndromes incorporated in these networks included emotional disorders such as Involuntary Emotional Expression Disorder (IEED), delusional misidentification syndromes, apathy, disinhibition, delusions and Geschwind Gastaut syndrome.

Stroke protocol

All patients had a standardized stroke protocol evaluation incorporating complete blood count, electrolytes, blood urea nitrogen, creatinine, lipid panel, homocysteine, C-reactive protein, chest radiograph, electrocardiogram, multimodality MRI (T1, T2, fluid attenuation inversion recovery (FLAIR), diffusion-weighted imaging (DWI) magnetic resonance angiography (MRA) (intracranial and cervicocephalic), echocardiography (transthoracic or transesophageal) and cervicocephalic duplex Doppler sonography. Standardized quantitative stroke scores included the National Institute of Health Stroke Score (NIHSS) (14) and Rankin scores (16).

Stroke severity and etiology

Lesion severity was graded with the NIHSS. Stroke etiology was evaluated according to the TOAST classification (22). An expanded version of the category 'other' was used that included cerebral venous thrombosis, vasculitis, prothrombotic disorders, dissection and other vasculopathy such as posterior reversible encephalopathy syndrome (PRES), eclampsia, cerebral vasospasm, dolichoectasia and migraine-related stroke (23).

Neuroimaging

Lesion location and cerebral localization by MRI was performed according to the three-dimensional co-planar stereotaxic digital human brain atlas, Cerefy Clinical Brain atlas version 2.0 (24).

Statistical analysis

Descriptive analysis, including mean values, 95% confidence intervals and standard deviations for continuous variables and frequency distributions for categorical variables, was obtained for all study parameters. *t*-Tests were used to compare mean values and a value of $P \leq 0.05$ was considered statistically significant. Associations between continuous variables were analyzed using Pearson's product moment correlation. All analyses were run in SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). A multivariate logistic regression was used to determine if there was any association between cognitive networks and etiological classifications. The cognitive networks of interest were left hemisphere, right hemisphere, frontal network syndrome (FNS), limbic-hippocampal circuit for memory and emotion, occipitotemporal network and miscellaneous. These dependent variables, based on COCONUTS scores were recoded as binary (yes/no) for each patient. The etiological classifications included in the models were cardioembolic, hemorrhage, large vessel disease, small vessel disease, TIA, other and unknown. These independent variables were also coded as binary (yes/no). Stepwise multivariate logistic regression analyses were used to determine the significant etiological and topographical associations for each cognitive network deficit.

Results

The demographic details of the patient cohort ($n = 2389$) included a mean age of 62.4 years (SD 16.38), gender – female 1187 (49.7%), race ethnicity included white 1717 (71.9%), African American 352 (14.7%), Hispanic 157 (6.6%) and other 163 (6.8%). Handedness included right 1664 (69.7%), left 45 (1.9%), ambidextrous 12 (0.5%) and uncertain in 668 (27.9%). Coma ($n = 216$) and encephalopathy ($n = 144$) were excluded from the analyses for cognitive evaluation in the registry except for the 11 who recovered from coma and the 65 (total subtracted from 2389 – 284 = 2105) who recovered from encephalopathy sufficiently within the first month to allow cognitive testing. One or more cognitive disorders were present in 1569 of 1796 (87%) stroke patients ($P \leq 0.001$) vs 112 of 309 (36%) TIA patients. The 309 TIA patients were not included in the remainder of the analysis yielding a study number of 1796.

Cognitive syndrome frequencies

1. Frontal network syndrome frequency was 908/1796 (51%) and only prefrontal was 581/1796 (32.3%). These included instances of impaired serial motor programming, reduced word list generation ability (executive function), impaired environmental autonomy (imitation behavior and utilization behavior), abulia, disinhibition, impersistence and perseveration.
2. The left hemisphere network syndrome frequency was 646/1796 (36%), which included aphasias (625/1796, 34.8%) and their component subtypes and related disorders. Broca's aphasia ($n = 225$), anomic aphasia ($n = 193$), global aphasia ($n = 151$), subcortical aphasia ($n = 85$), transcortical aphasia ($n = 15$), Wernicke's aphasia ($n = 12$), conduction aphasia ($n = 7$), aphemia ($n = 3$), pure word deafness ($n = 2$), Gerstmann's syndrome ($n = 10$) and the angular gyrus syndrome ($n = 11$).
3. The right hemisphere network included $n = 275$ (15.3%) instances with components of neglect ($n = 173$), anosognosia ($n = 115$), visuospatial dysfunction ($n = 70$) and aprosodia ($n = 43$).
4. The occipitotemporal network for complex visual processing $n = 107$ (5%) included instances of alexias ($n = 45$), simultanagnosia ($n = 22$), achromatopsias ($n = 15$), prosopagnosia ($n = 18$), object agnosias ($n = 25$), Anton's syndrome ($n = 4$), cortical blindness ($n = 5$), simple visual hallucinations ($n = 10$) complex visual hallucinations (including autoscopy, peduncular and palinopsias) ($n = 9$) and visual illusions ($n = 9$) (upside down vision, micropsia, polyopia, astereopsis and akinetopsia).
5. The hippocampal limbic network for amnesias and emotional disorders ($n = 397$, 22%), included instances of dysmemory ($n = 379$), emotional disorders, IEED ($n = 12$) and Geschwind Gastaut syndrome ($n = 6$).
6. The miscellaneous network syndromes ($n = 481$, 27%) with less well defined localization included apraxias ($n = 139$), acalculias ($n = 292$), delusional misidentification syndromes ($n = 33$), geographical disorientation or planotopagnosia ($n = 10$), disconnection syndromes ($n = 4$), tactile allesthesias ($n = 3$) and alien hand syndrome ($n = 1$).

Table 1 Multivariate analysis of cognitive networks by etiology and location

Cog network	Etiology (OR, *P*-value)	Location (OR, *P*-value)
Left hemisphere	Cardioembolism (1.61, 0.0029)	Left hem (9.26, <0.0001) Parietal (2.27, <0.0001)
Frontal network	Other (1.96, <0.0001)	Frontal lobe (5.19, <0.0001) Subcor/ws (1.91, <0.0001)
Limbic memory	Other (1.57, 0.0026)	Nil
Right hemisphere	Nil	Right hem (10.32, <0.0001) Parietal (2.39, <0.0001)
Occipitotemporal	Nil	Occipital (2.4, <0.0001) Left hem (1.84, 0.0183)
Miscellaneous	Nil	Brstem/cereb (1.65, 0.0283) Right hem (2.47, <0.0001)
Coma	Hemorrhage (2.49, <0.0001)	Nil
Encephalopathy	Hemorrhage (2.82, <0.0001)	Brstem/cereb (3.16, 0.0001) Right hemis (2.73, <0.0001)

Stroke etiology and their signature cognitive syndrome – multivariate analyses

Significant associations were noted for aphasia with cardioembolism, FNS and 'other' etiology (vasculitis, prothrombotic and dissection) and hippocampal limbic also for 'other' etiology (Table 1). According to the multivariate analysis model, small vessel disease, large vessel disease and cardioembolism may cause almost any CS in this study. Subgroup entities, such as vasculitis, cerebral venous thrombosis and posterior reversible encephalopathy syndrome (PRES), may also have what may be termed signature CSs. The smaller numbers in these groups do not allow any statistical analyses, but rather descriptive comments. If vasculitis was diagnosed, there was a clear preponderance of FNSs in these patients with 17/26 (65%) having associated FNSs. Prothrombotic states and cerebral venous thrombosis had FNS frequency rates of 24/68 (35%) and 10/29 (34%) respectively. With cerebral venous thrombosis, hippocampal limbic (9/29, 31%) and occipitotemporal networks (9/29; 31%) were the other most frequent cognitive impairment associations with some coexisting. The three patients in the registry with eclampsia as a subtype of the PRES syndrome all had simultanagnosia with two also satisfying the triad of Balint's syndrome. Predictably, coma and encephalopathy were significantly associated with hemorrhage.

Lesion localization affecting cognitive networks – multivariate analyses

With the advantage of accurate topographical diagnoses by multimodality MRI or CT brain scan imaging, it would be helpful to know what CSs may be most prominent or likely given a specific anatomic location. Not unexpectedly, a left hemisphere lesion was significantly associated with syndromes such as aphasia, Gerstmann's and angular gyrus syndrome. However, an FNS was associated not only with frontal lesions but also with subcortical lesions. The miscellaneous group of CSs and encephalopathy was significantly associated with brainstem, cerebellum and right hemisphere lesions (Table 1).

Neurological deficit by NIHSS and cognitive network syndromes

The five principal cognitive networks had widely differing NIH stroke scores. The left hemisphere network had the highest (mean 9.7, SD 8.1), followed by the right hemisphere (mean 9.5, SD 7.0) network, whereas frontal network (mean 5.2, SD 5.7), hippocampal limbic (mean 3.47, SD 4.2) and occipitotemporal networks (mean 6.0, SD 6.1) had relatively low scores. The right and left hemisphere NIHSS differed significantly from all others as did the frontal network and occipitotemporal. The hippocampal limbic circuit had the lowest mean NIHSS and differed from the previous two groups as well (Fig. 1).

Discussion

Brain lesion localization today is accurately depicted by multimodality MR or CT imaging. Rather than be localization obsessed, a more pertinent challenge is to ascertain degree and nature of neurological deficit and the likely etiology is to enable appropriate measurement, monitoring and treatment. MR imaging is a superb modality for depicting the localization of a lesion or lesions often well beyond the capabilities of clinical and cognitive examination. However,

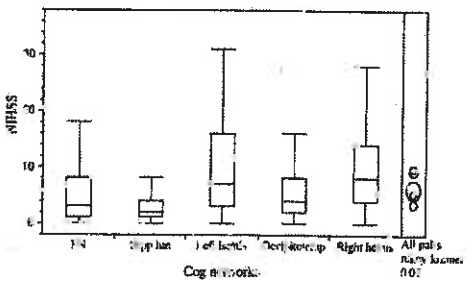

Figure 1. ANOVA of NIHSS by cognitive networks. FN, frontal network. Hipp Lim, hippocampal limbic; Left Hemis, left hemisphere; Occipito-temp, occipitotemporal; Right hemis, right hemisphere; NIHSS, National Institute of Health Stroke Scale.

revealing non-relevant other lesions and clinically silent lesions is a potential pitfall. Contrariwise, advanced neuroimaging may not even show the lesion at all despite a clear-cut clinical syndrome.

In addition to the CSs and likely mechanism depicted in Table 1, with FNS for example, mostly due to TOAST 'other' mechanism and aphasias most likely due to cardioembolism, some of the subcategories within the other group associations were notable, such as vasculitis and cerebral venous thrombosis. For example, if vasculitis is diagnosed, with the clear preponderance of FNSs (17/26; 65%), the corollary is to precisely establish the nature and degree of the diagnosed FNS to help monitor the patient. Disorders that frequently manifest with relatively small diffuse, multiple or widespread cerebral insults such as prothrombotic states and cerebral venous thrombosis also had relatively high FNS frequency rates of 24/68 (35%) and 10/29, respectively (34%), again underscoring the need to monitor FNS in such patients so as to enable a pronunciation of improvement or deterioration neurologically. With cerebral venous thrombosis, hippocampal limbic and occipitotemporal networks, both occurring in approximately one-third of patients, were the other most frequently occurring cognitive impairment associations. In such patients, in addition to monitoring more elementary neurological syndromes such as headache and seizures, these CSs are the most likely to be present and require periodic assessment. In some syndromes, a specific CS is almost invariable, as in the three patients in the registry with eclampsia as a subtype of the PRES syndrome all of whom had simultanagnosia (and two with Balint's syndrome). In a much larger series of eclampsia patients, the frequent association of simultanagnosia has previously been reported, emphasizing the importance of this CS in that particular pathophysiological entity (25).

Although it may appear self-evident that a left or right hemisphere lesion is expected to be associated with a left or right hemisphere cognitive network syndrome, the frontal subcortical networks, hippocampal limbic and parieto occipital networks have more challenging associations. Notably, any subcortical lesions is invariably associated with an FNS (OR 1.91, $P < 0.0001$), a clinical feature also seen in multiple sclerosis, diffuse axonal injury and basal ganglia disorders. The large group of miscellaneous disorders had a significant association with brainstem, cerebellar lesions as well as right hemisphere lesions. This may imply that we have a great deal to learn from the cerebral network localization that may emanate from lesions affecting the brainstem, cerebellum and right hemisphere. The association of frontal disorders with cerebellar lesions and the entity of peduncular hallucinosis with brainstem lesions are cases in point. Importantly, the encephalopathy group of disorders were clearly associated with brainstem, cerebellar or right hemisphere lesions, all components of the attentional matrix. The negative association of memory disorders with any pathophysiological entity speaks of the widespread and diffuse nature of memory storage as well as our rudimentary knowledge of memory function.

There were significant differences in NIHSS among the different cognitive networks with right and left hemispheric lesions having higher scores. This may constitute a bias in rating elementary neurological deficits such as sensorimotor deficits over that of cognitive impairment – a moot point. Having one cognitive deficit over another would incur different handicaps in different individuals. This underscores the need for a comprehensive cognitive assessment in addition to an appreciation of more elementary neurological impairments such as weakness, numbness, visual field loss that are most weighted in the NIHSS.

Cognitive impairment is the earliest, commonest and subtlest manifestation of cerebrovascular disease (8) and one in six patients has cognitive impairment before stroke (26). In addition, the number of neuropsychiatric syndromes identified in this study (apathy, abulia, disinhibition, delusional misidentification syndromes, anosognosia, Geschwind Gastaut syndrome, IEED, sensory hallucinations and illusions) emphasizes the importance of a cross-disciplinary approach to CSs seen in patients with stroke. Cognitive competence and quality of life are closely related and cognitive well-being is the most important for institutionalization and a more powerful predictor than age and physical impairment (27). There is also a growing literature of the commonalities in risk factors and pathophysiology of stroke and Alzheimer's disease. Statistically, for every person with Alzheimer's or stroke, two have vascular cognitive impairment (28, 29).

In conclusion, with CSs occurring in most stroke patients, it is useful to know that certain stroke mechanistic subtypes are associated with specific CSs. Moreover, specific signature CSs result from lesions that affect the different major, anatomically based, cognitive networks. Neuroimaging may be viewed as a kind of compass, which in turn should suggest certain CSs as well as likely mechanisms. In addition to improved monitoring of the deficits, this information can expedite stroke mechanism determination and then appropriate treatment. This testing approach also represents an opportunity to re-establish the pivotal importance of the

clinical method of neurology and its rightful resurrection in the era of advanced neuroimaging.

