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Clinical Neuropsychology in the Era of Neuroimaging

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Introduction

Neuropsychology interfaces with the brain as a physical entity (neuro-) and the psyche as a mental (psycho-) construct. Clinical neuropsychology has emerged as a diagnostic discipline stemming from a simple, yet revolutionary paradigm – the possibility of assessing human brain function inferentially through recourse to cognitive and behavioural measures (Ruff, 2003). Combined with the ‘lesion method', neuropsychological assessment became the foundational methodological framework for clinical neuropsychological research (Benton, 2003). Neuropsychological evaluations are integral in providing recommendations for daily living and treatment planning for patients with brain disease such as neurodegenerative dementia, brain injuries/dysfunction (Casaletto and Heaton, 2017). This chapter provides a critique of current neuroimaging methods used in neuropsychological research and clinical practice, limitations and challenges of integrating neuroimaging findings within clinical neuropsychological practice, as well as potential future directions.

One of the earliest attempts to obtain a direct *in vivo* representation of the brain's morphology can be attributed to Franz Joseph Gall, founder of the now discredited field of phrenology that mistakenly used the skull shape as a proxy for the development of the underlying brain areas, corresponding to the strength/weakness of specific ‘mental faculties'. Subsequently, ‘localizationists’ including Paul Broca and early connectionists (e.g., Carl Wernicke and Joseph Jules Dejerine) proposed the localization theory of brain function (Sutterer and Tranel, 2017). Alexander Luria's qualitative neuropsychological approach (Luria, 1966) was founded on the premise that a given cognitive deficit can result from the impairment of different brain areas, and emphasized the necessity of cross-evaluating patients’ functioning via different tasks and situations (cf. Angus, 1985).

This qualitative approach has influenced other developments such as testing limits[2] in Kaplan's Boston Process Approach (White and Rose, 1997) and in neuropsychological rehabilitation (Christensen and Uzzell, 2000). In line with objective standardized psychometric testing principles, ‘fixed battery’ approaches such as

the Halstead–Reitan Neuropsychological Battery (HRNB; Reitan and Wolfson, 2013), and the Luria-Nebraska Neuropsychological Battery (LNNB; Golden, 2004) were established. In contrast to standardized batteries, Lezak promoted a subjective 'flexible battery' approach, where only measures directly related to presenting symptoms are administered (Lezak et al., 2012).[3] However, shorter neuropsychological batteries run the risk of drawing erroneous diagnostic inferences (Larrabee, 2008).

Over the last 25–30 years, there has been a rapid increase in use of high-resolution magnetic resonance neuroimaging (MRI) allowing visualization of brain anatomy. In contrast to structural neuroimaging (sMRI) methods, functional neuroimaging (fMRI) allows visualization of brain activity (Roalf and Gur, 2017). Structural lesions in brain-injured patients may relate causally to neurocognitive, neuromotor and sensory-perceptual sequelae. However, neuroimaging itself cannot directly provide insight into cognitive processing (cf. Stippich, 2007). According to Weinberger and Radulescu (2016),

> *MRI research – particularly structural MRI, resting-state functional MRI, and diffusion tensor imaging – are highly sensitive to common artifacts (e.g., head motion and breathing effects) that may dominate the results. Because these and other important confounders of MRI data (e.g., smoking, body weight, metabolic variations, medical comorbidities, psychoactive drugs, alcohol use, mental state) tend to vary systematically between patient and control groups, the evidence that findings are neurobiologically meaningful is inconclusive and may represent artifacts or epiphenomena of uncertain value. … uncritically accepting … findings that may represent fallacies of all sorts carries the risk of misinforming practitioners and patients about biological abnormalities*.

Given these apparent limitations of neuroimaging, several key questions arise about its ability to inform clinical neuropsychological practice. This situation raises several key questions. Specifically, what are the challenges presented by neuroimaging and how does neuroimaging relate to the practice of clinical neuropsychology? And, what is its role and place in a future marked by technological advances that continue to create new tools for monitoring the structure and functioning of the human brain?

What is Neuroimaging?

'Neuroimaging' is an umbrella term that includes diverse methods such as computerized tomography (CT scanning), positron emission tomography (PET), magnetic resonance imaging (MRI), near-infrared spec-

troscopy (NIRS) and encephalography[4] (M/EEG; Pernet et al., 2019). Neuroimaging can provide important diagnostic information, particularly about neurodegeneration associated with dementia, brain injuries and/or brain tumours. These approaches vary along three main axes, namely *invasiveness* (PET and CT being more invasive than MRI or EEG); *resolution* (encompassing different domains; for instance, MRI has high spatial resolution but relatively low temporal resolution whereas EEG has low spatial but relatively high temporal resolution); and *scope* (structural imaging provides information on the physical state of the brain whereas functional imaging focuses on its activity at any given moment). An overview of both structural and functional neuroimaging of the brain in regard to temporal and spatial resolution, and the axis of paradigm and invasiveness is provided in Figure 4.1.