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Appendix 1

COCONUT: Comprehensive Cognitive Neurological Test

Name	Gender	Age
Education years (schooling, college, other)		
Handedness (Edworth Scale). Circle.		Right / Left / Ambidextrous
Cognitive Risk Factors: Family history of Alzheimer's, head trauma		

Appendix 1 (*Continued*)

Name	Gender	Age
Vascular Risk Factors. Hypertension, diabetes mellitus, dyslipidemia, smoking, ethanol abuse homocysteine elevation, cardiac, atrial fibrillation, coronary artery disease, valvular heart disease, patent foramen ovale, dilated cardiac chamber, leukoaraiosis, BMI ≥30.		
Neuropsychiatric (DSM IV):		
Depression, anxiety, obsessive compulsive disorder, substance abuse		
A. General attentional systems		
1. Orientation 5 items – score 1 for each error, 0 is normal		
Date (3 for day, month, year), day of week (1), place hospital (or clinic) (1)		/5
2. Attention and calculation – score 1 for each error, 0 is normal 5 serial 7's, if unable double to 128		/5
B. Left hemisphere network for language, Gerstmann's, Angular gyrus syndrome		
3. Speech and language – score 1 for each error, 0 is normal		
Naming. Name 3 objects (pen, watch, ID card) and name 3 colors		/6
Fluency grade as fluent (0), non-fluent (1), mute (2)		/2
Comprehension: Close your eyes, squeeze my hand. Score 1 for each failure		/2
Repetition: "Today is a sunny and windy day". No word repeated (2), partial (1), all (0)		/2
Write a sentence. What is your job ? Must contain subject and verb and make sense		/3
Reading: "close your eyes". No words read (2), partial (1) or all words (0)		/2
4. Motor speech		
Dysarthria. During interview are words slurred? Nil (0), mild slurring 1, marked slurring (2)		/2
Hypophonia (normal 0, voice softer than normal (1), very low volume, barely audible (2)		/2
5. Praxis		
Rating scale: Impaired1, unable 2, smooth execution 0		
Melokinetic. Thumb-finger opposition test. Compare R + L (only if ≥4/5 power)		/2
Buccolingual. Lick your lips, blow up your cheeks		/2
Ideomotor apraxia (clumsy action with pen or eating utensils)		/2
Ideational. Fold piece of paper in half, write your name and place inside a file or book		/2
6. Right, left and body part orientation.		
Left pointing finger on right ear (one point for each error)		/2
C. Hippocampal limbic network for memory and emotion		
7. Memory – score 1 for each error, 0 is normal		
Short term memory. Register five words (orange, ocean, courage, rapid, building)		
Test recall at 5 min. Score one for each omission		/5
Remote memory. Recite last 3 presidents or 3 important personal dates (graduations)		/3
8. Emotions		
Lability – laughs or cries easily out of context. Rarely (1), sometimes (2), frequently (3), never (0).		/3
Geschwind Gastaut Syndrome. Stroke or new lesion induced new evidence of viscous personality, metaphysical pre-occupation and altered physiological drives		
i) Viscous personality. One or more of the following. Circumstantiality in speech, over inclusive verbal discourse, excessive detail of information, stickiness of thought processes, interpersonal adhesiveness, prolongation of interpersonal encounters and hypergraphia		
ii) Metaphysical pre-occupation. One or more of the following: Overly philosophical pre-occupation, nascent and excessive intellectual interests in religion, philosophy and moral issues		
iii) Altered physiological drives. One or more of the following. Hyposexuality aggression and fear		
Scoring. Two out of 3 components required for diagnosis.		
Score as 3 components (3), 2 components (2), 1 component (1), nil (0)		/3
D. Prefrontal network, subcortical network for executive function and comportment		
9. Serial motor programming. Luria motor sequence test (fist palm hand). Demonstrate Sequence until patient able to replicate. Then do 5 cycles.		
Score 1 for each error in sequence		/5
10. Word fluency. Say as many words starting with S in one minute (no names or places)		
Grading: >15 (0), 13–15 (1), 10–12 (2), 7–9 (3), 4–6 (4), 0–3 (5)		/5

Appendix 1 (*Continued*)

Name	Genre	Arp
11. Environmental autonomy (imitation and utilization behavior).		
Imitation behavior: Maintaining eye contact, examiner puts side of face and then claps the hands without suggesting patient to follow suit.		
Scoring: copies all actions spontaneously (2), copies some (1), nil (0)		/2
Utilization behavior: Place three objects in front of patient: key, cell phone and pen		
Scoring: unsolicited manipulation of 1 or 2 objects (1) or all (2)		/2
12. Interference and inhibitory control (Go No Go paradigm).		
If examiner taps once, raise your finger. If examiner taps twice do not raise finger		
Do three cycles: 1-1-2, 1-2-1, 2-2-1. Score 1 for each incorrect response		/3
13. Abulia. Poverty of action and speech. Grade as marked 2, somewhat 1, nil 0		/2
14. Disinhibition, comments or actions during interview. Occasional 1, frequent 2, nil 0		/2
15. Impersistence. Discontinues Luria's sequences, despite repeated coaxing = 2		/1
16. Perseveration. During Luria sequence test, duplicates same hand position		/1
E. Dorsal right parietofrontal network for visuospatial function, attention, emotion and prosody		
17. Visuospatial		
Copy a 2 D image of examiner's drawn flower. Impaired 1, marked 2, nil 0		/2
Copy a 3 D image representation of examiner's cube. Impaired 1, marked 2, nil 0		/2
18. Neglect syndromes		
Tactile. Simultaneous stimulation of both arms. Omission of one side score 1		/1
Auditory. Simultaneous stimulation of both ears Omission of one side score 1		/1
Visual. Simultaneous stimulation of both fields Omission of one side score 1		/1
Motor Neglect. Bisect10 cm line. More than 1/4 (2.5 cm) distance from midline. score 1)		/1
19. Anosognosia		
Recognizes weakness 0, underestimation 1 or complete denial of deficit or illness 2		/2
20. Prosody		
As per family speech has become flat or monotone, then score1 if not score 0		/1
Cannot comprehend different intonations (happy/sad) (then score1 if not score 0		/1
Cannot make altered intonation (happy/sad), then score1 if not score 0		/1
F. Ventral occipitotemporal network for object and face recognition		
21. Complex visual processing		
Object agnosia. Cannot name 3 objects by visual inspection, but can by touch or sound		/3
Achromatopsia (cannot distinguish 2 different hues or colors) Score 1 for each error		/2
Simultanagnosia: CTPT, identify all 3 persons (score 1) or analog time telling (min/s)		/3
Optic ataxia: Touch examiners finger under visual guidance. Score 1 for a miss		/1
Optic apraxia: Look left, right, up or down to command. Score 1 for any error		/1
Prosopagnosia, Does not recognize family or friends by visual appearance. score 1		/1
Line orientation. Draw 45° and 30° lines. Match 2 lines to figure.		
Score one for each error		/2
Subjective report of impaired motion perception (akinetopsia) Score 1 if present		/1
Subjective report of depth perception impairment (astereopsis). Score 1 if present		/1
Hallucinations: Simple (colors, shapes), complex (scenes, people, animals) or experiential (out of body experience or autoscopy) Score 1 if present		/1
Illusions of shape or size: Score one if present. Example macropsia or micropsia		/1
Denial of cortical blindness (Anton's syndrome). Score 1 if present		/1
G. Syndromes with ill defined neural networks		
22. Disconnection syndromes – Score 1 if present, 0 if absent		
Alien hand syndrome: The one hand interferes with the other during routine tasks		/1
Alexia without agraphia: Can write but cannot read		/1
Pure word deafness. Hears environmental sounds but not spoken speech.		/1
23. Delusional misidentification syndromes (incorrect ID of people or place). If present 1		
Reduplicative paramnesia (person thinks that are living or geographically elsewhere)		/1
Capgras or Fregoli's syndrome. Familiar people appear strange or vice versa		/1

Appendix 1 (*Continued*)

Name	Gender	Age
H. Miscellaneous syndromes		
Amusia – may be receptive (poor appreciation of music or expressive where no longer able to play or sing. Score 1 if either is present		/1
Allesthesia. During neurological examination, transfers perceived tactile stimuli from left to the right		/1
Autoscopy. During interview reports out of body experience		/1
Synesthesia. Activation of one sensory system induces perceived sensation in another		/1
Geographical disorientation or planotopagnosia		/1
Cognitive Score Total		

Critique of Vascular Cognitive Syndromes: relation to stroke etiology and topography

This study determined that cognitive syndromes were even more common in stroke (87%), than in the initial registry (36%). Furthermore the relationship between stroke causes and subtype of CS, was expounded with important clinical consequences. These findings help with monitoring, treatment and outcome predictions.

3. Emotional Intelligence (EI) as an important subcomponent of frontal function

This FNS component has been rarely addressed, in neurological patients to date, including the most common ones, such as dementia, stroke traumatic brain injury and multiple sclerosis. It is well established that EI may be one of the most important, if not the most important "intelligence" for success in career advances, as well personal and social achievement. Using the stroke pathophysiological model, emotional intelligence was found to be affected by diverse lesions of the brain, however with certain areas of predilection, namely the frontal, temporal, subcortical and subtentorial structures. In addition there was a strong correlation with the other principal frontal syndromes of disinhibition, abulia (both emotionally related syndromes) and executive function [81].

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RESEARCH ARTICLE Open Access

The impact of stroke on emotional intelligence

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Abstract

Background: Emotional intelligence (EI) is important for personal, social and career success and has been linked to the frontal anterior cingulate, insula and amygdala regions.

Aim: To ascertain which stroke lesion sites impair emotional intelligence and relation to current frontal assessment measurements.

Methods: One hundred consecutive, non aphasic, independently functioning patients post stroke were evaluated with the Bar On emotional intelligence test, "known as the Emotional Quotient Inventory (EQ-i)" and frontal tests that included the Wisconsin Card Sorting Test (WCST) and Frontal Systems Behavioral Inventory (FRSBE) for correlational validity. The results of a screening, bedside frontal network syndrome test (FNS) and NIHSS to document neurological deficit were also recorded. Lesion location was determined by the Cerefy digital, coxial brain atlas.

Results: After exclusions (n = 8), patients tested (n = 92, mean age 50.1, CI: 52.9, 47.3 years) revealed that EQ-i scores were correlated (negatively) with all FRSBE T sub-scores (apathy, disinhibition, executive, total), with self reported scores correlating better than family reported scores. Regression analysis revealed age and FRSBE total scores as the most influential variables. The WCST error percentage T score did not correlate with the EQ-i scores. Based on ANOVA, there were significant differences among the lesion sites with the lowest mean EQ-i scores associated with temporal (71.5) and frontal (87.3) lesions followed by subtentorial (91.7), subcortical gray (92.6) and white (95.2) matter, and the highest scores associated with parieto-occipital lesions (113.1).

Conclusions: 1) Stroke impairs EI and is associated with apathy, disinhibition and executive functioning. 2) EI is associated with frontal, temporal, subcortical and subtentorial stroke syndromes.

Background

Emotional intelligence (EI) is a concept that may be defined in different ways by the psychological and medical disciplines that are concerned with its importance. The four-branch model (perceiving emotions, facilitating thought, understanding emotions, managing emotions) of emotional intelligence definition by Mayer and Salovey is a concept that appears popular [1]. Additionally, Bar-On has conceptualized the EI construct as comprising the ability to (i) understand emotions and express feelings, (ii) understand how others feel and relate with them (iii) manage and control emotions, (iv) use emotions in adapting to one's environment and (v) generate and use positive affect to be self-motivated in coping with daily demands, challenges and pressures [2]. EI is important for personal, social and career success [3]. EI has been studied in both healthy people and after brain illness. For example studies of specific healthy populations including nurses and doctors have also determined that high EI results in improved patient relationships and outcomes. Suboptimal physician patient communication has been correlated with increased risk of patient complaints and malpractice claims in a Canadian study of patient physician communication scores [4-6]. Studies of the most common cerebral disorders, namely stroke and dementia are beginning to implicate dissolution of the components of emotional intelligence. Frontotemporal lobe disorders (FTLD), the most common cause of dementia under the age of 60, present with frontal and behavioral symptoms and syndromes, including disorders of emotion, empathy violation of social and moral norms [7]. Furthermore, stroke, Alzheimer's disease (AD) and FTLD are regarded as a continuum of disorders in a clinical phenotypic, pathologic and genotypic sense [8], with overlap syndromes common and the need for

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even more precise clinical acumen to differentiate these disorders.

EI has been linked to the frontal anterior cingulate, insula and amygdala regions [9]. EI and stroke have rarely been formally investigated with only 2 references found by Pubmed search [10,11] in addition to other brain lesion models [12]. The overall approach for holistic brain injury assessment should be neurological, neuropsychiatric, cognitive, behavioral and emotional. Only neurological deficit is recorded in current stroke assessment scales, yet the others may be the most important from a family, social, career and rehabilitative point of view. EI has been embraced by the corporate world because of its perceived translation into social and career success [13-15]. Importantly, it is amenable to cognitive and behavioral intervention programs [16,17].

Aim

To ascertain which stroke lesion sites impair emotional intelligence and how this relates to contemporary frontal assessment measurements.

Methods

Consecutive patients, aged 18-90 years were accrued through a prospectively coded, dedicated cognitive stroke registry, as part of a tertiary care primary JCAHO (Joint Commission on Accreditation of Healthcare Organizations) and comprehensive AHCA (Agency for Health Care Administration) Stroke Center from January 2003 to December 2006. All patients (n = 2389) were examined and managed by board certified neurologists. The cognitive bedside tests were administered by trained stroke team members comprised of residents and stroke research nurses who also graded stroke severity. This cognitive bedside test screened for a range of cognitive disorders in addition to the assessment of aphasia. The Stroke registry was approved by the University Institutional Review Board and in compliance with HIPAA regulations. All patients signed informed consent for the evaluation and the collection of the their neurological, medical and neurocognitive data. Non aphasic, independently functioning patients post stroke were evaluated with the Bar-On emotional intelligence test (EQ-i) which is a self report, Likert scale assessment, yielding an Emotional Quotient and is a standardized psychometric measure of various aspects of emotional and social intelligence [2]. The test was usually administered within the first month after stroke but with a range from 1 week to 6 months post stroke. In addition, frontal tests that purport to measure executive function and other cognitive domains were used. These included the Wisconsin Card Sorting Test (WCST) [18] and the Frontal Systems Behavioral Inventory (FRSBE) [19], for correlational validity. The FRSBE is a family and self rated, normed, scoring instrument that reports measures before and after illness for apathy, disinhibition, executive function as well as a total score. A screening, bedside frontal network syndrome test (FNS) [20] for initial cognitive evaluation and NIHSS [21] to document neurological deficit were also recorded. Lesion location was determined by the Cerefy digital coxial brain atlas [22].

Exclusions

A history of dementia or other neurodegenerative disease, moderate or severe depression (because of its effect on cognitive testing), inability to complete all the subtests, substance abuse and less than 8 years educational level. Persistent obtundation, metabolic derangement, encephalopathy or coma was recorded but cognitive testing performed only in those recovering sufficiently within a month. Completion of both the screening and cognitive metric tests was necessary for inclusion in the series which yielded 100 patients for analysis.