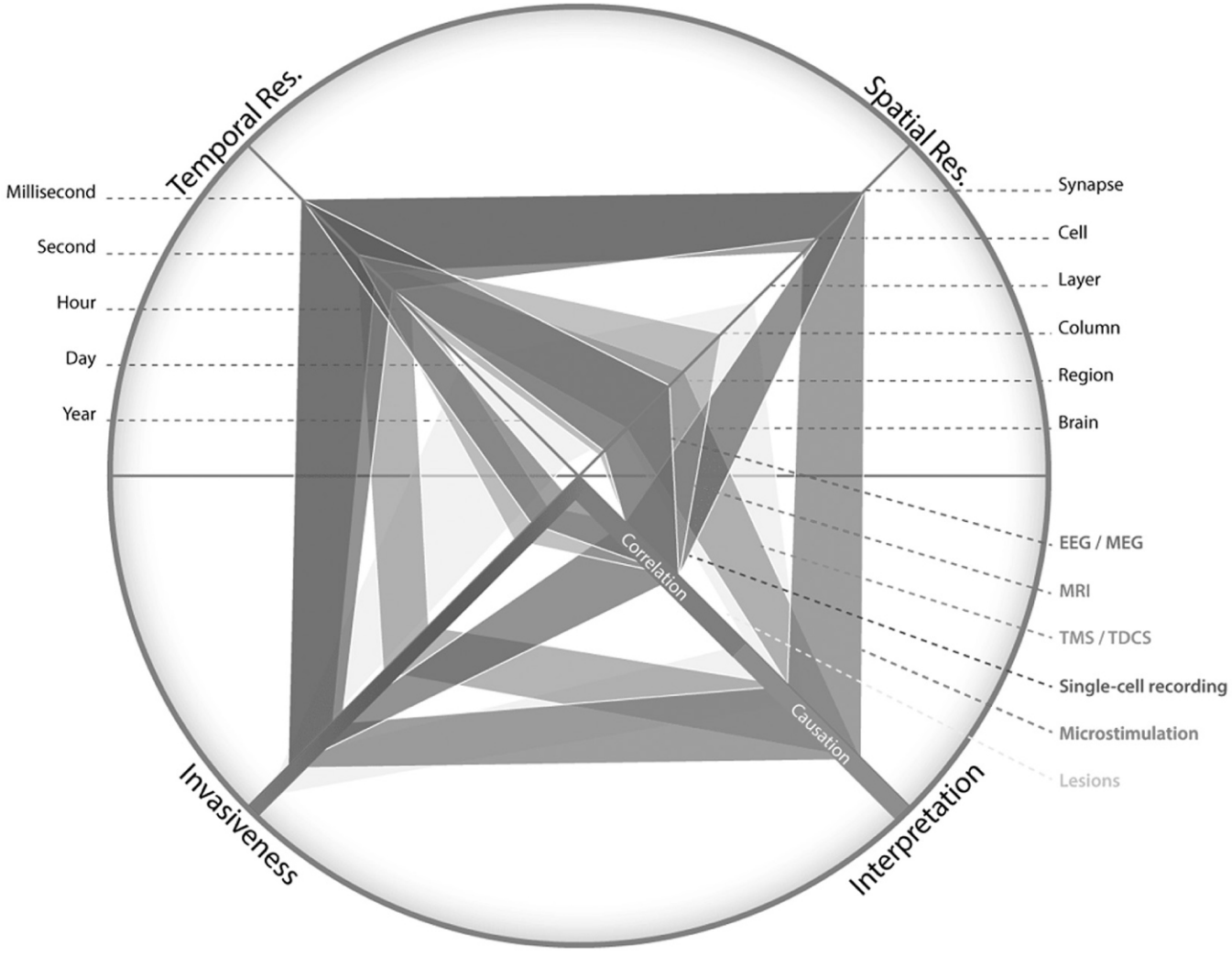

Figure 4.1 A radar chart representing the profile of different techniques mapped on four dimensions: temporal resolution, spatial resolution, interpretation (whether correlational or

causal inference can be made – through brain interference) and invasiveness. EEG/MEG and MRI are both non-invasive and correlational and differ primarily in their temporal and spatial resolution. Single-cell recording and microstimulation share a high invasiveness and temporal and spatial resolutions, and differ in their paradigm (measuring vs interfering with brain activity, respectively). Brain lesions, which come in different shapes and forms (and thus cover large portions of the resolution dimensions), are inherently considered as invasive (often resulting in permanent damage to the brain)

Structural Neuroimaging Techniques

Computerized Tomography (CT)

While the first usage of proto-neuroimaging can be tracked back to 1895, when X-rays were used to localize bullets within the skull (Fulham, 2004), it was not until 1972 that an accurate representation of the brain was made possible through CT scanning. A CT scanner measures the linear reduction in the X-ray beam as it passes through matter, which is the amount of radiation not absorbed (e.g., by the brain, allowing reconstruction of the subcortical and cortical tissues). As the X-ray beam is rotated through 180 degrees at equally spaced intervals (slices), a three-dimensional representation is produced. CT scanning (including of the brain) is widely used in medical settings, especially in emergency situations where a rapid scan is needed to detect potential brain lesions. CT scanning not only detects brain lesions, but also is sensitive to skull fractures, brain haemorrhage, hydrocephalus, tumours and encephalopathy. The procedure causes minimal discomfort to patients, and although it exposes them to a small dose of ionizing radiation, it is largely without any significant side effects or health risks (Igbaseimokumo, 2009).

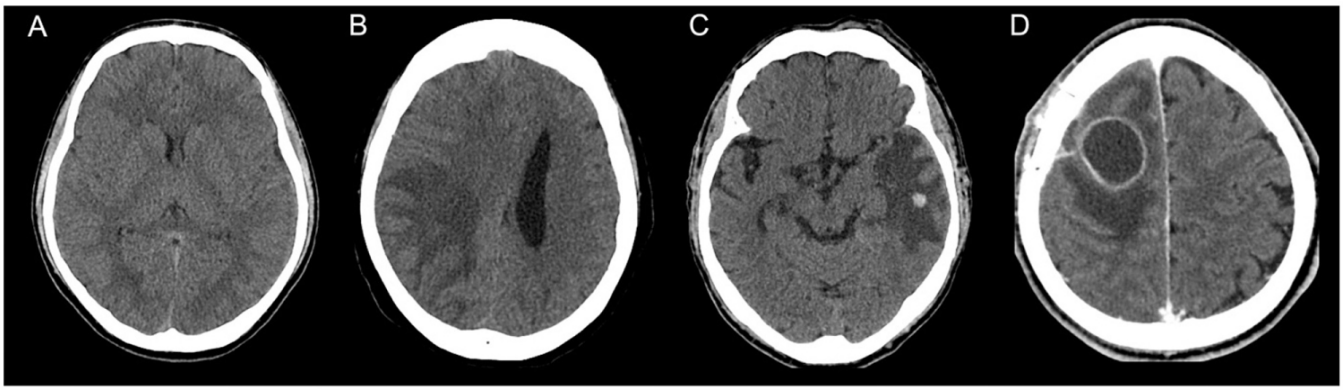

Figure 4.2 Computerized tomography (CT) brain images: (A) healthy 22-year-old male; (B) 71-year-old female with meningoencephalitis; (C) 63-year-old male with brain metastasis from lung cancer; (D) 27-year-old male with brain abscess. (Courtesy of Hung-Wen Kao, Department of Medical Imaging, Hualien Tzu Chi Hospital, Taiwan.)

Magnetic Resonance Imaging (MRI)

Previously known as *nuclear* magnetic resonance imaging, MRI technology uses a high-field magnet to detect changes in the magnetic properties of hydrogen atoms (basically protons). The MRI scanner produces the main static magnetic field often at 1.5 Tesla (T) or 3T in most medical settings. In recent years, 7T MRI scanners have also received clearance from the American Food and Drug Administration (FDA) for General Electric and Siemens scanners. The head (radiofrequency) coil delivers energy at the resonance frequency of protons (e.g., in the brain or other bodily tissue) perturbing the equilibrium state. The gradient coils in the scanner can be turned on and off to alter the magnetic field strength over space. The energy of excited protons as they return to their equilibrium states is received by the head coil to construct 2D or 3D images by tomography. The non-ionizing radiation produced by the radiofrequency is not harmful to the patient, and is non-invasive. The images produced are of high spatial resolution and are better at visualizing soft tissue than CT scans. MRI scans have now been widely used in clinical settings to detect brain lesions resulting from diffuse axonal injury, tumours, infarcts, and encephalopathy, as well as from atrophy and structural changes in deep subcortical structures. Common structural MRI sequences include T1-weighted images (cerebrospinal fluid (CSF) is dark and brain tissue is lighter), T2-weighted images (CSF is bright and brain tissue is darker) and T2-Fluid Attenuated Inversion recovery (FLAIR) (where lesions remain bright while CSF is darker) and

T2* (‘T2-star'; iron, blood, bone and calcium appear dark) (see Grover et al., 2015).

Advances in MRI technology have made it possible to generate pulse sequences to brain tissues whereby an image is produced using different contrasts. For example, diffusion weighted imaging (DWI) has unparalleled sensitivity to water movements within brain tissues with no requirement for contrast agents. Modelling of the DWI images allows indirect measurement of the fibre tracts through diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI). DSI allows better modelling of the fibre tracks than DTI due to the increase in the direction of water diffusion acquired. Diffusion MRI techniques have been applied to aid tumour resection and track white matter abnormalities occurring in conditions such as multiple sclerosis, neurodevelopmental, neurodegenerative and neuropsychiatric diseases. It has provided insights into the nature of relationships between structural connectivity and neurocognitive functions (Drake-Pérez et al., 2018). For example, in tumour resection, tractography with other functional neuroimaging data and neurocognitive performance information could help neurosurgeons to achieve maximal tumour resection while avoiding post-operative neurological deficits (see Duffau, 2020).

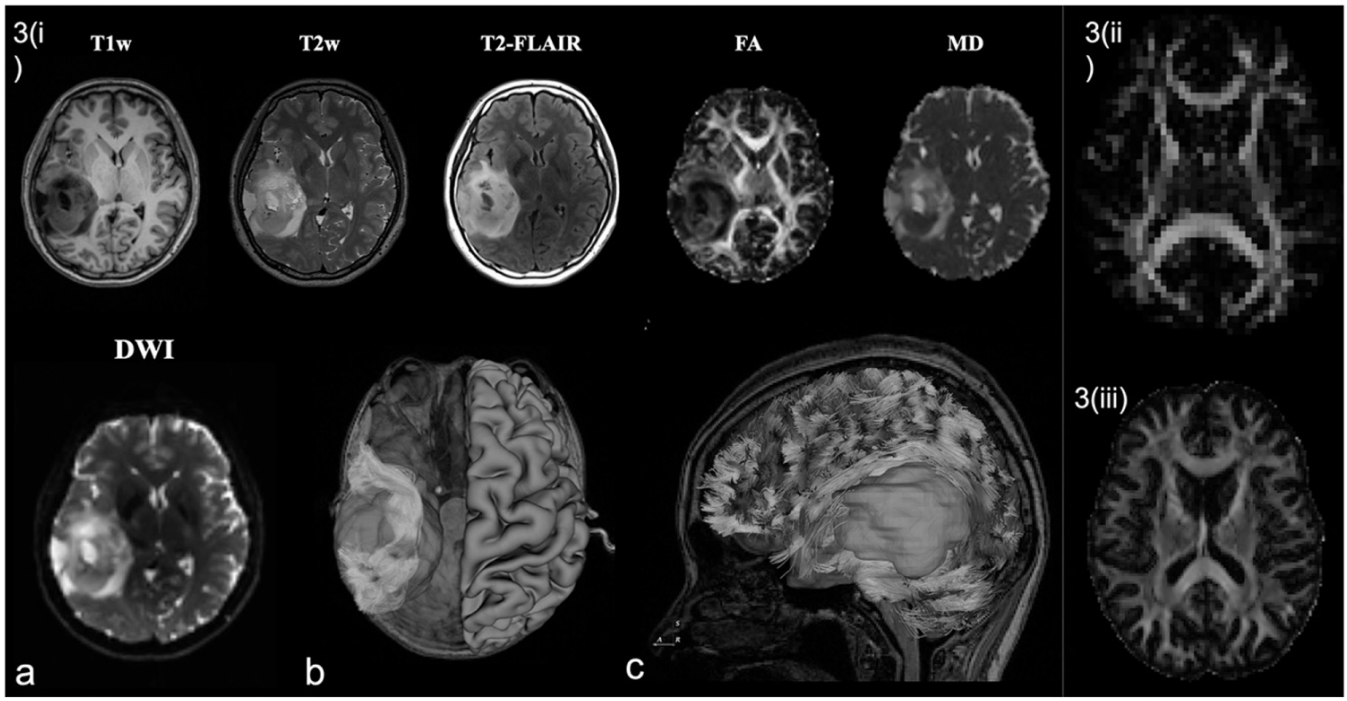

Figure 4.3 Magnetic resonance imaging (MRI) brain images (i) 41-year-old female with heterogeneous mass over left temporal lobe (with mild perifocal edema). Images show high resolution MR T1-weighted (T1w), T2-weighted (T2w), T2-FLAIR images, FA (fractional anisotropy) and MD (mean diffusivity) map; (a) Diffusion weighted image (coronal), (b) Diffu-

sion tensor imaging (coronal) showed superior displacement of left Wernicke's area with intact arcuate fasciculus projecting to left premotor and left Broca areas, (c) Diffusion tensor imaging (sagittal) showed displacement of tracts. (ii) Color fractional anisotropy (FA) image from a 50-year-old healthy female volunteer. Diffusion tensor imaging (DTI) imaging performed on a 3T Siemens Prisma™ using 128 different directions of diffusion sensitization (slice thickness = 1.5 mm) representing the principal diffusion directions and hence the direction of the white matter tracts. (Images (2i, 2ii) are Courtesy of Shin Tai Chong, National Yang Ming Chiao Tung University, Hsinchu, Taiwan.) (iii) Color fractional anisotropy (FA) image from a 21-year-old healthy male volunteer. Diffusion tensor imaging (DTI) imaging performed on a 3T Siemens Prisma™ using 128 different directions of diffusion sensitization (slice thickness = 3 mm). (Images are Courtesy of SH Annabel Chen, Clinical Brain Lab, Nanyang Technological University, Singapore.)

Functional Neuroimaging Techniques

Functional neuroimaging (fMRI) techniques depict blood flow (and oxygen uptake) to activated brain regions. Since the 1990s, use of fMRI has made it possible to track brain activity during specific tasks. fMRI techniques can be broadly categorized into (1) voltage-sensitive, (2) radioisotope-based and (3) hemodynamic-sensitive techniques.

Voltage-Sensitive Techniques

Electroencephalography (EEG) is a neurophysiological technique used to monitor overall brain electrical activity from the surface of the scalp. It is useful in identifying seizure focus and frequency in epilepsy (Tatum et al., 2018), stages of sleep and consciousness (including anaesthesia and coma depth (Gosseries et al., 2011) and in locating areas of abnormal electrical activity associated with brain lesions and even the differentiation of dementia subtypes (Hampel et al, 2014). While EEG methods benefit from the simplicity of instrumentation, they suffer from protracted set-up time and low spatial resolution. In comparison, magnetoencephalography (MEG) detects brain magnetic fields associated with brain activity and has a higher spatial resolution. How-

ever, it requires sophisticated and costly instrumentation and measurement methods, and therefore its use is mostly restricted to large medical centres for epilepsy and presurgical planning (Burgess, 2020; De Tiège et al., 2017; Stapleton-Kotloski et al., 2018). Optically pumped magnetometers (OPM) offer a new paradigm for MEG measurements aimed at addressing some of the limitations of traditional MEG systems based on superconducting quantum interference device (SQUID) magnetometers (limitations include high maintenance cost, fixed sensor position, fixed helmet size), but these new methods are not yet available in most research and clinical settings (Borna et al., 2020).