Results

1. Demographics of patient study group (n = 100)

After exclusions, one hundred consecutive patients were eligible for analysis but because of missing data (n = 8), patients tested included (n = 92, mean age 50.1, CI: 52.9, 47.3 years), men n = 53 (58%), women n = 39 (42%) race ethnicity, Black (n = 10), Hispanic (n = 8), White (n = 72), other (n = 2). The mean education level in years was 13.8 years (95% CI: 14.4; 13.3, maximum 20 years and minimum 8 years). Overall, 38/92 (41%) of patients tested, irrespective of stroke lesion site, had abnormal EI scores as assessed by published normative data [2].

2. Correlational validity

EI total scores were negatively correlated with all FRSBE T sub-scores (apathy, disinhibition, executive, total) and the self-reported scores correlated better than family reported scores. The WCST error percentage T score did not correlate with the EI scores (Table 1). The screening frontal examination (FNS) correlated well with total EQ (0.408, $p < 0.01$).

3. Lesion site

The analysis of variance (ANOVA) test indicated that there were significant differences between the EI scores among the 6 lesion sites (F value 5.12, p = 0.0004). The lowest EI scores (reported in standard scores where 85-115 is within the normal range) were in the temporal lobe lesions (71.5), followed by the frontal lesions (87.3), subtentorial (91.7), subcortical gray matter lesions (92.6), subcortical white matter lesions (95.2) and parieto occipital lesions (113.1), (Figure 1). Of the 72 supratentorial lesion sites (subtentorial n = 20), the laterally

Table 1 EQ Total and EQ sub-scores versus FRSBE scores

FRSBE	EQ Total score	EQ intrapersonal	EQ interpersonal	EQ stress management	EQ adaptability	EQ mood score
S	-0.540	-0.518	0.353	-0.621	0.403	-0.483
SD	-0.456	0.330	-0.313	-0.369	-0.447	-0.219
SE	-0.379	0.402	-0.233	-0.486	-0.614	-0.390
ST	0.595	-0.500	-0.305	-0.524	0.584	-0.406
FA	-0.340	-0.240	0.229	-0.351	0.375	-0.171
FD	-0.227	-0.196	-0.049	0.310	-0.325	-0.115
FE	-0.335	-0.24	-0.145	-0.408	-0.393	-0.103
FT	-0.386	-0.310	0.21	-0.426	0.402	-0.177

Legend
S: Self report.
F: Family report.
A: Apathy
D: Disinhibition.
E: Executive Function.
T: Total score.
* p-value at the 0.05 level of significance
** p-value at the 0.01 level of significance.

of stroke included right (n = 37; 51%), left (n = 25; 35%) and bilateral (n = 10) lesions, (Table 2). In addition in 24 cases lesions were in 2 or more sites in the brain such as stroke lesions involving more than 1 lobe of the brain or both subcortical and cortical lesions. Not unexpectedly, in the subtentorial group (n = 20), because of the central anatomical vascular distribution of the basilar artery, lesions were almost equally distributed, right (n = 9), left (n = 8) and bilateral (n = 3).

4. Five EI subcategory scores

Intrapersonal EI correlated with all the FRSBE scores except family reported disinhibition. Interpersonal EI correlated only with the FRSBE self reported scores and not family reported scores. The stress management and adaptability EI scores correlated with all the FRSBE scores. The EI general mood scores correlated only with the self reported apathy, executive and total scores (Table 1).

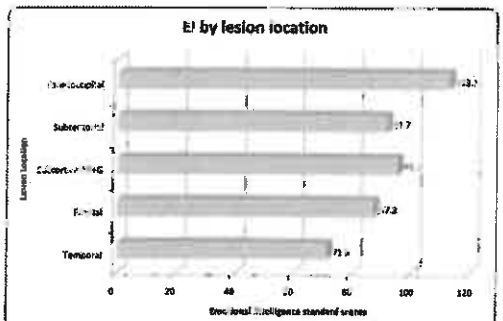

Figure 1 Emotional intelligence scores according to stroke lesion site.

5. Stroke severity and EI scores

There was a weak relationship between stroke severity as measured by the NIHSS and EI scores (Pearson correlation -0.239 significant at the 0.05 level).

6. Regression analysis

Age and FRSBE total scores were significant influential variables to total EI. With 1 year of age increase, the total EI will increase 0.29 ($p = 0.0144$) and with 1 FRSBE self report T score increase, the total EI will decrease 0.63 ($p < 0.0001$). The regression equation; Total EI = 117.838 + .279 (Age) - .621 (FRSBE-S-T).

Discussion

The main findings of this study concur with recent basic neuroscience postulates with respect to the widely distributed emotional circuitry in the brain as well as the close-knit emotion and cognitive processes. Perusal of figure 2 (with permission, Nature Publishing Group) of the more recently appreciated core and extended emotional regions of the brain does indeed represent a widely distributed cerebral network [9]. Our research with the "lesion method", agrees with this model in that diverse lesions within the stroke pathophysiological model were associated with lowered EI scores.

Clinical evidence implicating in particular the orbitofrontal cortex as part of the neural network for emotional intelligence has been suggested by previous researchers. Baron first reported emotional quotient impairment with orbitofrontal cortex lesions [10]. Likewise, in the study of Shamay-Tsoory et al, patients with

Table 2 Stroke neuro anatomical supratentorial lesion sites

Region of interest	Right	Left	Bilateral	Total
Temporal	5	1	0	6
Frontal	17	10	5	32
Subcortical Gray	4	5	2	11
Subcortical White	4	7	2	13
Parieto occipital	7	2	1	10
Total				**72**

prefrontal lesions, particularly with lesions of the orbitoprefrontal and medial frontal regions were significantly impaired in both cognitive and affective empathy as compared to parietal patients and healthy controls [11]. Furthermore, those with damage restricted to the prefrontal cortex, no matter which side, resulted in impaired empathy. Finally in their study, lesions involving the right hemisphere, patients with parietal lobe lesions were also impaired. We showed that a much more widely distributed lesion site network impairs EI, in keeping with the extensive contemporarily appreciated neurobiological emotional network. Many different brain lesions may affect EI and in our study, FI is associated with frontal, temporal, subcortical and even subtentorial stroke syndromes. However the strongest relationship at least by EI scores pertained to the frontal and temporal regions of the brain. This finding supports Pessoa's proposed extended emotional brain concept [9].

The neurobiological emotional network known as the Papez circuit, has been regarded as outdated and some have recommended that use of the term "limbic system" be abandoned [9,22]. The main reasons relate to the hippocampus, which is not part of the circuitry and the orbitofrontal cortex, which is part of it, but not included in the Papez circuit [23,24]. According to Pessoa, the emotional brain core components include the amygdala, nucleus accumbens, hypothalamus, orbitofrontal cortex, anterior cingulate cortex and ventromedial prefrontal cortex. Emotional brain extended areas include the brainstem, ventral tegmental area, hippocampus, periaqueductal gray matter, septum, basal forebrain, anterior insula, prefrontal cortex, anterior temporal lobe and posterior cingulate cortex [9].

There is evidence for a close interplay of cognitive and emotional brain circuits. The amygdala in particular, is viewed as the prime candidate for the emotion-cognition integration. The amygdala has a unique position at the geometric center of topological map and because of its extensive connections to other brain regions. Executive control is required for autonomy to override instinctive or prepotent responses with particularly important components in this network being the lateral prefrontal cortex (LPFC) for temporal information maintenance, the parietal cortex and PFC attention maintenance and the anterior cingulate cortex (ACC) for conflict detection and error monitoring. The orbito frontal cortex (OFC) and medical PFC are considered components in computing outcomes expectations. The neurochemical dimensions to these circuits include dopamine from VTA and SN (compacta) which projects to the nucleus accumbens (NA) and PFC for prediction and expectation of future rewards - a function of the dopaminergic system. Pessoa argues that one cannot separate cognitive

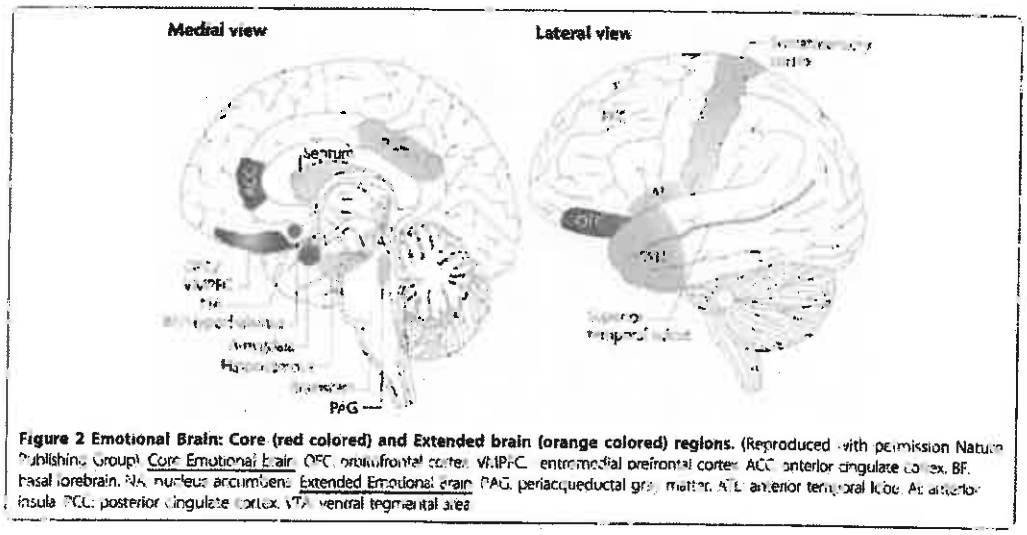

Figure 2 Emotional Brain: Core (red colored) and Extended brain (orange colored) regions. (Reproduced with permission Nature Publishing Group) Core Emotional Brain: OFC orbitofrontal cortex, vmPFC ventromedial prefrontal cortex, ACC anterior cingulate cortex, BF basal forebrain, NA nucleus accumbens. Extended Emotional Brain: PAG periaqueductal gray matter, ATL anterior temporal lobe, Ai anterior insula, PCC posterior cingulate cortex, VTA ventral tegmental area

and emotional brain contributions to executive control, "emotion and cognition conjointly and equally contribute to the control of thought and behavior. Each behavior has both affective and cognitive components, which have their biological basis in dynamic coalitions of networks" [9]. In our study, the emotion cognition interface was not specifically researched but the results of particular interest being that EI is correlated with executive function as well as apathy and disinhibition function scores.

Pathophysiological processes are important in our understanding of brain behavior relationships [25,26]. The stroke model is in a sense a "cleaner" more precise lesion method than neurodegenerative, traumatic, epilepsy or metabolic brain injuries. Cerebrovascular disorders frequently involve the frontal subcortical circuits involved in emotional and cognitive networks. Neither the commonly used stroke scales nor the bedside cognitive test, the Mini-Mental State Examination (MMSE) address these frontal network syndromes that may be the very first and most prominent manifestation of the disease. Neuropsychological tests including those focusing on frontal networks also do not capture the EI aspects at all. Specific EI tests such as the Bar-On [2] and MSCEIT (Mayer, Salovey, Caruso Emotional Intelligence Test) [27] are required to diagnose EI impairment although tests such as the FRSBE [19] and BRIEF [28] do provide some information about emotional disarray. These may be the most important deficits for people to realize, accommodate and treat.

Potential criticisms of the study relate to the methodology of testing EI and in the brain lesion determination. Self-report testing of EI as is done by the Bar-On EQ-i test as opposed to the MSCEIT remains an area of contention with some studies reporting a low correlation between two methodologies [29,30]. Brain lesions may be silent, old, incidental or undetected by standard multimodality MR imaging as is the case with diaschisis or neurochemical lesions without anatomical signature lesions (frontal hypometabolism with depression for example). Finally correlational analyses might be better performed with some of the newer composite frontal tests such as the DKEFS [31] or others focusing on specific areas such as the Iowa Gambling Test [32].

Conclusions

Stroke impairs EI and is associated with the three principal frontal syndrome complexes of apathy, disinhibition and dysexecutive functioning. In addition it was demonstrated that an extensive emotional network, at least by lesion analysis, impairs EI. Does EI testing really matter? Neuroplasticity is an inherent process whereby the brain shapes itself through repeated experiences. The corresponding neural connections are strengthened and the ones less used, weakened [33]. The discovery of the relatively late maturation of the prefrontal circuitry for modulation of emotion suggests a neurological window of opportunity for helping children (or adults), for example to learn the best EI repertoire [34]. With the newly appreciated concept of adult neurogenesis and ongoing neuroplasticity, one may extrapolate that this applies to people with stroke or traumatic brain injury.

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Authors' contributions

[illegible] conceived of the study, methodology with assistance, collected the data, helped and wrote the manuscript, RC performed all statistical analyses, BH contributed to the conception design of study and critical review of intellectual content of data and LRC contributed to the acquisition, presentation of data and review of intellectual content of data. All authors have read and approved the content of this manuscript.

Competing interests

The authors declare that they have no competing interests.

This includes:

1. Financial competing interests

In the past five years none have received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future.

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6. There are no other financial competing interests.

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Emotional intelligence (EI) assessment is even today, rarely performed, in the clinical setting, even less so in the subacute period of the first 2 weeks of a neurological illness such as stroke. Yet it is the most important and often the earliest presenting symptom of frontotemporal lobe disorder or dementia, the most common dementia under the age of 65 years. This research revealed that with vascular disease of the brain, the extensively distributed emotional circuitry, is invariably afflicted. This is of great import in the setting of FTLD where the initial neurodegenerative processes affects the core emotional circuitry of the brain.

B. Results – prospective component

4. Frontal Network Syndrome Testing: Clinical tests and PET brain imaging help distinguish the 3 most common dementia subtypes

The focus of this aspect of the research problem was to combine simple, yet accurate clinical tests together with a biomarker (in this case neuroimaging in the form of PET scanning). The importance of the latter was both to improve diagnosis, but also to account for the component of cognitive reserve in the individual patients.

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Frontal Network Syndrome Testing: Clinical Tests and Positron Emission Tomography Brain Imaging Help Distinguish the 3 Most Common Dementia Subtypes

Michael Hoffmann, MD[1,2,3]

Abstract

Background: Dementia diagnosis and the various subtypes are challenging in the absence of biomarkers. **Aim:** To examine available tests and neuroimaging procedures that may help distinguish these disorders. **Methods:** Alzheimer's disease (AD), cognitive vascular disorder (CVD), and Frontotemporal lobe disorders (FTLD) were tested with a hierarchical neuropsychological battery that included the Frontal Systems Behavior Scale, Mini-Mental State Examination, Montreal Cognitive Assessment Test, and subtests. All patients had multimodality magnetic resonance imaging and ^{18}F fluorodeoxyglucose-positron emission tomography (FDG-PET) brain scans. **Results:** Of the 161 patients evaluated for dysmemory and cognitive impairment, 31 satisfied the full protocol. The mean *T* scores for the 3 principal frontal system syndromes for the AD group were all abnormal save disinhibition. For the CVD and FTLD groups, all the 4 subcategory scores were abnormal. Disinhibition differed significantly between the AD and FTD group (analysis of variance [ANOVA], $P = .02$) and there was a strong association between the memory for 5 words test and a significant difference in the word list generation test score among the 3 groups (ANOVA, $P = .0233$). There was a strong association between the FDG-PET and the disease subtype ($P < .0001$). **Conclusion:** Evaluation for disinhibition, word list generation, 5-word memory testing and PET brain imaging may help distinguish the 3 most common dementia subtypes.