Radioisotope-based imaging

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are neuroimaging techniques that evaluate neurophysiological function and biochemical changes of molecular targets. SPECT and PET rely on the injection of a radioactive tracer into the bloodstream and measure the decay of the radionuclide, during which emission of positrons or gamma-rays are captured by scanners to reconstruct an image of the brain activity. As the ligands produce ionizing radiation, they are harmful to the body and are therefore somewhat invasive. The radioisotopes applied in SPECT have longer half-life (from six hours to almost three days) and emit only a single gamma-ray during decay that is measured directly. In comparison, PET records decay of two gamma-rays emitted 180 degrees apart that are measured indirectly. These radioisotopes have a very short half-life (e.g., Oxygen-15 [^{15}O] measuring regional cerebral blood flow [rCBF] – about two minutes and fluoro-deoxyglucose [FDG] measuring glucose metabolism – about 109 minutes), and a cyclotron facility is required to be within close vicinity to the scanner to deliver the radioactive tracer before it decays. Both SPECT and PET have high sensitivity with relatively good spatial resolution and high penetration depth. Thus, apart from detecting cancer (FDG is used extensively as a cancer biomarker) both SPECT and PET have been applied in clinical studies of numerous diagnoses, such as: neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), essential tremor, attention deficit-hyperactivity disorder (ADHD), autistic spectrum disorder (ASD), inflammatory demyelinating diseases such as multiple sclerosis (MS) and genetic disorders such as Huntington's disease (HD). However, SPECT has much lower sensitivity as compared with PET, but is less expensive and allows longitudinal scans with the longer half-life. In particular, *in vivo* quantification of amyloid deposits in AD has been made possible by using radiological compounds of ^{18}F-FDDNP and Pittsburgh Compound-B (^{11}C-PIB) in PET. Radioisotopes

are also available for SPECT and PET to image neuroinflammation in AD and the dopaminergic system in PD (e.g., 18F-dopa in PET). For other clinical applications see Lu and Yuan (2015) and Morgan and Ricker (2018). However, the need for measuring rCBF via SPECT or PET has largely been supplanted by the non-invasive fMRI imaging techniques over the last two to three decades.

Hemodynamic-Sensitive Techniques

Functional MRI (fMRI) measures blood flow changes in the brain over time. The most common pulse sequence employed to measure the ratio of oxygenated/de-oxygenated blood (the hemodynamic response function; HRF) of blood-oxygen-level-dependent (BOLD) response is gradient-echo echo-planar-imaging (EPI). As a task is performed in the scanner, the HRF can be statistically modelled based on the presentation of the task design (event-related, block or mixed) to reconstruct activation maps correlated with task conditions. The spatial resolution, temporal resolution and signal-to-noise ratio are superior to that for either PET or SPECT. In addition, with its non-ionizing radiation properties task-fMRI has largely replaced ^{15}O-PET in visualizing brain activity related to cognition. Clinical fMRIs are applied in medical centres in presurgical planning and mapping for brain tumours or epilepsy. The paradigms used in the clinical application of fMRI strive at maximizing the elicitation of robust and reliable activation while minimizing duration and complexity. As such, they consist of simple tasks (that can be tolerated by patients) for motor abilities, visual perception, language and memory. Findings from clinical fMRIs are usually evaluated together with findings from a comprehensive neuropsychological evaluation, EEG monitoring, MRI and Wada test (Wada, 1949) – all information obtained in presurgical planning for epilepsy. Although clinical fMRI (sometimes together with MEG mapping) increasingly is replacing the more invasive Wada test (an intra-carotid injection of sodium amytal), it is noted that while language lateralization is robust, memory lateralization is still poor (Massot-Tarrús et al., 2020; Qadri et al., 2021). Newer analytical methods of functional connectivity allow the acquisition of resting-state fMRI (rs-fMRI) where cognitive tasks are not required to be completed while in the MRI scanner to assess brain activity. Group studies from clinical research have shown very robust resting networks such as the default mode network (DMN), executive control network (ECN) and salience network (SN). These networks have also been shown to be disrupted in neurological and neuropsychiatric conditions (Menon, 2011). However, applicability for the individual patient undergoing clinical investigations is still somewhat limited (see Specht, 2020).

Functional near-infrared spectroscopy (fNIRS), as with fMRI, detects the changes in hemodynamics in the

brain but uses optical sensor devices (optodes) that emit laser beams shone through the scalp. It leverages the differences in optical absorption by the brain tissues to reconstruct brain activation maps. It is more portable and less restricting for the person than the MRI scanner. However, it only penetrates 3–4 cm into the cortical mantel and is therefore not able to measure activity in the subcortical structures. Although it is increasingly being used in research, its clinical application is still limited by the lack of anatomical specificity, suboptimal temporal resolution and poor intra-individual reproducibility. Nevertheless, with the advancement of technology, and potential combination with EEG, it is thought to have promising clinical applications (Chen et al., 2020).

Stability of Characteristics

Aside from properties specific to the nature of the neuroimaging techniques discussed above, we can introduce an additional dimension pertaining to the stability of characteristics measured by the specific technique. This is particularly the case for functional neuroimaging, which can be used to assess both dynamic and dispositional aspects of brain activity. Indeed, early applications of functional neuroimaging were focused on evoked activity during a specific task (see Fox et al., 1986; Ogawa et al., 1992, for the first human studies using functional PET and fMRI imaging, respectively). They examined the pattern of activity corresponding to the engagement of a specific cognitive process, such as watching a stimulus and retaining it in memory, or recalling an event from memory. In contrast, other lines of work pursued the functional correlates of dispositional trait constructs (cf. Boyle et al., 2008a, b; 2015). For instance, recent studies have examined the presence of distinct neural networks using resting-state fMRI. Their properties, such as prevalence, strength, balance and interconnectivity, have been correlated with certain features, such as cognitive control (Reineberg et al., 2015), personality trait measures (Nostro et al., 2018) and the presence of disorders (e.g., Lin et al., 2018). These technological features also appear to be sensitive to detection of brain plasticity, including changes following psychotherapeutic interventions (Crowther et al., 2015), or meditation (Froeliger et al., 2012; Jang et al., 2011). However, one might also adopt a critical perspective towards the sensitivity to change and reliability/stability of rs-MRI networks in individuals (cf. Branco et al., 2018; Song et al., 2012; Thomason et al., 2011). As Takao et al. (2021) have pointed out, the stability of resting-state (rs-MRI) networks in normal ageing, '*generally declines with progression to MCI and AD*'.

Neuroimaging techniques not only measure and quantify brain processes related to specific cognitive tasks,

but can also measure task-unrelated features (such as network connectivity). Moreover, the ability of neuroimaging to capture and investigate precise brain regions, network connectivity and temporal dynamics may render theoretical disputes about *localizationist vs connectionist* paradigms obsolete (Sutterer and Tranel, 2017). However, it must be acknowledged that resting-state fMRI may be meaningless in the absence of explicit cognitive tasks to relate network activity to, and that it measures brain function at a very different level from that of traditional neuropsychological assessment (cf. Biswal, 2012; Lv et al., 2018). For barriers to incorporating rs-fMRI into clinical protocols, see O'Connor and Zeffiro (2019).

Promises and Challenges of Neuroimaging

The advent of non-invasive functional neuroimaging techniques has greatly impacted neuropsychological investigations into brain and behaviour relationships over the last 30 years or so (Roalf and Gur, 2017). However, there has been a critical focus on problems related to the robustness and reliability of neuroimaging techniques, and in particular fMRI which is perhaps the most popular of these techniques (for a balanced view see: Fostering reproducible fMRI research, 2017). Although early successes of fMRI might be described as a 'gold rush' of studies seeking to map various cognitive processes and dispositions onto specific brain areas (Sutterer and Tranel, 2017), newer studies and meta-analyses have raised concerns regarding the reliability of neuroimaging measurements. Shortcomings have been highlighted such as the '*correlative nature of the approach, as well as overly zealous interpretations of (often) poorly-defined cognitive constructs*' (Sutterer and Tranel, 2017). This concern about the inferential quality of fMRI data continues to feed scepticism about much of the existing fMRI research (Shulman and Rothman, 2019; Szucs and Ioannidis, 2020). Indeed, the vast majority of fMRI studies conducted between 2007 and 2011 have adopted a localizationist framework, and only 11 percent of these studies tested explicitly defined cognitive models (Tressoldi et al., 2012). As an aside, it is noteworthy that there is a conspicuous absence of neuroimaging markers in the major neuropsychiatric diagnostic classification manual, the DSM-5 (APA, 2013), and a lack of consensus as to whether this omission will change in the near future (Aydin et al., 2019; Etkin, 2019; First et al., 2018; Henderson et al., 2020; Rosen and Savoy, 2012).

Concerns about 'replicability' (Turner et al., 2018) and 'reproducibility' (Open Science Collaboration, 2015) of both psychological and neuroimaging studies have arisen. Methodological issues raised with systematically

accumulated shortcomings within the scientific literature have cast doubt over the integrity of the whole field (see John et al., 2012; Simmons et al., 2011). In neuroimaging studies (and fMRI studies in particular), evidence of this replication and reproducibility crisis has included reliance on flawed statistical procedures, small sample sizes and career incentive structures that emphasize rapid publication of questionable findings, while disincentivizing studies that report null findings (Button et al., 2013; Fanelli, 2012; John et al., 2012; Ritchie, 2020; Szucs and Ioannidis, 2017; Turner et al., 2018; Weinberger and Radulescu, 2016). In the current research culture, there is evidence of questionable research practices, such as engaging in ‘p-hacking’ (Head et al., 2015; Nelson et al., 2018), involving post-hoc data-analytic procedures, turning non-significant into significant ‘findings’ (e.g., adoption of a less stringent *p-value* cut-off for estimating ‘significant differences') (cf. Bennett et al., 2009; Vul et al., 2009). Another dubious research practice involves coding or extraction bias (Petticrew and Roberts, 2008), whereby researchers make biased decisions as to which studies are selected for inclusion/exclusion in systematic reviews or meta-analyses. Neuroimaging studies are especially prone to this bias as such studies yield a high number of effects, in relatively disparate data, where authors have large degrees of freedom to choose what data to include in their reviews (e.g., Müller et al., 2018). Coding bias may explain why the majority of non-significant findings in sMRI studies into psychopathic personality disorder have virtually disappeared from the scientific review literature (Jalava et al., 2021). When coding bias occurs, the result is a skewed representation of the research in the literature, which may lead or contribute to misinformed clinical practice.

The professional neuroimaging community has taken these issues seriously, with a variety of initiatives being designed to tighten up research practices and by establishing multi-lab collaborations with shared protocols intended to increase statistical power (Eklund et al., 2017; Gorgolewski and Poldrack, 2016; Poldrack et al., 2017; Specht, 2020). However, translating neuroimaging research to neuropsychological evaluation and care of individual patients is not straightforward. Findings of brain–behaviour relationships obtained from observational studies at the population level (as in most neuroscientific studies) cannot be used directly to draw individual-level inferences, somewhat akin to a non-ergodic system (cf. Molenaar and Campbell, 2009). In clinical neuropsychological assessment, a failure to properly address this issue (known as the ‘ecological fallacy'; Thorndike, 1939; cf. Hamaker, 2012; Kurz, 2019) may result in misleading diagnoses and prognoses, misdirecting treatment strategies and so forth (Poldrack, 2018).

Neuroimaging (e.g., fMRI), has been widely viewed as a revolutionary tool for undertaking research into the structure and function of the human brain (Bandettini, 2012), as exemplified in major brain-imaging projects such as the Human Connectome Project (2009). A fundamental problem in neuroscience is that the more

precise and specific an investigation (such as mapping the brain's neural circuitry), the more sophisticated and complex a test procedure it requires (such as neuroimaging), and consequently the less reliable its measures arguably become. Indeed, for neuroimaging to be useful in a clinical setting, it must be able to map mental processes and their neural correlates in a sufficiently reliable and valid way. Consider, for example, the common clinical application of fMRI in discerning language lateralization and localization. Here, its reliability is comparable to that of the invasive Wada procedure (Janecek et al., 2013). fMRI has shown promising results for eliciting basic motor, sensory and memory functions, with simple task paradigms (e.g., moving a finger) to elicit robust and clinically relevant activations. Although useful in neurology or neurosurgical contexts, this type of information lacks the finesse to be sufficiently informative when it comes to more subtle or complex cognitive processes, which is typically the focus of clinical neuropsychological assessment. This simplicity–complexity problem[5] appears difficult to solve within the confines of current neuroimaging techniques and data-analytic procedures, although new avenues are being explored (e.g., see Cooper et al., 2019).

A potential silver lining has been found in resting-state fMRI, a seemingly simple and robust phenomenon able to activate networks identified through task-related fMRI, but without any complex tasks involved (cf. Biswal, 2012; Lv et al., 2018). When measuring resting state, participants are simply instructed to ‘rest’ (i.e., the task is to try to do ‘nothing'). Also, developing basic simple tasks could be particularly relevant, especially in patients with impaired behavioural performance (e.g., paralysed patients). Unfortunately, studies have shown significant variability in this paradigm (with different instructions leading to different outcomes), in its data acquisition (with outcomes depending on the parameters of the scanner) and in its data processing (with results potentially affected by pre-processing parameters and thresholds for multiple comparison corrections; see Specht, 2020). To increase comparability within and between individuals in such tasks, standardized protocols and guidelines are currently being developed – see: adni.loni.usc.edu (retrieved 16 September 2021).

Nevertheless, the extent of one-to-one correspondence between a detected blood-oxygen-level-dependent (BOLD) activation and the activity of a given cluster of neurones (related to a particular mental process) is an ongoing source of debate (Ekstrom, 2010). An fMRI signal can be modulated by other internal factors such as blood pressure, chronobiological rhythms, or external factors such as the often-substantial noise of the MRI scanner (Tomasi et al., 2005). Although the current tendency is to conduct multicentre studies with larger combined sample sizes (thereby increasing reliability of neuroimaging studies), for the further development of clinical fMRI, there is a parallel and vital need to improve single-subject fMRI paradigms and data-analytic methods (Bandettini, 2012). However, single-subject studies have their own methodological challenges, such as the threshold issue in drawing statistical inferences regarding brain activation (Gorgolewski et al., 2012;

Logan and Rowe, 2004) that would be sufficiently reliable to inform pre-neurosurgical planning for a given patient (Chen et al., 2009; Desmond and Chen, 2002).