Keywords

dementia, neuropsychological testing, frontal systems, PET brain scan

Background

Dementia diagnosis and the various subtypes are challenging in the absence of biomarkers. Four different frontotemporal lobe degeneration (FTLD) subtypes are recognized and at least 4 different clinical Alzheimer's disease (AD) subtypes, with both entities having a frontal variant with predominant behavioral presentation.[1] In addition, the neuropathology is becoming more complex with a steadily increasing stream of new discoveries. However, treatment options and clinical trials depend on accurate diagnosis.[2] For example, anticholinergic therapy is of proven benefit in AD, serotonergic therapy has moderate scientific support in the treatment of FTLD,[3] and cognitive vascular disorder(CVD) may benefit from dopaminergic, cholinergic as well as serotonergic therapies.[4] Importantly, all therapies are reliant on accurate diagnosis and incorrect treatment may lead to worsening.[5]It is a commonplace experience in clinical practice that cognitive evaluation is challenging in the various stages of dementia. In some, the degree of cooperation or attention is limited to no more than a few minutes at best. Research based and emanating from cognitive stroke registries, for example, revealed that higher function abnormalities, including frontal network syndromes (FNSs) were common in acute and sub-acute stroke.[6,7] In addition, FNS may manifest no matter where the brain lesion, whether frontally located, subcortically, posteriorly, or even subtentorially. An analysis of subtentorial stroke, found FNS in at least half of patients with this location of stroke. Many of these patients were unable to have comprehensive testing in these settings.[8]

Hypothesis

Frontal systems testing and neuroimaging do not distinguish the most important dementia disorders.

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Aim 1. To determine whether examination with frontal systems tests and neuroimaging the most common dementia disorders may be distinguished.

Aim 2. Evaluate the utility of a context-appropriate FNS test battery incorporating behavioral neurological, neuropsychiatric, and neuropsychological components and compared to magnetic resonance imaging (MRI) brain (structural) and metabolic PET brain scanning (functional) to facilitate the diagnosis of the 3 most common dementia syndromes: AD, CVD, and FTLD.

Methods

Setting. Consecutive cognitive and memory impairment patients, aged 18 to 90 years, were accrued through a prospectively coded, dedicated cognitive and memory disorders registry in a tertiary referral center. The Stroke registry was approved by the University Institutional Review Board and in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations. All patients signed informed consent for the evaluation and the collection of the their neurological, medical, and neurocognitive data. Analysis of the dementia subtypes was performed retrospectively.

Diagnosis of Dementias. The *Diagnostic and Statistical Manual of Mental Disorders* fourth edition criteria were used for AD and CVD diagnosis.[9] For the Frontotemporal lobe disorders (FTLDs), the core diagnostic criteria by Neary et al were used.[16] In brief, these included insidious onset and gradual progression, early decline in social interpersonal conduct, early impairment in regulation of personal conduct, early emotional blunting, and early loss of insight.

Neuropsychological Testing

A hierarchical and time-orientated clinical approach was adopted. A brief, intermediate, and comprehensive system of frontal tests for clinical application was devised. Assessment was tiered according to the clinical need and indications into 3 different time options, up to 5 minutes, 15 to 30 minutes, and several hour assessment protocols. The tests conform to the 4 core components of FNS, namely working memory, disinhibition, initiation, and monitoring in addition to neuropsychiatric syndrome diagnosis.

Hierarchical Clinical Assessment

1. A 5-minute FNS battery geared toward emergent assessment in the emergency room or primary care outpatient clinics using the Montreal Cognitive Assessment (MOCA).
2. A 15- to 30-minute battery that incorporates behavioral neurological and neuropsychiatric syndromes with abbreviated neuropsychological tests geared toward inpatients, neurology, and psychiatry outpatient clinics including the Frontal Systems Behavior Scale (FRSBE),[11] Mini-Mental State Examination (MMSE),[12] MOCA,[13] orientation for 5 items, serial 7s × 5, memory for 5 words at 5 minutes, word list generation test (WLT) using the letter "F"[14] and Luria Motor Sequence test.[15]
3. A longer version, typical duration of several hours that incorporates contemporary frontal behavioral neurological, neuropsychological, speech and language, and neuropsychiatric tests need for precise determination of nature and extent of cognitive deficit typically needed for research protocols, forensic situations, or covert brain lesions. These tests include the computerized Wisconsin Card Sorting Test,[16] the Tower of London Test,[17] Behavioral Rating Inventory for Executive Function (BRIEF),[18] FRSBE,[11] Emotional Intelligence Quotient (Bar-On),[19] computerized Iowa Gambling Test,[20] Stroop Test,[21] Comprehensive Trail Making Test,[22] and letter/category fluency tests.[23]

Neuropsychiatric and Behavioral Neurological

The FRSBE[11] is a self-administered and caregiver administered test, yielding scores from both before the onset of illness and at the time of illness. The Likert-type scale questions are converted to age, gender, and education normative data in T scores where scores more than 60 are abnormal.

Cognitive and Neuropsychological

The MMSE and components of the MOCA, orientation for 5 items, serial 7s × 5, memory for 5 words at 5 minutes, WLT using the letter "F," and Luria Motor Sequence test.

Neuroradiology

All patients had multimodality MRI. MRI T1 and T2, fluid-attenuation inversion recovery, diffusion-weighted imaging, and magnetic resonance angiography to exclude secondary dementia causes such as brain tumor, stroke, multiple sclerosis as well as assessing for leukoaraiosis and degree of generalized and focal atrophy. Positron emission tomography (PET) ^{18}F Fluorodeoxyglucose (FDG-PET) brain scans were performed if any uncertainty existed with respect to dementia subtype in accordance with the Food and Drug Administration regulations. In addition, they provided an indication of cognitive reserve pertaining to a particular individual.

Following intravenous injection of FDG, with a dose of 15 milli Curies, the patient was kept in a quiet, darkened room for 60 minutes during the uptake phase. Standard acquisition time was 15 minutes. A single bed PET and co-acquired, low dose computed tomography scan of the same areas were performed. Attenuation-corrected PET images of the brain were created in sagittal, coronal, and transverse projections and reviewed on a computer workstation. Using GE cortex ID software (General Electric Company Corporate Office & Headquarters, Wildwood Pkwy, Atlanta, GA, USA), with comparison to age-matched normal, z scores of regional hypometabolism were obtained in 10 regions of interest and a z score of 2.0 or greater regarded as

Table 1. Disinhibition Test (FRSBE) Versus the 3 Major Dementia Syndromes.[a]

	Disinhibition test				
Disease	N Patients	Mean	SD	Median	N Missing
AD	11	55	11	59	3
CV	9	83	17	80	1
FTLD	11	86	33	84	1

Abbreviations: AD, Alzheimer Disease; CV, Cognitive Vascular Disease; FTLD, Frontotemporal Lobe Disorder; ANOVA, analysis of variance; FRSBE, Frontal Systems Behavior Scale; SD, standard deviation.
[a] Interpretation: ANOVA test shows there is a significant difference in the disinhibition test score among the 3 groups (F ratio 4.35, $P = .02$).

Table 2. Memory for 5 Words Recalled at 5 Minutes Test Versus the 3 Major Dementia Syndromes.[a]

Table of Memory 5 Words by Disease				
Memory 5 Words	Disease			
Frequency	AD]	CV	FTLD	Total
0	3	0	1	5
1	4	0	0	4
2	1	1	3	5
3	3	8	1	12
4	0	0	1	1
5	0	0	1	1
Total	11	9	7	28
Frequency Missing = 4				

Abbreviations: AD, Alzheimer disease; CV, cognitive vascular disease; FTLD, frontotemporal lobe disorder.
[a] Interpretation: Fisher exact test indicates that there is a strong association between the 5 word memory test and the disease ($P = .002$). Among the 12 patients with AD, 8 (67%) of their memory 5 score was either 0 or 1, while only 1 patient with FTLD memory score was 0.

statistically significant. A General Electric Brilliance LS camera (General Electric Company Corporate Office & Headquarters, Wildwood Pkwy, Atlanta, GA, USA) was used.

Results

Of the 161 patients presenting with dysmemory and cognitive impairment, 31 of 161 (130 of 161, 80.7% excluded) were evaluated according to the protocol including a PET brain scan. Most exclusions were due to the inability to complete (inattention, imperssistence, abulia) the cognitive testing, and others included uninterpretable test results or inability to undergo the neuroimaging protocols. Demographic characteristics included 12 women and 19 men, with 11 patients, each, in FTLD and AD groups and 9 in the CVD group. The mean age in years, AD 71.3 (SD 7.1), CVD 62.3 (SD 9.5), FTLD 66 (standard deviation [SD] 9.6), (analysis of variance [ANOVA] F value 2.1260, P value .319) and the mean education in years, AD 13.8 (SD 2.1), CVD 14.6 (SD 3.1), FTLD 14.8 (SD 3.2), (ANOVA F value 0.303, P value .5612).

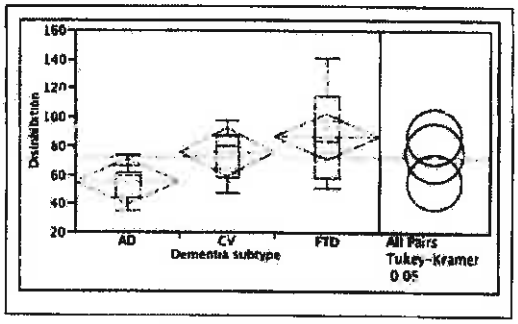

Figure 1. One-way analysis of disinhibition by dementia subtype Box-and-Whisker Plots (red) and Quartiles (green).

Table 3. FAS Test Versus the 3 Major Dementia Syndromes.[a]

	FAS Test				
Disease	N Patients	Mean	SD	Median	N Missing
AD	11	10	6	12	0
CV	9	13	4	12	0
FTLD	11	6	5	5	0

Abbreviations: AD, Alzheimer disease; ANOVA, analysis of variance; CVD, cognitive vascular disease; FTLD, frontotemporal lobe disorder; SD, standard deviation.
[a] Interpretation: ANOVA test shows there is significant difference in the FAS test score among the 3 groups ($P = .02$). Tukey studentized range test, indicates the FAS scores in AD and CVD are significantly higher than the one in FTLD ($P < .05$).

Neuropsychological Testing

Behavioral Neurological and Neuropsychiatric Measurements. The mean T scores (normal 50 ± 10) for the 3 principal frontal system syndromes for the patients with AD were abnormal for apathy 80 ± 19, executive function 75.7 ± 18, and total score (76 ± 18) but normal for disinhibition 55 ± 12. For the CV group, the scores were all abnormal, apathy 78 ± 17, disinhibition 83 ± 27, executive function 87 ± 16 and total 90 ± 17. For the FTLD group, all the scores were abnormal: apathy 91 ± 21, disinhibition 75 ± 34, executive function 85 ± 22 and total 92 ± 23. The ANOVA testing revealed that disinhibition differed significantly between the AD and FTD group ($P = .02$) in that the latter score was abnormal. T score mean of 55 ± 12 in the AD group, which was in the normal range, and 75 ± 34 in the FTLD group.

For between-group (the 3 principal dementia syndromes) analysis, disinhibition was the only component revealing significant differences (Table 1, Figure 1) with apathy (ANOVA, $P = .3650$), executive function (ANOVA, $P = .2937$), and total score (ANOVA, $P = .1797$) showing no intergroup differences.

Cognitive Measures (MMSE, MOCA, and FAS Test). With regard to cognitive test, there were no differences among the 3 dementia

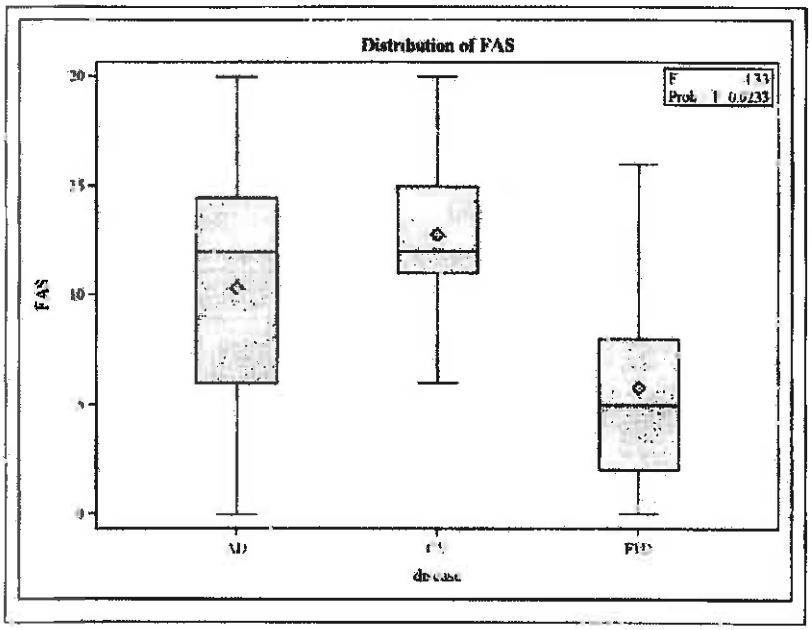

Figure 2. The FAS Box and Whisker plots of the FAS (word list generation task, "how many different words with the letter "F" can you recite in one minute?")

groups in terms of MMSE scores, with ANOVA test revealing no significant difference in the MMSE test score among the 3 groups. ($P = .3627$). Similarly Orientation testing by the Fisher exact test indicated no significant association between the orientation score and the disease ($P = .5610$). Serial-7 calculation testing by the Fisher exact test indicated no significant association between the serial 7 score and the disease ($P = .4831$). However, the memory testing using 5 words at 5 minutes revealed a significant association with AD (Table 2). With respect to the WLT (FAS Test), ANOVA testing showed significant difference in the FAS test score among the 3 groups with scores in AD and CVD significantly higher than the one in FTLD (Table 3, Figure 2).