Neuroimaging as a Neuropsychological Tool

Neuroimaging and neurodiagnostic techniques have been mentioned as a key component of didactic experience in clinical neuropsychology training in North America in the Houston Conference Guidelines (Hannay et al., 1998) for internships and postdoctoral residency (Smith, 2019). With development of the current procedural terminology (CPT) codes[6] (Bobholz et al., 2007) in the United States for clinical fMRI as an essential clinical tool, it is not uncommon to have this procedure conducted there as part of presurgical planning with neuropsychology as part of the multidisciplinary team, for epilepsy (Duncan et al., 2016) and tumour resection (Pillai, 2010) in major medical centres. A survey of neuropsychologists from the International Neuropsychological Society and the American Academy of Clinical Neuropsychology found about 70 percent of neuropsychologists to have neuroimaging training exposure (Benitez et al., 2014). Thus, contemporary neuroimaging–neuropsychology collaborations are indeed very feasible and are already being conducted in North America in circumscribed medical settings as mentioned above. A survey of core competencies in clinical neuropsychological training noted knowledge of neurodiagnostic techniques to be a key component across quite a few countries (Hessen et al., 2018). However, the use of clinical neuroimaging by clinical neuropsychologists is more varied in other parts of the world. For example, in Europe where clinical neuropsychology training is becoming more standardized (Hokkanen et al., 2020), only about 4 percent of neuropsychologists are involved in performing language mapping using clinical neuroimaging in epilepsy centres with the majority (about 66 percent) done by neuroradiologists (Bargalló et al., 2020). fMRI in clinical practice has also become a mainstream neuroimaging modality in epilepsy and brain tumour evaluations in Australia (Barras et al., 2016). The involvement of neuropsychologists in these multidisciplinary medical teams has a long history (cf. Wong et al., 2021).[7] In Asia, clinical neuropsychology practice is still relatively young, and focus has mostly been on clinical training and developing normative databases for neuropsychological measures (Lee et. al., 2016). However, early efforts in applying clinical fMRI in collaboration with clinical neuropsychological evaluation have been reported (Chen et al., 2008).

Evidently, there are important contemporary neuroimaging–neuropsychology collaborations. To take just one example, a clinical neuropsychologist employed at the University of Texas MD Anderson Cancer Center, '*con-*

ducts comprehensive neuropsychological assessments, presurgical fMRI of higher order cognitive function for neurosurgical planning, and offers interventions to adult cancer patients suffering from the central nervous system effects of cancer, cancer treatment, or other illnesses' (see: faculty.mdanderson.org/profiles/jeffrey_wefel.html, retrieved 17 September 2021). This has also been a longstanding clinical practice and training at the Neuropsychology Division, Medical College of Wisconsin where, '*In addition, neuropsychologists provide specialty brain mapping services including intra-operative cognitive mapping for brain tumor and epilepsy patients, functional MRI for mapping language prior to brain surgery, and intra-carotid sodium amytal testing to lateralize language and memory prior to brain surgery*' (see www.mcw.edu/departments/neurology/divisions/neuropsychology, retrieved 19 September 2021).

Thus, neuroimaging as a measurement tool clearly falls within the purview of clinical neuropsychologists (Figure 4.4), since neuroimaging is routinely carried out alongside traditional neuropsychological evaluations in order to draw more accurate conclusions for diagnosis and treatment purposes (including presurgical planning prior to brain tissue resection for, say, epilepsy or tumours). It is evident that clinical neuropsychologists, neurologists, radiologists and neurosurgeons all confer together as a team in making such presurgical planning decisions in relation to individual patients (Tanner et al., 2015).

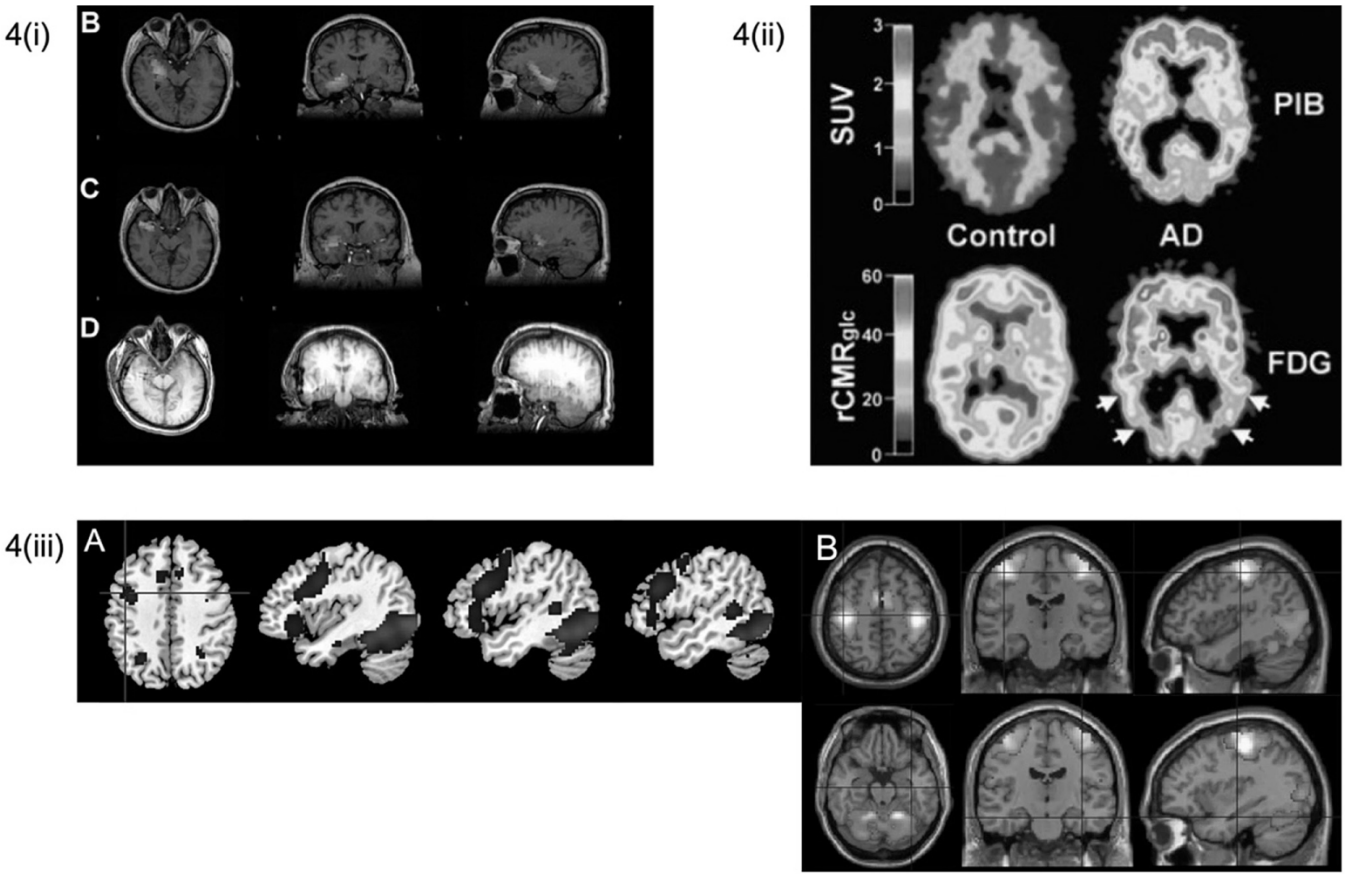

Figure 4.4 Functional neuroimaging brain maps. (i) Activation maps constructed from magnetoencephalography (MEG) sensor data during a seizure. (B) The synthetic aperture magnetometry (SAM) (g2) statistical parametric maps indicated a right hippocampal focus as well as (C) a focus in the amygdala. (D) A computerized tomography (CT) scan reveals the placement of the hippocampal and amygdala depth electrodes, as well as the location of the hippocampal focus (cross) as identified by SAM(g2). (Reproduced with permission from Stapleton-Kotloski et al (2018) (CC-BY 4.0).) (ii) PIB standardized uptake value (SUV) images of PIB retention in a 79-year-old AD patient (right) and a 67-year-old HC (left). The high PIB retention of the AD patient is seen in the frontal and temporo-parietal cortices (top right). A typical pattern of 18FDG hypometabolism of AD patient is shown in the temporoparietal cortex (arrows; bottom right) along with preserved metabolic rate in the frontal cortex. (Reproduced with the permission from Klunk et al (2004); Copyright 2004 Wiley and Sons. PIB, Pittsburgh Compound-B; AD, Alzheimer's disease; HC, healthy control.) (iii) (A) Brain activations for Chinese-English bilinguals (N=32) reading English real words, showing activity in the left inferior frontal areas, superior temporal gyrus, middle temporal gyrus and ventral occipito-temporal areas. (B) Brain activations for young healthy adults (N=25) performing hand gripping, activating bilateral motor cortex and cerebellum. (Courtesy of SH Annabel Chen, Clinical Brain Lab, Nanyang Technological University, Singapore.)

Neuroimaging can also provide information for subsequent more targeted neuropsychological investigations (e.g., along the lines of the ‘flexible battery’ approach advocated by Lezak et al., 2012). However, there is no ‘gold standard’ for analysing the complex signals obtained with MRI scanning over time as (1) most neuroimaging techniques require complex protocols, which can be costly, labour-intensive and time-intensive to be administered prior to routine cognitive examinations, (2) the availability of neuroimaging facilities may serve as a barrier and (3) training is needed for clinical neuropsychologists to undertake neuroimaging investigations. This will require incorporation of a whole new set of skills and technical knowledge into neuropsychology curricula, including physics and signal processing to understand the nature of the tools and data, as well as neurobiology and reading of radiological scans as part of the holistic approach to neuropsychological evaluation. Such training is currently provided in radiology and neurology academic programmes, as well as in some clinical neuropsychology academic programmes and postdoctoral residency in the United States

(Benitez et al., 2014; Bobholz et al., 2007). Likewise, training in administration of neuroimaging is also part of specialized clinical neuropsychology programmes in Europe (e.g., EFPA, 2018).

Another consideration in the conjoint application of clinical neuroimaging and clinical neuropsychological examinations is the use of normative data. Clinical neurocognitive tests are normed on specific neuropathology patient groups, together with the provision of normal comparison group norms (including provision of cut-off points on neuropsychological tests – such as the Halstead Category Test – see Boyle, 1988) to enable the correct interpretation of a neurological patient's test scores. This is an important component of neuropsychological research and practice, but is seemingly absent from neuroimaging, especially functional neuroimaging, in which individual scores are seldom extracted and analysed in terms of population-based normative data, partly due to their high volatility and dependence upon external factors. This is also the case for structural neuroimaging. Atrophy measures and Fazekas scores are always absolute in nature, not related to a reference of healthy individuals (in which atrophy and white matter lesions also occur; see Fazekas et al., 1987). Indeed, structural neuroimaging studies have suggested the possibility of extracting relevant and stable indices predictive of behavioural outcomes. For instance, in one study a composite index of white matter integrity (e.g., fractional anisotropy) correlated positively with processing speed (Penke et al., 2010). Despite these group-level findings, the absence of adequate normative or reference data and established indices arguably puts neuroimaging somewhat at odds with the typical normative reference group approach adopted in clinical neuropsychological assessment.

At the same time, we should not assume that the ‘neuropsychological way’ is the ‘gold standard’ to which all other diagnostic disciplines should aspire. For example, reliance on semi-arbitrary thresholds points (cut-off values), score transformations and interpretive guidelines that may be loaded with unverified statistical assumptions such as normally distributed scores, are among the weak points of current neuropsychological assessment practices (Bilder and Reise, 2019). Perhaps it is unfair to require clinical neuroimaging to develop norms and standardized metrics, since a well-validated machine-learning algorithm may be accurate, and provide important diagnostic information. This is one aspect in which neuroimaging (especially fMRI) potentially could excel – for example, by allowing for the compilation, curation, centralization and making open and accessible large datasets (e.g., see *OpenNeuro: A free and open platform for sharing MRI, MEG, EEG, iEEG, ECoG, ASL, and PET data*. www.openneuro.org, retrieved 17 September 2021).

Although fully automated diagnostic methods hold considerable promise for some medical fields (Aggarwal et al., 2021), fully computerized neuropsychological assessments cannot provide 100 percent of the detailed

and highly nuanced information currently detectable through clinical assessment (Gorgolewski et al., 2016; Miller and Barr, 2017; Poldrack et al., 2017). Clinical neuropsychological evaluation can provide information regarding the pattern of neurocognitive and behavioural deficits and their severity profiles (Tanner-Eggen et al., 2015), standardizing the semantics used to describe these profiles (Gallagher and Zahavi, 2020; Larsen and Hastings, 2020), as well as developing case conceptualizations to further inform prognosis and intervention strategies (Harvey, 2012). Both neuroimaging and neuropsychological testing have limitations, and a trained clinician is needed to put the data that they provide in context. As an important technological advance though, neuroimaging has been presented as superior to clinical neuropsychological assessment in describing lesion characteristics. Clearly, clinical neuroimaging is fundamentally different from clinical neuropsychology, and as a result, there are hurdles in the way towards a tighter integration of the two vastly different diagnostic approaches (see Figure 4.5).