The results suggest that the behavioral measure of disinhibition, as measured by the FRSBE test is a frequent accompanying symptom in both FTLD and CVD. The cognitive measures of episodic memory (5-word memory test) is poor in AD and CVD and the executive measure (FAS test) is also much more impaired in FTLD than both AD and CVD. Based on the variables of the FAS test, receiver–operator characteristic curve analyses were performed and revealed good associations between FTLD and CVD (good) and FTLD and AD (good) and less so for AD and CVD (fair; Figures 3–5). Only two pairs were compared (FTLD vs CVD; AD vs FTLD, AD vs CVD). The results were therefore based on each of the 2 subgroups. The value of these comparisons were to determine how well the test score can discriminate the subgroups and therefore comparisons would be FTLD versus no-FTLD, AD versus no-AD, and CVD versus no-CVD. The area under the curve AUC and P values appear in Table 4. Based on Bonferroni correction, the new significant level is $0.05/3 = 0.0167$, indicating that FAS can be a useful marker to distinguish FTLD versus no-FTLD.

The hierarchical clinical assessment stage 3 comprising neuropsychological testing of duration of several hours was possible only in a minority of our patients (less than 25%, due to inattention, impersistance, language, and other impairments) hence data from these were not further considered. The Luria Motor Sequence test component results were similarly considered noninterpretable due to a high proportion (approximately 66%) encountering difficulty with the test.

Neuroimaging

Structural Neuroimaging. There was a strong association between the MRI brain scan and the disease as calculated by the Fisher exact test ($P = .0049$). The MRI brain scans of all the 11 patients with AD were abnormal, but only 5 of the MRI brains scans of the 11 patients with FTLD were abnormal which entailed significant leukoaraiosis, atrophy, or infarcts (Table 5).

Functional Neuroimaging. Fisher exact test indicates there is a strong association between the FDG-PET result and the disease

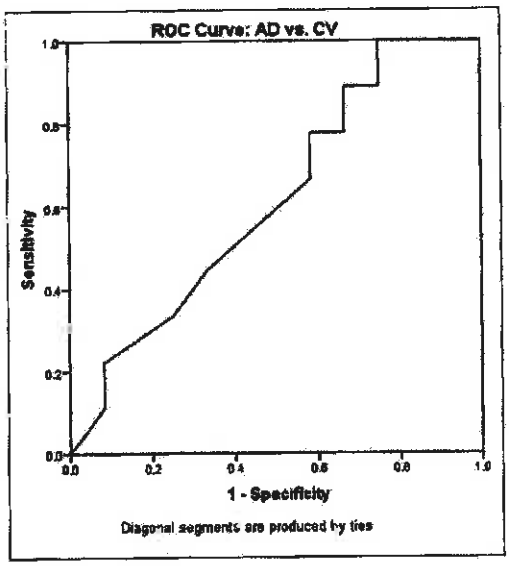

Figure 3. Receiver–operator characteristic (ROC) curves for pairwise comparison, Alzheimer's disease versus cognitive vascular disorder (area under the curve AUC value 0.61).

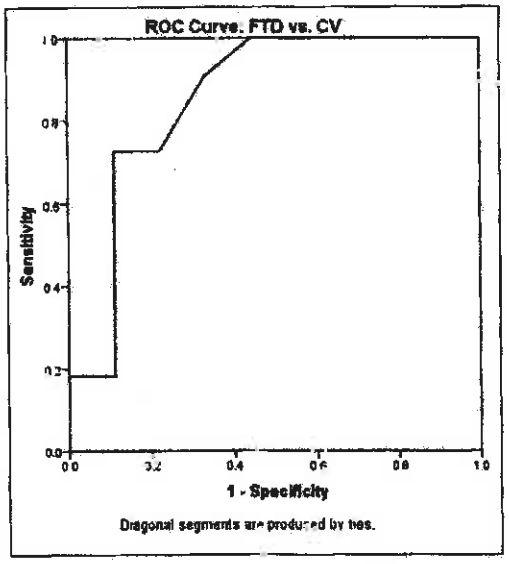

Figure 4. Receiver–operator characteristic (ROC) curves for pairwise comparison, frontotemporal lobe disorder versus cognitive vascular disorder (area under the curve AUC value 0.854).

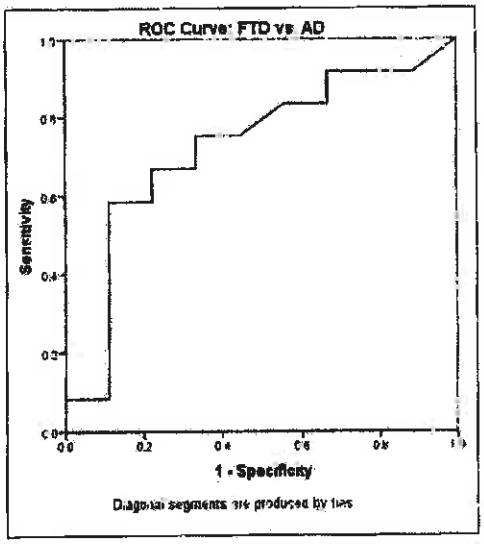

Figure 5. Receiver–operator characteristic (ROC) curves for pairwise comparison, ADAlzheimer's disease versus frontotemporal lobe disorder (area under the curve AUC value 0.722).

($P < .0001$, Table 6). Among the 11 patients with AD who had FDG-PET, 10 (91%) of the 11 revealed bilateral temporoparietal hypometabolism, while the FDG-PET results of 7 (100%) of the 7 patients with FTD revealed bifrontal and/or temporal hypometabolism.

Discussion

Neuropsychological testing usually evaluates 5 principal domains of cerebral functioning. These include executive function, attention, intelligence, language, and memory. Behavioral syndromes (apathy, abulia, disinhibition, loss of social graces, and empathy) are not typically evaluated by standardized testing. In this study, disinhibition, an important component of FNSs was found to be significantly associated with FTLD and CVD but not AD.

Behavioral abnormalities dominate completely the FTLD, the most common dementia under the age of 60 years. On the other hand, cognitive deficits, such as executive dysfunction, typically do not feature in the disease during the initial years at a time when the disease is subclinical or classified as mild cognitive impairment. During this phase, however, the behavioral components may dramatically impact then occupation, family, and interpersonal relationships and may cause fiscal disasters. For these reasons, earlier detection is paramount.

Table 4. Receiver–Operator Curves: AUC Table.

Based on FAS test		
Outcome	AUC	*P* value
AD	0.5556	.6161
CVD	0.7196	.0203
FTLD	0.7831	.0052

Abbreviations: Abbreviations: AD, Alzheimer's disease; AUC, area under the curve; CVD, cognitive vascular disease; FTLD, frontotemporal lobe disorder.

Table 5. MRI Brain Scan Result Versus the 3 Major Dementia Syndromes.[a]

Table of MRI by disease				
MRI	Disease			
Frequency	AD	CV	FTLD	Total
Abnormal	11	7	5	23
Normal	0	2	6	8
Total	11	9	11	31

Abbreviations: AD, Alzheimer's disease; CVD, cognitive vascular disease; FTLD, frontotemporal lobe disorder; MRI, magnetic resonance imaging.
[a] Interpretation: Fisher exact test indicates there is a strong association between the MRI brain scan and the disease ($P = .005$). MRI brain scans of all the 12 patients were abnormal, while only 4 MRI brains scans of the 9 patients with FTLD were abnormal (significant leukoaraiosis, atrophy, or infarcts).

Table 6. PET Brain Scan Versus the 3 Major Dementia Syndrome.[a]

	PET result		
Disease status	TP	Global	FT
AD	10	1	0
FTLD	0	0	7
CV	1	5	3

Abbreviations: AD, Alzheimer's disease; FTLD, frontotemporal lobe disorder; CVD, cerebrovascular dementia; TP, temporoparietal hypometabolism; FT, frontotemporal hypometabolism; MMSE, Mini Mental State Examination; PET, positron emission tomography.
[a] Interpretation: Fisher exact test indicates there is a strong association between the PET result and the disease ($P < .0001$). Among the 11 patients with AD who had PET test, 10 (91%) of the results are TP, while the PET results of 100% of the patients are FT.

The method of clinical detection remains challenging. In the last few years, there has been the more widespread adoption of the MOCA test as a screening test for higher cognitive functions in favor of the MMSE, the mainstay test for this purpose for the last several decades. The main advantage of the MOCA versus MMSE, is the sampling of FNSs including executive function, which is not addressed by the MMSE. However a major shortcoming of the MOCA and in fact of neuropsychological assessments in general, is the paucity of behavioral assessments, such as disinhibition, apathy, abulia, gambling tendency, promiscuity, irritability, rage attacks as well as the so-called neuropsychiatric syndromes such as obsessive behavior, compulsive behavior, and content-specific delusional behavior. These entities dominate the early years of FTLD and these behavioral abnormalities may also be the dominant features of other conditions such as stroke, multiple sclerosis, and traumatic brain injury.

With respect to memory testing, the common application of using 3 (MMSE) or 5-word (MOCA) or more (California Verbal Learning Test, Wechsler Memory Scale, and others) does not do justice to the contemporary understanding of the differing dysmemory phenotypical categories. The dementias may present with various memory disorders,including deficits in working memory (short term, localized to the frontoparietal network), episodic (long term, medial hippocampal), semantic (lateral hippocampal), and procedural (cerebellum, basal ganglia). A clinical approach to memory loss, frontal subcortical (affecting working memory, procedural), and medial temporal (episodic memory) as the 2 principal may be more useful, as these differ clinically, radiologically, and in terms of prognosis.[24] However, neither working memory nor procedural memory processes are adequately tested by our current screening tests, and attention to these may improve our clinical assessment of dementias.

The WLTs have long been considered a good bedside executive measure. In this study, subgroup comparisons of 2 pairs (FTLD vs CV, AD vs FTLD, AD vs CVD) were performed to determine how well the test score can discriminate the subgroups (Figures 3–5 and Table 4). The FAS test was found to be a useful marker to distinguish FTLD versus no-FTLD.

In addition to the clinical evaluations that were included in this study, disinhibition, word list generation and 5-word memory testing, PET brain imaging may help distinguish the 3 most common dementia subtypes. Although many different neuropsychological tests as well as a variety of behavioral inventories (FRSBE, BRIEF, Frontal Behavioral Inventory) exist, people with dementia or cognitive impairment due to stroke, traumatic brain injury, or other brain injury are rarely able to concentrate for long. Furthermore, certain disease states such as stroke mandate rapid evaluation of patients within minutes because time is brain and in other common illness states such as traumatic brain injury, markedly reduced attention and volition are major factors in the preference for quick, yet informative cognitive/behavioral testing. Finally, restricted caregiver–patient interaction time in the clinic forced by low reimbursement rates all conspire to give us distressingly little time to perform adequate testing. The disinhibition tests, word list generation, 5-word memory test that were found to significantly differentiate the disease categories in the foregoing and are relatively rapidly administered, at least within 20-30 minutes.

Looking to the future, the recent advent of diagnostically accurate functional brain imaging and cerebrospinal fluid (CSF) biomarkers afford clinicians a more comprehensive spectrum of clinical, neurocognitive, laboratory, and neuroimaging armamentarium to-had that will likely lead to improved diagnostic acumen in this complex conundrum of dementing conditions. There is increasing evidence from clinical, functional MRI, and PET brain scan studies supporting what has been termed the cognitive reserve hypothesis.[25] Briefly, normality or subclinical disease may paradoxically be associated with extensive disease

such as dementia. Therefore, a combination of cognitive evaluations, metabolic brain scanning, and CSF biomarkers (phosphorylated tau and A Beta amyloid 1-42) will most likely yield the most accurate assessment for the complex dementia syndromes.[26,27] Not only will it be important to ascertain the degree of cognitive reserve but also the degree of compensation.

> In this study, PET brain imaging was employed because of its established use in differentiating brain disorders especially in the context of normal anatomical brain imaging by MR scanning. In fact, no direct relationship exists between the extent of pathology and clinical manifestation of the underlying disease or damage for that matter. In our study, the PET brain imaging results were profound and correctly classified 7 of 7 patients with FTLD and 10 of 11 patients with AD and excluded FTLD or AD in 5 of 9 patients with CVD.

Functional imaging studies support the neural reserve and neural compensation reflecting individual compensatory differences to pathology. For example, 2 people with the same cognitive impairment may have markedly different degrees of underlying AD pathology. This is clearly important for the diagnosis of preclinical AD, as patients mild cognitive impairment may have both minimal pathology or more extensive pathology. The cognitive reserve hypothesis, is used to describe this variability and is considered an important part of the assessment therefore. Clinical evaluation alone cannot be relied on and biomarkers will need to be part of the workup.[28] In this study using PET scanning to establish whether significant hypometabolism existed in the context of the so-called normal cognitive functioning was not found. However, the nature of patient recruitment depended on some form of cognitive complaint in the first place. Clearly, we may be missing a proportion of the so-called normal people with already mild or even moderate disease.Functional MRI shows promising results regarding the imaging of the default mode network and other recently appreciated network such as the salience network. This network-opathy approach remains under evaluation, at present, in context of mild cognitive impairment diagnosis.[29]

Potential criticisms of this study include the relatively small sample size of the groups, which impacts the generalizability of the results. The many variables in each disease category are also of potential concern, and it is conceded that the diagnoses in these dementia categories remain in the probable range.

Conclusion

Evaluation for disinhibition, word list generation, 5-word memory testing, and PET brain imaging may help distinguish the 3 most common dementia subtypes. Despite the compounding influence of cognitive reserve, it appears that these simple, quickly executed bedside tests may be robust enough to alert the clinician to an impending brain failure. This research supports the use of relatively simple and rapidly administered bedside type cognitive and behavioral testing even for complex dementia syndromes. Many people have neither the residual cognitive faculties nor the necessary attentional capacities required for neuropsychological testing. The important concept of considering cognitive status in the context of cognitive reserve was also supported in this research.

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Critique of Frontal Network Syndrome Testing: Clinical tests and PET brain imaging help distinguish the 3 most common dementia subtypes.

The need for brief, more detailed and comprehensive testing is a clinical reality that was successfully tested in this study. Despite the design and use of relatively mild to moderately afflicted people with cognitive impairment, the majority of patients were not able to undergo comprehensive testing. Fortunately simple bedside tests yielded sufficient distinguishing features and statistical significance to differentiate the three dementias. The testing approach was termed hierarchical, in that a progressively longer and more in depth assessment was used, depending on the clinical status and capability of the patient to undergo testing. This flexibility of the testing approach is consistent with the realities of clinical presentations and yields information that may not be obtained, if only applying a lengthy test procedure to someone with impaired attention for example. A potentially challenging area for future assessment, that of cognitive reserve evaluation was included in this assessment and helped improve detection.

Chapter 6. General Discussion

How has this research contributed to our thinking about diagnosis and measurement in frontal network syndromes and what are the implications for the future?