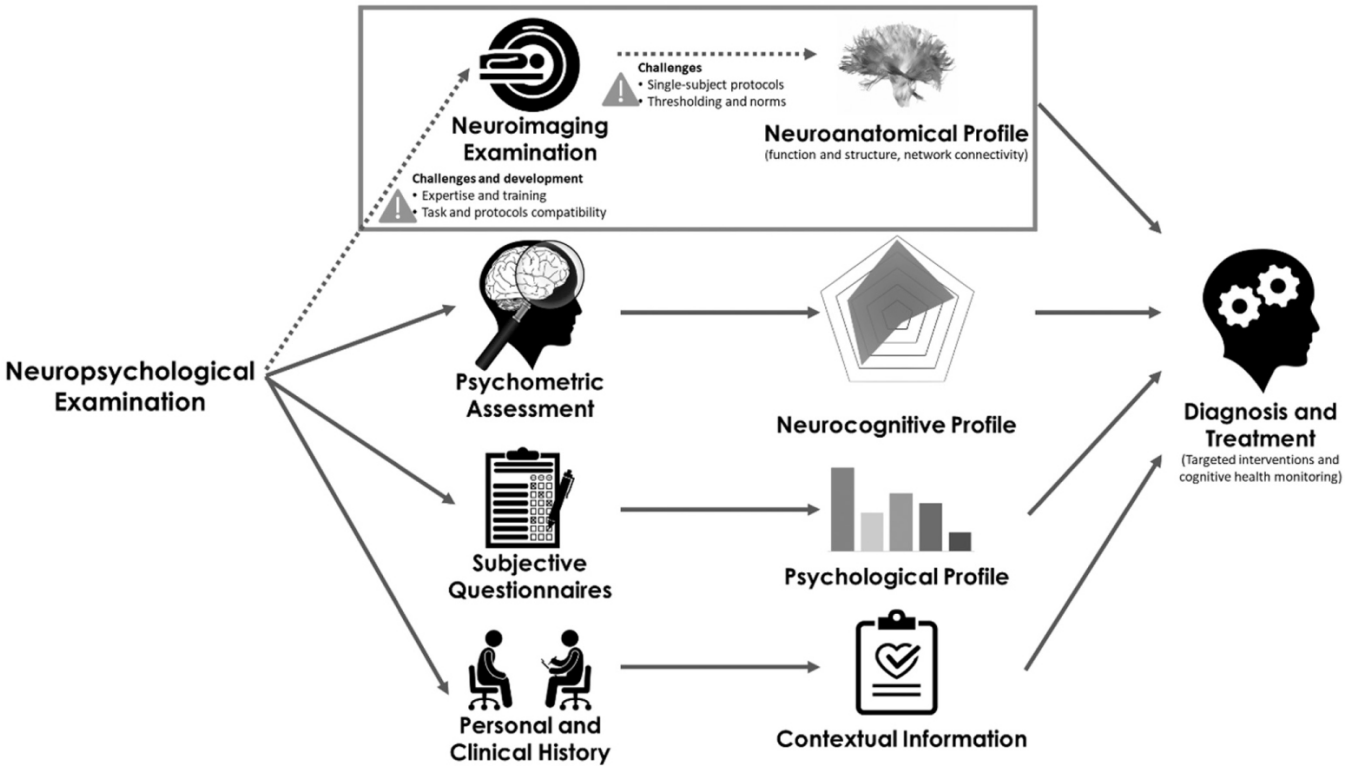

Figure 4.5 A schematic representation of the limitations pertaining to the usage of neuroimaging as an additional tool and source of information for neuropsychologists. These sets of different techniques aim at providing different information about how the brain works to help establishing diagnosis and treatment plan. However, the integration between neuropsychology (and its practitioners) and neuroimaging tools, as well as the generation

of a solid and reliable neuroanatomical profile for single subjects, brings about further limitations

Summary and Conclusions

Over recent years, there has been a shift by many clinical neuropsychologists away from their initial diagnostic and psychometric assessment mission, towards clinical neuropsychological rehabilitation (Hom and Nici, 2015; Ruff, 2003; Russell, 2012). This change of focus among many neuropsychologists may reflect the role of neuroimaging as a powerful diagnostic tool. Also, some concerns have been raised about the ecological validity of neuropsychological indices (such as test completion time). Performing specific tasks, intended to measure an isolated cognitive process (e.g., response inhibition or working memory updating), may not adequately reflect an individual's everyday idiosyncratic life circumstances (Chaytor and Schmitter-Edgecombe, 2003).

To address this shortcoming, researchers have developed ecologically valid forms of assessment using real-life stimuli, such as naturalistic kitchens (Robertson and Schmitter-Edgecombe, 2017; see also Ch. 3,Volume 2). Although some attempts have successfully combined virtual reality (VR) with fMRI (Campbell et al., 2009), most of these integrations employ a limited version of VR, usually in the form of a first-person experience displayed on a screen that lacks the immersion, interactivity, embodiment and reality of fully immersive VR set-ups (cf. Parsons, 2015, 2016; Plancher et al., 2008; Rizzo et al., 2004; Schultheis et al., 2002). However, there are promising emerging research developments, such as an augmented-reality fNIRS-based brain-computer interface (Benitez-Andonegui et al., 2020), a mobile EEG (Park et al., 2018), as well as the new generation of portable MRIs designed for brain imaging (e.g., Hyperfine; see hyperfine.io/, retrieved 16 September 2021).

The rapid development of technology aimed at elucidating brain functions *in vivo* with non-invasive neuroimaging places clinical neuropsychology within an exciting era. With careful considerations and appreciation of the above-mentioned limitations, the conjoint administration of clinical neuroimaging and clinical neuropsychological evaluations continues to be an enticing and beneficial prospect for the future. Clinical neuropsychologists, having extensive training and knowledge in brain and behaviour relationships, are uniquely placed to advance the integration, interpretation and practical usage of neurocognitive data together with neuroimag-

ing findings in clinical practice.

Notes

1 In memory of …

This chapter is dedicated to Scott O. Lilienfeld, a colleague with a ‘big heart’ and wisdom who facilitated the advancement of clinical psychological science. He was a Professor of Psychology at Emory University and also an Honorary Professor at the University of Melbourne. He will be fondly remembered. Deceased 30 September 2020.

2 Testing the limits allows the participant to proceed beyond time limits or other standardized requirements, to evaluate if the item can be completed or better performed under alternate conditions.

3 For a detailed discussion of the merits of fixed vs flexible neuropsychological batteries, see Russell et al. (2005).

4 Note that the term ‘image’ of ‘neuroimaging’ has sometimes been misunderstood as referring to actual images, in the sense of pictures, therefore excluding from its category techniques like EEG or MEG, for which one of the representations commonly takes the form of time series. There are many other types of visual representations of electrophysiological data akin to ‘pictures’ (including topographic maps). More importantly, the word ‘image’ has to be understood in its conceptual sense as referring to any *representation* of the object of interest.

5 More broadly, psychometricians refer to this problem as *method–mode mismatch*: certain techniques, although useful for certain assessment purposes, may be intrinsically poorly suited for other assessments or applications (Haynes et al., 1995).

6 CPT codes are used to report medical, surgical, and diagnostic procedures and services for medical billing of procedures in the United States. The 3 CPT codes for fMRI procedures are:

70554 fMRI brain by technologist: Includes test selection and administration of repetitive body part movement and/or visual stimulation, not requiring physician or psychologist administration.

70555 fMRI brain by physician/*psychologist*: Requires physician or *psychologist* administration of entire neu-

rofunctional testing.

96020 functional brain mapping (must be used with 70555): Neurofunctional testing selection and administration during non-invasive imaging functional brain mapping, with test administered entirely by a physician or *psychologist*, with review of test results and report.

7 In Australia during the early 1970s, the fourth author (GJB), whom at that time was an honours student at the University of Melbourne working under the supervision of pioneering Australian neuropsychologist Dr Kevin Walsh, undertook a 12-month research project – as part of a comprehensive medical team also comprising neurologists, radiologists and neurosurgeons – that involved the administration of an extended version of the HRNB battery to brain-injured patients before and after neurosurgery (including several temporal lobectomies for recalcitrant epileptic seizures) at the Austin Hospital, Melbourne (e.g., see Boyle, 1975, 1986; Darby and Walsh, 2005; Walsh, 1987, 1991).

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- neuroimaging
- clinical neuropsychology
- brain
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