Several lines of evidence have indicated to clinicians that assessment of brain function, requires reappraisal. Firstly, one of the most compelling is the dismal state of stroke medicine, in which the majority of pharmacological agents tested in animal models were positive but to date every one has failed in human clinical trials. Secondly, a normal brain scan, including a state of the art, 3.0 Tesla, multimodality MRI brain scan, in the setting of sometimes marked cognitive derangement such as in schizophrenia, severe depression or Parkinson's disease, is a frequent clinical experience. Thirdly, considering the vast panoply of human cognitive experience, cognitive neuroscientists are well aware that we have a relatively limited number of tests that interrogate such functions. A recent example is the introduction of an assessment tool for emotional intelligence, considered by many brain clinicians to be one of the most important if not the most important attribute for success in life.

Yet, the busy clinical environment, with progressively less time allocated for assessment, demanded a method of at least determining cognitive impairment, an appreciation of the subtypes, in an attempt to determine the more important

subtypes, as they related to outcome and a monitoring tool for evaluation of clinical improvement or deterioration. The first part of this study had delineated that HCFD's or CS occur in the vast majority of stroke presentations and that FNS were present in at least a third. The COCONUT assessment tool was an attempt to embrace and span the manifold symptoms and syndromes that are vested in other disciplines (to neurology), yet may be directly related clinically as well as to the management and treatment issues. This is the first tool to the author's knowledge that combines many of the behavioral neurological, neuropsychiatric and neuropsychological tests in relatively rapid (approximately 20 minute assessment duration) evaluation of several dozen different cognitive brain syndromes.

The traditional question of lesion localization in the brain, particularly germane to neurology was questioned in the light of the highly accurate depiction of lesions in the order of 0.5 to 1 mm in diameter by standard MRI scanning and rather concentration on the question of; given a particular lesion localization, what are the likely cognitive syndromes expected from that, in addition to the standard elementary neurological deficits such as sensorimotor or visual impairment.

The search for newer FNS tests, such as measuring EI is particularly relevant to the frontotemporal lobe dementias, an ever expanding constellation of syndromes that affect the most sophisticated human qualities and also the most difficult to test. Nevertheless we have in our armamentarium, simple and rapidly

applied bedside tests, than can be most useful in the emergent situation, the poorly cooperative patient and when time is limited as exemplified in the fourth study in this thesis.

General Discussion (The Future)

1. The importance and rationale of considering cognitive reserve status in conjunction with cognitive or neuropsychological testing

In the fourth study, PET brain imaging was employed because of its established use in differentiating brain disorders especially in the context of normal anatomical brain imaging by MR scanning. In fact, no direct relationship exists between the extent of pathology and clinical manifestation of the underlying disease or damage, for that matter. Portrayed initially by the famous case of Richard Wetherill, a University Professor and avid chess player who realized he had dementia when he could only think five moves ahead in chess instead of eight, he was evaluated neurologically, neuropsychologically and with neuroimaging, with no abnormality found. However, his autopsy about two years later revealed extensive Alzheimer disease pathology [82]. In a similar study by Katzman et al, this time a case series of ten elderly normal women, with advanced AD pathology also supported this premise of the clinical-neuropathological mismatch. Katzman speculated that their brains were larger with more cognitive reserve [83].

The brain may cover up impairments and do the opposite as well, in that it can make up things that are not there. The latter observation is best demonstrated by the optical blind spot, we all have and the demonstration of optical illusions. This is an important concept, as the appearance of cognitive dysfunction may be completely masked, at least as we can ascertain by our clinical tests, in the face of sometimes rampant neurodegenerative disease. Briefly, cognitive reserve is considered to include;

A. Brain reserve capacity (correlate – hardware), brain size, neural count or synapse count.

B. Cognitive reserve (correlate – software). Attempting to cope with brain damage using cognitive compensatory approaches. Higher education, bilingualism, literacy and participation in hobbies for example, allow people to withstand brain damage better. Cognitive reserve in turn has been divided into;

1. Neural reserve; Cerebral networks less susceptible to disruption due to greater inherent efficiency.

2. Neural compensation

Post brain damage, additional or nonconventional networks are deployed to compensate for brain damage [84].

Functional imaging studies support the neural reserve and neural compensation reflecting individual compensatory differences to pathology. For example, two people with the same cognitive impairment may have markedly different degrees of underlying AD pathology. This is clearly important for the diagnosis of preclinical Alzheimer's disease, as mild cognitive impairment (MCI) patients may have either minimal pathology, or more extensive pathology. The cognitive reserve (CR) hypothesis, is used to describe this variability and is considered an important part of the assessment therefore. Clinical evaluation alone cannot be relied on and biomarkers are required. Currently we have only two groups of biomarkers, namely CSF analysis (tau and amyloid beta 1-42) or PET metabolic imaging that would need to be part of the work up [85].

In a study of 12 high educated (15 or more years) and 13 low educated patient with the same degree of cognitive deterioration, were evaluated with PET brain scanning using both [^{11}C] PIB and ^{18}F-Fluorodeoxyglucose as ligands. The high-educated people showed increased PIB uptake in the lateral frontal cortex as well as lower glucose metabolic rate in the temporoparietal cortical regions compared to low educated people [86]. This provides further support for the CR hypothesis.

2. New imaging modalities: Default mode network (also called resting state network or intrinsic connectivity networks) imaging and other (molecular) networks

In the quest for more refined and accurate neuroimaging tools, one that appears particularly promising is the Default Mode Network (DMN), which is concerned with imaging specific networks in the brain. The DMN be imaged by functional MRI and reflects the basal or default mode activity of the brain. It links particular brain regions that include the posterior cingulate, the precuneus, lateral parietal, lateral temporal and medial frontal areas (figure 1). DMN impaired connectivity has already been shown in AD, FTLD, schizophrenia, epilepsy, autism and late life depression [87]. The DMN is active during rest and becomes less active during cerebral task engagement. It is implicated in the pathophysiology of AD, as the distribution of the DMN is similar to the fibrillar amyloid deposition in patients with AD (amyloid PET scanning) [88]. It has been surmised that over-activity of DMN (posterior cingulate, later parietal, medial frontal) in younger life may lead to a metabolic impairment predisposing people to amyloid deposition in later life [89].

The DMN is known to sub-serve several key memory processes including episodic encoding, retrieval, autobiographical, meta-memory processes, moral decision-making and theory of mind. Petrella et al reported lower connectivity in DMN in patients with MCI who subsequently were diagnosed with AD over a 2-3

year period [88]. This type of functional connectivity MRI or fc-MRI, is an attractive tool because MRI scanners with blood oxygen level dependent (BOLD) capability are widely available and fc-MRI is non invasive, can be repeated multiple times and have short acquisition time of 5-8 min [89]. One study showed 5 different neurodegenerative syndromes corresponding to 5 different intrinsic functional connectivity networks [90] and in particular the salience network has been shown to correlate with frontotemporal lobe dementia (figure 2) [91]. This relatively novel approach of brain analysis, called connectomics by some, is showing promising results. Assessment of brain connectomics is regarded as an area of priority in future cognitive research [92].

A likely hierarchical approach to using surrogate neuroimaging in cognitive patients may be as follows;

1. Resting State Network Imaging (DMN, Salience and others) by f-MRI
2. Beta amyloid accumulation assessed by PET brain PIB (also CSF assays)
3. The subsequent synaptic dysfunction assessed by FDG-PET brain
4. Finally, neuronal loss follows, as assessed by volumetric MRI

All occur prior to the onset of dementia. Note that steps 2-4 are already in routine clinical use and resting state network imaging already used in some centers experimentally, and expected to be the most sensitive technique of all.

3. Molecular Networks

Two brain regions are known to have neurogenesis; the subventricular zone and the dentate gyrus of the hippocampus. Adult hippocampal neurogenesis is a trait that is central to humanity rather than an outdated heritage from our evolutionary past. A new hypothesis posits that adult hippocampal neurogenesis is a late evolving trait (rather than ancient) and possessing a dentate gyrus with this kind of plasticity gave mammals a specific advantage in adapting to their environment with increased cognitive flexibility and adaptability. Hence, even though adult neurogenesis is known widely amongst animals and is a phylogenetically old mechanism, this was modified and refined in humans relatively recently [93].

Therefore it is not surprising that the hippocampus has been implicated in a wide range of neurological conditions (Alzheimer's disease, stroke, depression, schizophrenia). Importantly, sub-regions of the hippocampus have been shown to be differentially involved in these different diseases. A recent review has proposed a system of hypometabolic conditions (AD, cognitive vascular disease, aging) and hypermetabolic (schizophrenia, depression and PTSD), based on functional imaging studies with PET scanning and f-MRI scanning (figure 3). From this, a metabolic or molecular functional map has been proposed which reveals that the entorhinal cortex is involved in brief retention, the subiculum in retrieval, the CA1 in input integration, the CA3 in pattern completion and the dentate gyrus in pattern separation (figure 4). The next challenge is to devise

neuropsychological tests for these sub-regions of the hippocampus, that are guided by this functional map based on neurobiological evidence [94].

Yet another possible future approach to more refined cerebral testing in subclinical and mild dementia, may hinge on functional imaging of the hippocampus.

4. Future Treatments

How can this data translate into improved clinical care?

The more precise the neurobiological and neurochemical diagnosis, the more likely we are able to provide specific treatment. By delineating key frontal syndromes at fault in the differing dementias, this provides opportunities for targeted treatments. Fore example, the newly appreciated epigenetic process is understood to be a mechanism whereby genes are switched on and off without interfering with the DNA itself. It is of particular importance in neuropsychiatric conditions. This form of gene regulation, the main function appearing to be a process that allows for the short-term adaptation of a species to allow for reversible phenotypic variability. The mechanisms by which this occurs include; DNA methylation, histone acetylation or via micro RNA's mechanisms [95]. Lifestyle, eating habits and even cognitive behavioral therapy are factors that can translate into epigenetic changes and it may be transgenerational. Aggressive

risk factor control for dementia and stroke, which are largely the same (hypertension, smoking, diabetes, hyperlipidemia, elevated body mass index, hyperhomocysteinemia) require renewed emphasis for this population. For example, an elegant study was done by Gons RAR et al, using MRI diffusion tensor imaging, to measure white matter fiber tracts and compared to neuropsychological scores in smokers and those who had stopped. It was shown that smoking affects the microstructural integrity of white matter and is associated with impaired cognition. Quitting smoking reversed the impaired structural integrity [96].

Seven frontal subcortical circuits (FSC's) are currently recognized as the neurobiological substrate of all frontal syndromes including the majority, if not all psychiatric syndromes (figure 5). They are all similar in that they connect the frontal cortex via the striatum, then globus pallidus, thereafter with the thalamus and back to the frontal cortex completing the circuit. Two examples of the circuitry are depicted for the dorsal lateral prefrontal cortex executive circuit (figure 6) and the emotional circuit beginning and ending in the anterior cingulate cortex (figure 7). Within each of these, there are 3 orders of connectivity and each has direct and indirect pathways. There are cortico-cortico connection circuits with the other FSC's and open connections to areas outside the FSC's [97].

Connections to the hippocampus, for example, is important, as the appreciation of so called molecular anatomy in this region is also a type of "melting pot" for

traditional psychiatric and neurological disease. There is regional vulnerability across the brain and within the hippocampal formation. For example, the CA1 subfield is particularly vulnerable to vascular disease because of the relatively high expression of NMDA receptors in the CA1 subfield. On the other hand, the dentate gyrus is vulnerable in the context of post adrenalectomy because of relatively high levels of mineralocorticoid receptors here. As an overview therefore, Alzheimer's disease, cognitive vascular disorder and normal ageing are regarded as hypometabolic (by functional and structural MR imaging) and schizophrenia, depression and PTSD as hypermetabolic, each in different parts of the hippocampal formations (figure 8) [98].

Neurotransmitter systems integral to these circuits, include the principal on-off glutamate and GABA respectively and the modulatory aminergic state dependent influences of the dopamine, noradrenaline, serotonin and acetylcholine and histamine networks that have the nuclei in the pons and midbrain and ramify diffusely in the neocortex, but principally in the frontal lobes. Dopamine is the principal neurotransmitter in this regard [97].

Preliminary data for aminergic cognitive enhancing therapy in frontal disorders

Serotonergic and noradrenergic therapy is already established for the treatment of depression, a frontal syndrome, and acetylcholine alleviates dysmemory. Cognitive enhancing agents and memory enhancers are approved therapies for

Alzheimer's disease and include Donepezil, Galantamine, Rivastigmine and Memantine. Serotonergic and noradrenergic agents are used for depression as well as for a variety of neuropsychiatric disorders including attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorders (OCD) and psychoses [99-102]. Successful treatment for frontal lobe disorders have been reported for the attentional disorders that accompany them with Methylphenidate, Dextroamphetamine, Pemoline and Modafanil, with at least one successful randomized double blinded placebo controlled trial [103]. Serotonergic therapy using selective serotonin reuptake inhibitors have been shown to improve naming ability in mild to moderate fluent aphasia and shown to correlate with improved mood and decreased perseveration [104]. Some success has been reported in the modification of disinhibition behaviors seen in patients with orbitofrontal injuries with antipyschotics, benzodiapezines, Buspirone, Carbamazepine, Trazadone, Propranolol, Valproate, antidepressants and Lithium [105]. In addition, cholinomimetic agents (Donepezil, Galantamine, Rivastigmine) incur modest improvements in memory as well as other cognitive functions such as psychosis, agitation, apathy, disinhibition and aberrant motor behavior [106].

Rationale of dopaminergic therapy for dysexecutive syndromes

The beneficial effects of dopamine therapy has been reported for a number of different frontal syndromes. The apathy accompanying the medial frontal syndrome has been shown to improve anecdotally to psychostimulants or

dopamine receptor agonists [107]. The abulia/akinetic mutism spectrum of disorders has been successfully treated in some patients with Bromocriptine [108]. Neglect syndromes have similarly responded to Bromocriptine more so than Methylphenidate [109]. Motor speech disorders localized to the left frontal regions such as expressive (Broca's type) aphasia and the dysexecutive syndrome have similarly responded to dopaminergic therapy [110-113]. These reports derive from case series and isolated case reports from heterogeneous pathophysiological entities such as dementia, trauma, encephalitis and stroke. Despite the multitude of different neurotransmitters involved in cognition pertaining to the cognitive circuitry of the frontal network systems, dopamine, serotonin, noradrenaline and acetylcholine are the most important [104,105,114].

Functional neuroimaging has revealed that for many different kinds of cognitive demands, three frontal regions are recruited by diverse cognitive demands. These include the mid dorsolateral, mid ventrolateral and dorsal anterior cingulate cortex. This is regarded as a function of the anatomical fact that any small region of frontal cortex is connected both to an immediately adjacent region, as well as a widespread network of small, structured patches of cortex [115]. Three frontal syndromes are frequently enunciated including the dysexecutive (dorsolateral prefrontal cortex), apathetic (anterior cingulum) and disinhibited (orbitofrontal). The latter is less likely to respond to dopaminergic therapy from the preliminary data available. Rather, disinhibited syndromes are

more likely to benefit from other neurotransmitter modifying agents including Carbamazepine, Valproate, Lithium and serotonin reuptake inhibitors [116-121].

Other treatments and interventions

Cognitive therapies may comprise of potential treatments by the following approaches;

- Small molecules (stimulant therapy)
- Growth factors
- Cell based therapies
- Electromagnetic stimulation (transcranial magnetic stimulation)
- Other device based therapies
- Task orientated and repetitive training [122].

At the time of writing, it appears that a reasonable hypothetical approach, would be to establish whether combination therapy (a cocktail therapy), more specifically a combination of aminergic (norepinephrine, serotonergic, dopaminergic) cholinergic (Galantamine, Donepezil, Memantine) and stimulant (Modafanil) therapy, improve subtypes of frontal network syndromes. Such therapy may translate into profound benefits at a personal and societal level. Conceivably in the future all of the above approaches might be used in an individual patient.

It is readily apparent that on a neurobiological basis, the disciplines of neurology, psychiatry and neuropsychology, represent only a superficial, human induced division. Furthermore, there is a strong movement in psychiatry to view psychiatric disorders on dimensional or numeric scales, rather than dichotomizing conditions, as is portrayed by the DSM-IV/V classification. This is supported both by the polygenic mode of inheritance and the clinical observations that psychiatric conditions are better described on a continuum overlapping with normality [123].

In addition to the 3 principal frontal behavioral syndromes of apathy/abulia, disinhibition and executive dysfunction, the major neuropsychiatric syndromes such as schizophrenia, bipolar disorder, obsessive compulsive disorder, Tourette's syndrome and depression are best considered in terms of frontal subcortical circuit disturbances, that may be deconstructed into the core frontal syndromes of working memory, initiation, disinhibition and monitoring disorders (figure 8). These then facilitate the targeting of specific treatments.

Implications for health care policies

Health policy planners have long needed an index of frontal dysfunction to determine eligibility for long-term care benefits. The improved imaging capability of MRI, SPECT and PET scanners has delineated frontal impairment in patients

without gross frontal lesions. There is a strong link between impaired frontal function by testing and impaired performance in the goal directed behavior in the natural environment, most notably careers and employment [124].

Brain disorders cost the European Community 1 trillion dollars per year (800 billion Euros). The European Brain Council has determined that this is more than cardiovascular disease, cancer and diabetes combined and exceeds the gross domestic product of the Netherlands, for example. Furthermore the greatest clinical impact and cost benefit would be through the prevention of these diseases. Yet, at the same time the pharmaceutical industry is shying away from drug development in this arena because of the complexities and difficulties associated with these brain disorders. Only a better understanding of the neurobiology of brain function and frontal systems in particular will yield effective treatments [125].

Chapter 7. Conclusion and Concluding Remarks

Conclusion

The culmination of these research papers, established that cognitive syndromes, in particular FNS are critically important in assessing and monitoring brain function. In the realm of the dementia avalanche that is due and test the budgets of most countries of the world in the next decades, it was shown that evaluation for disinhibition, word list generation, 5 word memory testing and PET brain imaging may help distinguish the three most common dementia subtypes. Despite the compounding influence of cognitive reserve, it appears that these simple, quick, executed, bedside tests may be robust enough to alert the clinician to an impending brain failure. This research supports the use of relatively simple and rapidly administered bedside type cognitive and behavioral testing, even for complex dementia syndromes. Many people have neither the residual cognitive faculties, nor the necessary attentional capacities required for prolonged neuropsychological testing.

Concluding remarks

The important concept of considering cognitive status in the context of cognitive reserve was also supported in this research. At the same time, the parallel contributions of sophisticated metabolic, network and molecular neuroimaging are making major strides in understanding brain function and dysfunction. The current status has been reviewed and integrated with the clinical research findings presented.

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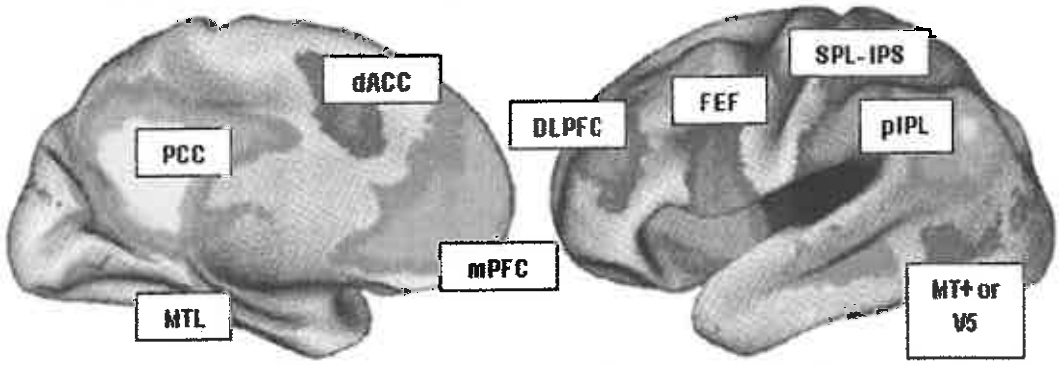

Figure 1. Default Mode Network (orange/yellow) and Attentional Networks (blue)

PCC posterior cingulate cortex, dACC – dorsal anterior cingulate cortex, mPFC – medial prefrontal cortex, MTL – medial temporal lobe, SPL-IPS – superior parietal lobe, inferior parietal lobe, FEF – frontal eye field, DLPFC – dorsal prefrontal cortex, pIPL – posterior inferior parietal lobe, MT or VS – medial temporal. Carhart-Harris RL, Friston KJ. The default mode, ego functions and free energy: a neurobiological account of Freudian ideas. Brain 2010;133:1265-1283 (with permission)

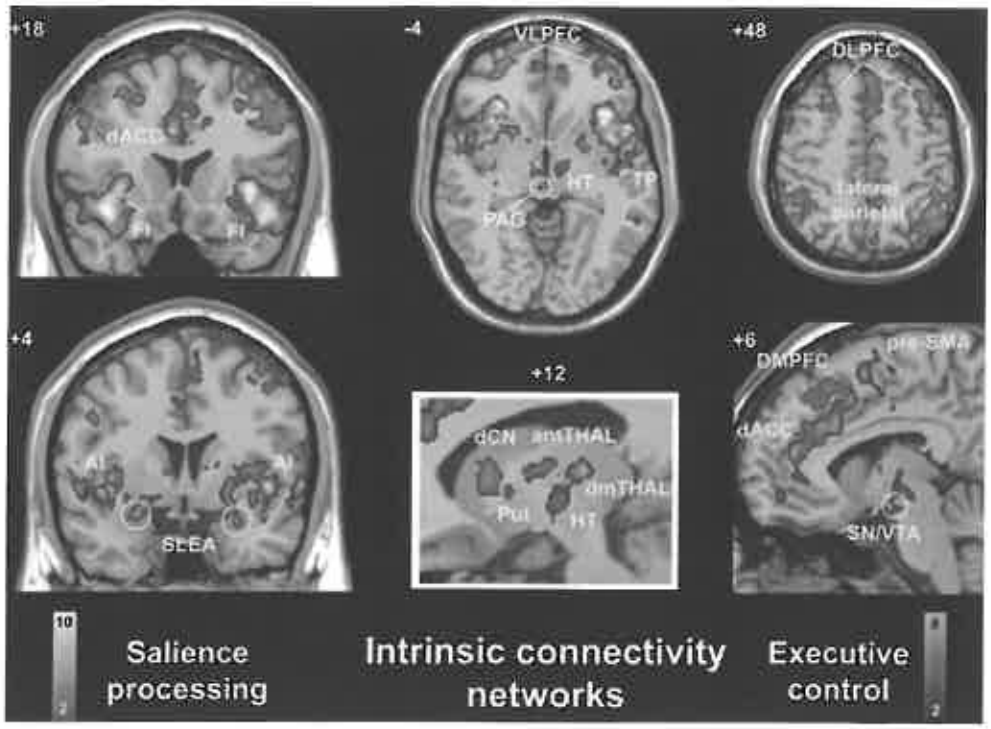

Figure 2. The Salience network anchored by the anterior cingulate and orbital fronto insular cortices (red) compared to executive control network (blue) a network of the dorsolateral prefrontal cortex and parietal regions.

The scans are by task free functional MRI with the BOLD signal presented in t-score color bars. Reference: Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. The Journal of Neuroscience 2007;27:2349-2356 (figure reproduced with permission).

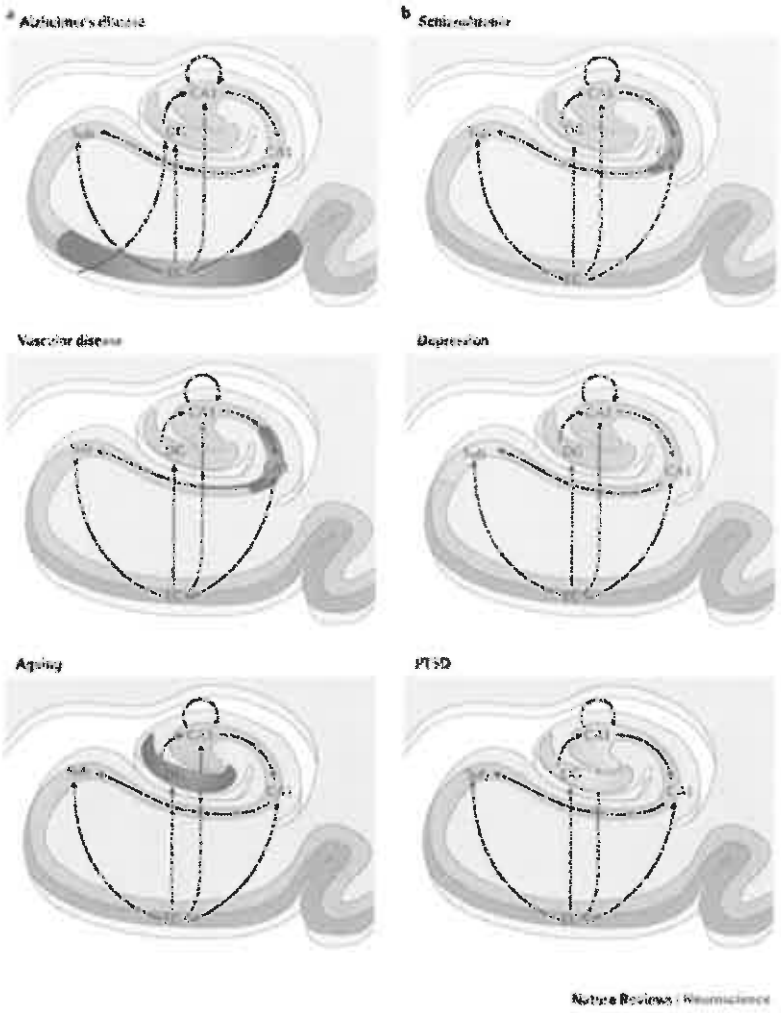

Figure 3. Hippocampal syndromes according to sub-region and hypo or hyperactivity.

Small SA, Schobel SA, Buxton RB, Witter MR, Barnes CA. A pathophysiological framework of hippocampal dysfunction in ageing and disease. Nature Reviews Neuroscience 2011;12:585-601 (Nature publishing with permission).

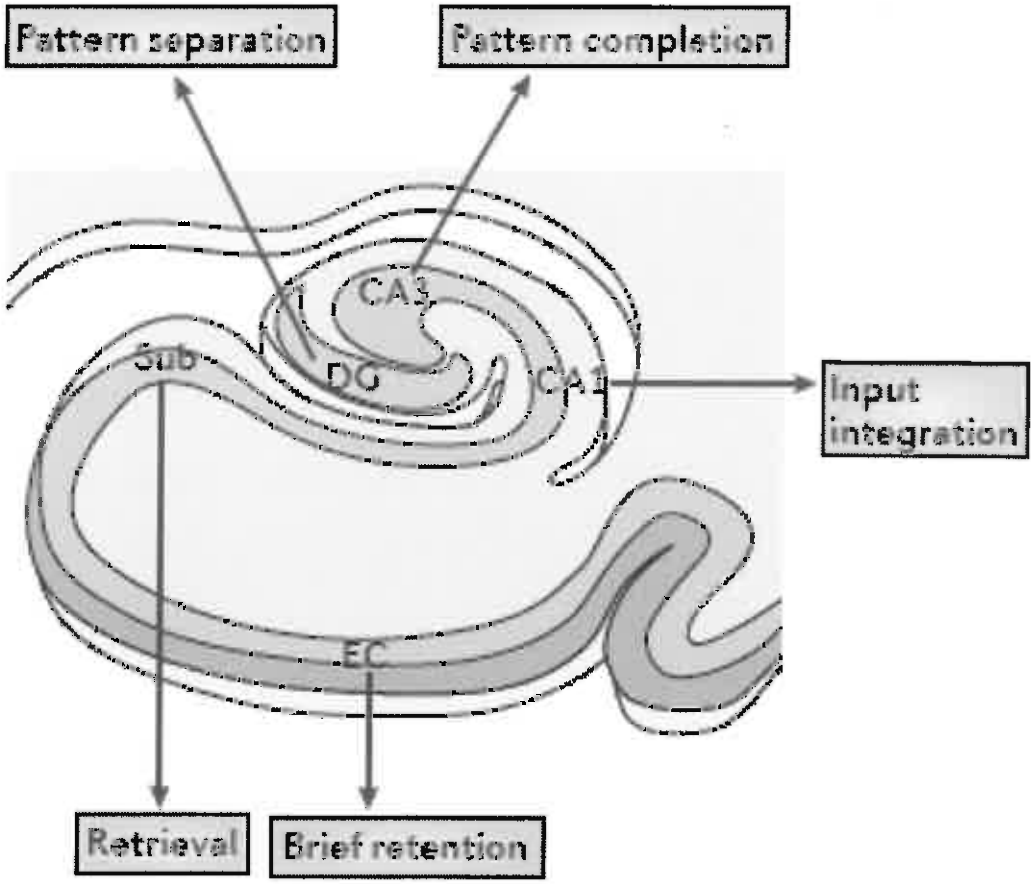

Figure 4. Putative hippocampal functional map with each of the major divisions of the hippocampus performing a distinct cognitive process

Integration of inputs (CA1), pattern separation (dentate gyrus), pattern completion (CA3), memory retrieval (subiculum) and brief retention in memory tasks (entorhinal cortex). (Nature publishing with permission).

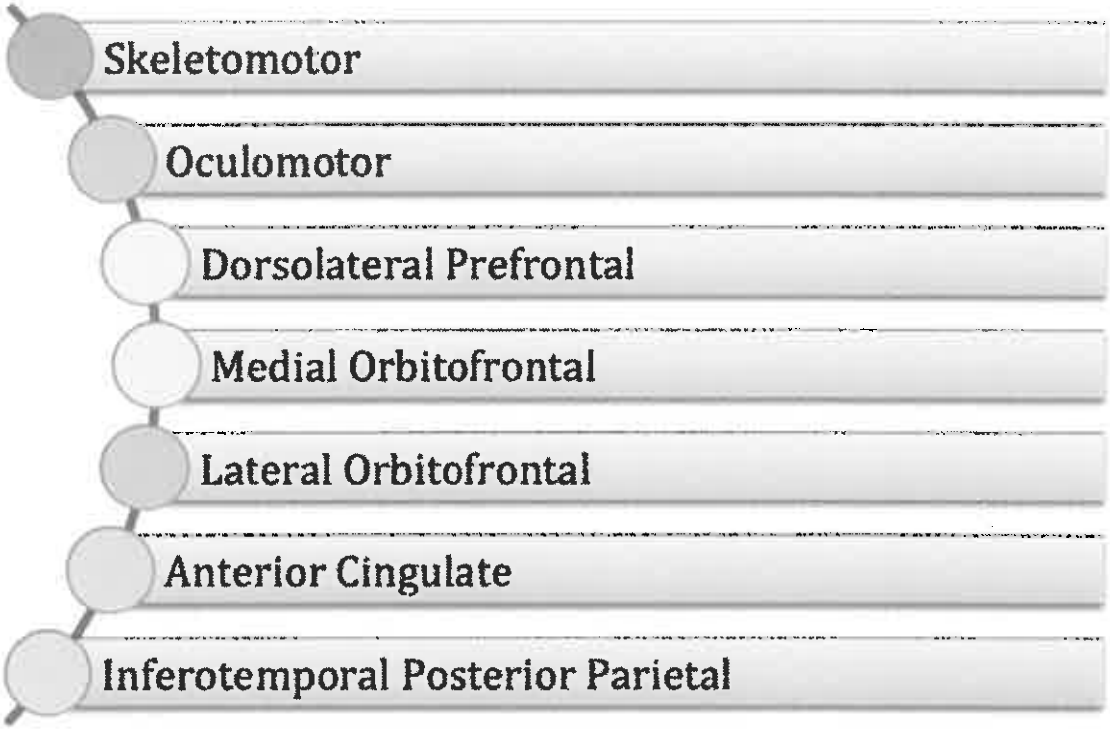

Figure 5. The 7 frontal subcortical circuits
Middleton FA, Strick PL. A Revised Neuroanatomy of Frontal – Subcortical Circuits. In Lichter DG, Cummings JL (eds). Frontal subcortical circuits in Psychiatric and Neurological Disorders. 2001,Guilford, London

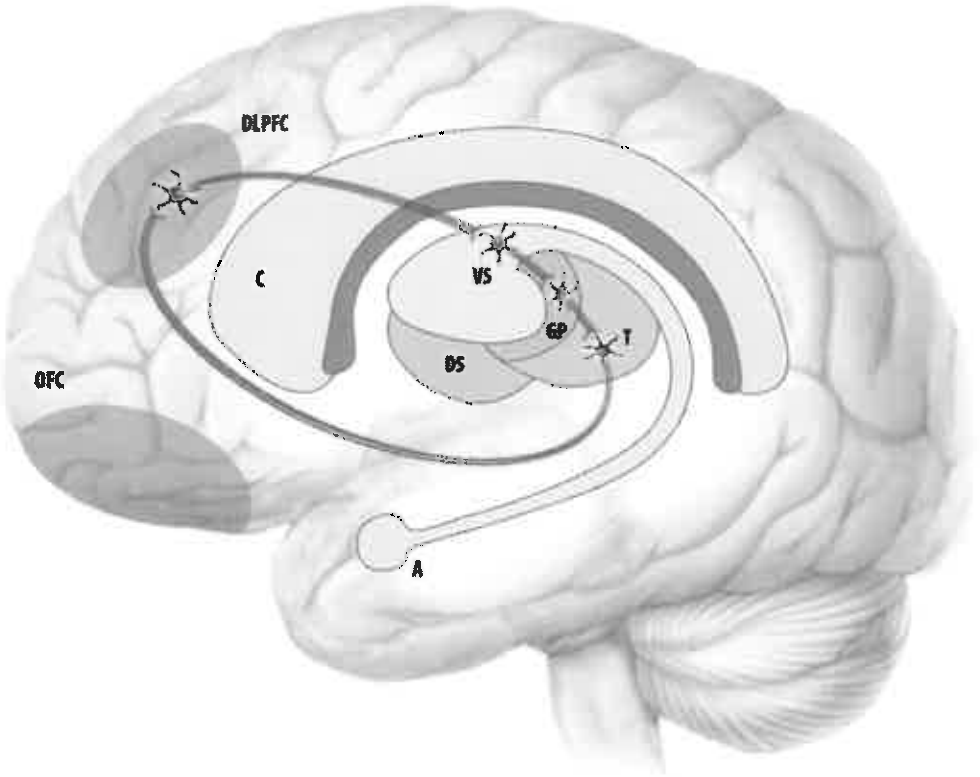

Figure 6. All frontal subcortical circuits follow the pattern of connectivity from the frontal cortex – striatum – globus pallidus – thalamus – frontal cortex.

This figure demonstrates the FSC for the executive loop beginning and ending in the dorsolateral prefrontal cortex.

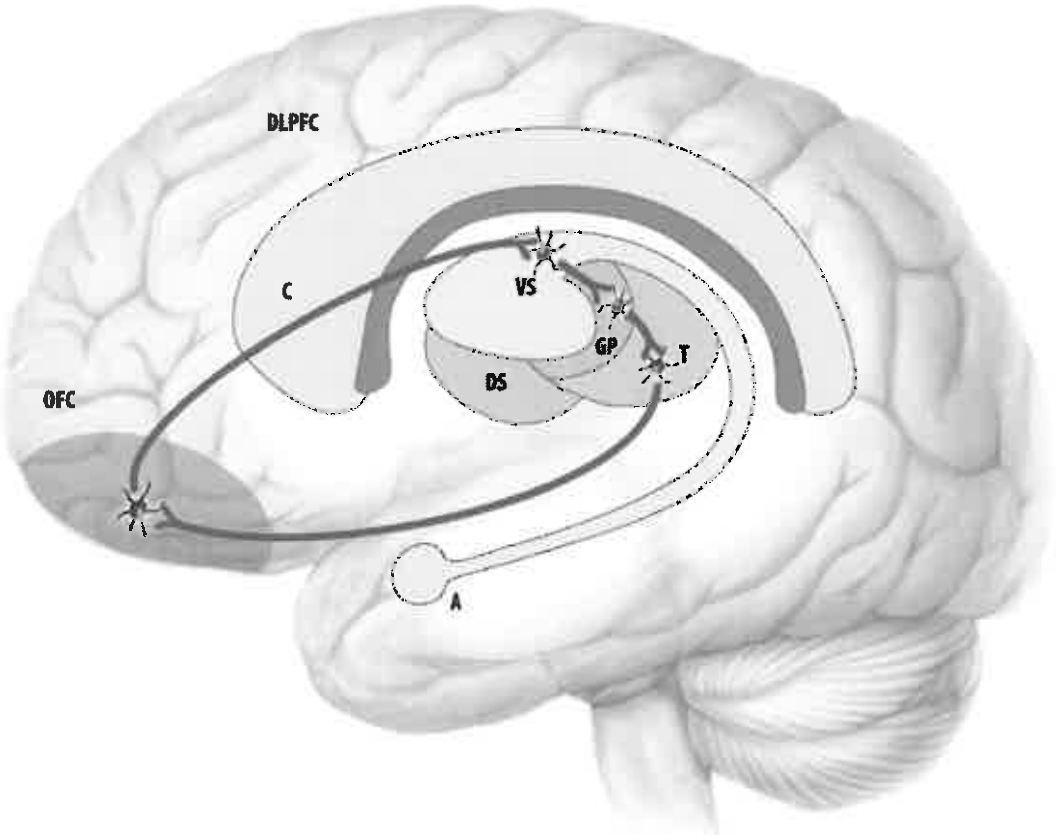

Figure 7. All frontal subcortical circuits follow the pattern of connectivity from the frontal cortex – striatum – globus pallidus – thalamus – frontal cortex.

This figure demonstrates the FSC for the emotional loop beginning and ending in the anterior cingulate gyrus.

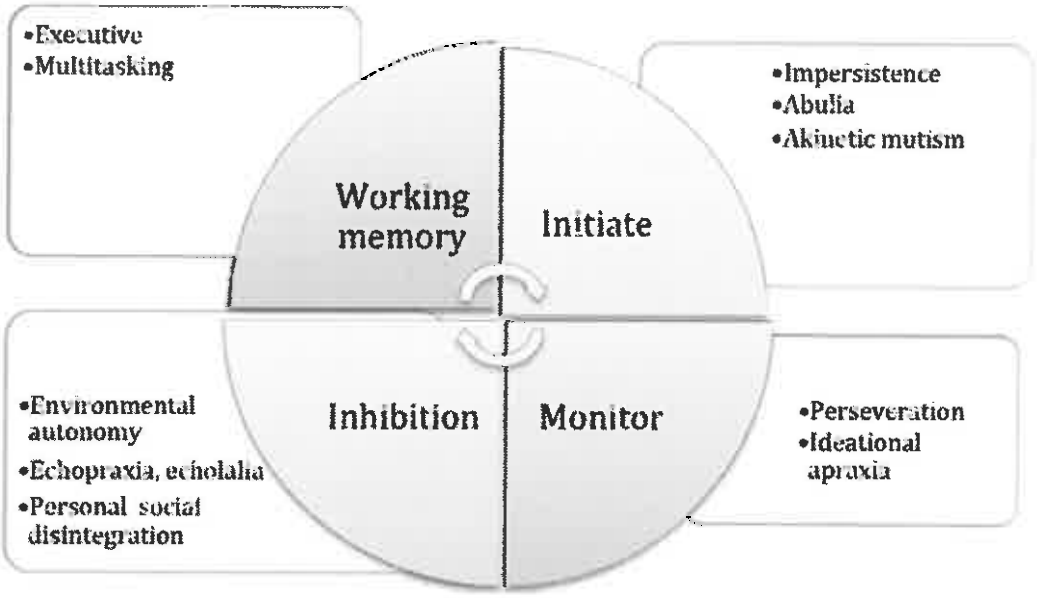

Figure 8. The 4 principal frontal core functions. From these derive the multiple secondary phenotypical frontal network syndromes.

Appendix 1

The four separate IRB approved cognitive stroke registries using cognitive vascular disorders as the brain lesion model.

1. The NIH-NINDS Stroke Data Bank (New York)

Under the following contracts;

N01-NS 2-2302, N01-NS-2-2384, N01-NS-2-2398, N01-NS-2-2399, N01-NS-6-2305

Status of stroke research fellow (1990-1991)

2. The Durban Stroke Data Bank. IRB approval University of Natal, Durban, South Africa (memorandum dated signed)

Status: Principal Investigator (1992-1998)

3. The USF-TGH Stroke Registry. IRB # 102354 (University of South Florida)

Status: Principal Investigator (2002-2006)

4. The USF-Cognitive Stroke Registry. IRB # 106113 (University of South Florida)

Status: Principal Investigator (2007-2010)

Appendix 2

1. Postgraduate Education Committee letter of acceptance of candidate

2. Biomedical Research Ethics Committee acceptance of USF IRB approval in lieu of BREC approval

UNIVERSITY OF
KWAZULU-NATAL

11 October 2010

Student no: 873876039

Dr M Hoffman
mhoffman@health.usa.edu

Dear Dr Hoffman

Doctor of Philosophy: "Frontal Network Syndrome Testing: A hierarchical and time oriented approach."

I have pleasure in advising you that at a meeting of the Postgraduate Education Committee held on the 05 October 2010, it was recommended to the Faculty Board that you be accepted as a candidate for the above degree to be supervised by Professor JV Robbs and co-supervised by Professor B Pillay. (Behavioural Medicine).

Enclosed please find the following.

- Guide to the procedures for Postgraduate study
- Hand Book - Nelson R Mandela School of Medicine
- Guide for presentation of Dissertation/Thesis

Please ensure a full protocol is submitted to the Postgraduate Office within six months of registration. Research application forms will be e mailed in due course.

I trust that your research will be both stimulating and productive, and wish you success in this venture.

Yours sincerely

Professor SJ Botha
Chair: Postgraduate Education Committee

Cc: Professor JV Robbs Head of Department: Professor BJ Pillay

Studies may not begin without Postgraduate and Ethics approval.
A research application form is accessible on the UKZN Website. Completed forms are to be submitted to Postgraduate Education Administration.

Postgraduate Education Administration
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RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
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KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

15th October 2012

Professor M Mars
Academic Leader
Nursing and Public Health
Howard College Campus
mars@ukzn.ac.za

Dear Professor Mars,

RE: PhD Dr Michael Hoffman *Frontal network syndrome testing: A hierarchical and time oriented approach.*

Our conversation in July 2012 refers.

We have reviewed the documentation carefully and recommended the following to the DVC (Research):

1) That the lack of UKZN BREC ethics review and approval be condoned as a good faith error on the part of the candidate;
2) That the US IRB ethics approval (USF IRB dated 4th May 2011) be accepted in lieu of BREC approval
3) That both supervisors (Professors John V Robbs and Basil Pillay) be advised that this thesis should not have proceeded without BREC approval and that they are advised to have sight of a BREC approval letter before allowing research (including for higher degrees) to proceed. A letter to this effect has been sent to both supervisors.
4) That no further action be taken.

The DVC (Research) has endorsed these recommendations.

The PhD may thus be examined as usual when it is ready for submission on the understanding that the US IRB approval is accepted, in this particular case only, in lieu of BREC approval.

It may be pertinent to advise all supervisors and researchers in the College to familiarise themselves with the University's ethics policies and that supervisors in particular should insist on seeing each student's final letter of BREC approval before allowing data collection to commence. We are trying

to send copies of all correspondence to supervisors but this is not routinely possible until our systems are upgraded.

Kindly acknowledge receipt of this letter.

Yours sincerely.

Prof D R Wassenaar
Chair: Biomedical Research Ethics Committee

Appendix 3

Permission letters from journals for permission to reproduce figures 1-4.

1. Brain – figure 1

2. Journal of Neuroscience – figure 2

3. Nature Neuroscience Reviews – figures 3 and 4

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William W. Seeley, Vinod Menon, Alan F. Schatzberg, Jennifer Keller, Gary H. Glover, Heather Kenna, Allan L. Reiss, and Michael D. Greicius
Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control
The Journal of Neuroscience, 28 February 2007, 27(9):2349-2356; doi:10.1523/JNEUROSCI.5587-06.2007

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Dear Sirs/Mesdames

May I please request the use of figure 2 from the article by Seeley WW et al. Dissociable intrinsic connectivity networks for salience processing and executive control. The Journal of Neuroscience 2007 27 2349-2356

The purpose is for use in a Phd thesis

Thanking you in advance

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Corrigenda

1. Manuscript # 4 on table 2 has been noted to have an error post publication and should read 4 rather 5 people in the first line yielding a total of 27 and not 28.