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Commonalities and discrepancies in the relationships between behavioural outcome and the results of neuroimaging in brain-damaged patients

Hans J. Markowitsch[1] and Pasquale Calabrese[1,2]

[1]Physiological Psychology, University of Bielefeld, Bielefeld, and [2]Neurological University Hospital (Knappschaftskrankenhaus), Ruhr-University, Bochum, Germany

Correspondence to: H.J. Markowitsch, Physiological Psychology, University of Bielefeld, PO Box 100131, D-33501 Bielefeld, Germany

Variables which are of influence in establishing clear predictions of neuropsychological alterations from neuroradiological data (and *vice versa*) are documented and discussed. It is concluded that personality factors and the kind and locus of brain lesions are the most crucial determinants. The locus of the brain damage may have cumulative effects either when it is situated in a strategic place (usually within the white matter, affecting interneuronal communication) or when various types of lesions appear superimposed (combination of focal and diffuse lesions). Consequently, the consideration of the patient's personality background and of as many neuropsychological facts as possible may considerably increase the validity of outcome predictions. When static or dynamic neuroimaging fails to show abnormalities in spite of obvious psychological alterations, an intensive neuropsychological documentation may even replace neuroradiology.

Keywords: Brain damage – Magnetic resonance imaging – Computer tomography – Neuropsychological assessment

INTRODUCTION

The availability of cranial computer tomography (CT) has revolutionized the diagnostic power for patients with brain damage, and the subsequent appearance of magnetic resonance imaging (MRI), positron emission tomography (PET) and functional magnetic resonance imaging has further increased and refined the power of relating brain tissue changes to behavioural alterations. Nevertheless, there are numerous case reports in which neuroimaging and neuropsychological data indicate a different prognosis, thereby leading to an improper rehabilitation treatment of the patient.

Part of the discrepancy may be explained by the false assumption of linear relationships between lesion size and behavioural outcome (e.g. Irle, 1987, 1990; Grafman *et al.*, 1986), but other parts are most likely due to insensitive measurement on the imaging or the psychological level. Alesch *et al.* (1991), for instance, found that CT is quite insensitive to the identification of lymphomas although gliomas are readily detected. Similarly, although subdural empyemas and most sterile effusions and chronic subdural haematomas appear similar in CT scans, they are much more readily distinguishable on the basis of signal intensity differences in MRI (Takamura *et al.*, 1995); and Kertesz *et al.* (1987) concluded from their analyses that MRI surpasses CT scanning in the early detection of cerebral infarcts. CT on the other hand should be the method of choice to rule out intracerebral bleeding when a patient is screened initially. For detecting anatomical correlates of abnormal behavioural functioning, such as in psychogenic amnesia, conventional static imaging techniques have been useless up to now, although dynamic methods, such as PET imaging, may reveal cerebral blood flow changes indicative of abnormal processing (Amsterdam and Mozley, 1992; Markus *et al.*, 1992).

Congruence and incongruence of neuropsychology and neuroradiology are the topics of this commentary. We will first illustrate various mismatches between morphological findings as documented with static brain imaging techniques and neuropsychological results in the same individuals. Secondly, we will concentrate on possible sources of this evident discrepancy by taking into consideration behavioural and genetic variables as potential factors of variability.

Then we will focus on functional–anatomical factors which are to be considered in the interpretation of structure–function relationships. This will be done cursorily as there is a large amount of literature covering this field in general and in detail (von Cramon, 1990; Markowitsch, 1988; Meier *et al.*, 1987; Schneider, 1979). Finally, in a third concluding section we try to illustrate how all the aforementioned variables may influence each other.

ESTIMATION OF BRAIN LESIONS BY CT AND MRI – EXAMPLES OF (PARTIAL OR POSSIBLE) MISMATCH BETWEEN NEUROIMAGING AND NEUROPSYCHOLOGICAL ASSESSMENT

Present-day neuroimaging provides a picture of the brain at a high degree of resolution and consequently leads to the implication that we see 'a lesion', though at best we actually only see a difference in density (CT), signal intensity (MRI), or nuclide binding capacity (in single photon emission tomography [SPECT] and PET) from which we infer the likely existence of a lesion.

Although for a number of practical reasons application of CT has proven its usefulness — especially in the detection of haematomas and blood clots after acute head trauma — this technique turned out to be rather insensitive in the identification of parenchymal damage and also in the estimation of lesion extent (Snow *et al.*, 1986). This point was illustrated by Snoek *et al.* (1979) who found a normal CT scan in 38% of their cases with severe head trauma (without haematoma). In the same study even 26% of the non-survivors had CT scans without signs of abnormality. In another study comparing the sensitivity of CT and MRI to structural damage in head trauma patients, Jenkins *et al.* (1986) observed CT-based changes in only half of their cases, though MRI scanning resulted in structural abnormalities for 92% of them. Such a gap between techniques in the sensitivity for non-haemorrhagic lesions was confirmed repeatedly (e.g. Gentry *et al.*, 1988; Shores *et al.*, 1990). The reversed condition was recently demonstrated by Lopez *et al.* (1995); CT results were more specific than MRI in predicting subsequent symptomatic cerebrovascular disease.

Studies in which only dynamic brain imaging revealed the likely extent of affected brain tissue increase progressively. Pappata *et al.* (1994) showed the likely existence of additional microscopic white matter lesions and/or neocortical neuronal loss in a case with Marchiafava–Bignami disease, Masdeu *et al.* (1994) demonstrated that SPECT can show the consequences of mild head trauma on the brain where CT and MRI cannot, and Lucchelli *et al.* (1994) described an amnesic patient in whom MRI failed to show brain damage while PET showed a hypometabolism of the left medial temporal cortex and the thalamus.

In fact, if we had *in vivo* techniques corresponding to those available today in neurohistology, we would have nearly ideal possibilities for relating (or predicting) anatomico–functional relations. Histology, including light and electron microscopy, would reveal tissue alterations which are presently not detectable by the outcome from brain imaging equipment. For example, most conditions of hypoxic brain damage remain undetected on the basis of CT or MRI, as we cannot precisely determine the status of all brain tissue. In some situations, we approach adequacy of the conditions, but for others the available technology is still inadequate. Koudstaal *et al.* (1991), for instance, made a survey of CTs of a large number of patients who had transient ischaemic infarcts with or without a 'real' infarct; as CT scans were normal for the majority of the patients, it was impossible to predict the likelihood of an infarction on the basis of the nature or time course of the symptoms.

Another example demonstrates the situation where a prediction from the behavioural (neuropsychological) level is not supported by the neuroradiological outcome. Strub (1989; p. 1024) described the case of a patient whose behavioural changes were "characterized by apathy and lack of motivation, features commonly associated with bilateral frontal lobe disease". MRI instead revealed bilateral globus pallidus lesions and therefore a kind of brain damage which would normally be related to motor disturbances instead of motivational ones.

Another instance in which CT as well as MRI scans do not necessarily show pathological signs — although such patients may present with striking neuropsychological alterations and focal neurological disturbances — is the non-herpetic type of viral encephalitis. We recently studied the case of a 24-year-old patient who during a study visit to the USA presented with sudden drowsiness and developed generalized epileptic seizures. While herpes screening was negative, St Louis virus was suspected. This patient had a complete loss of retrograde memory for the two months prior to hospitalization. Her whole trip to the USA could only be fragmentarily reconstructed on the basis of photographs she had taken during her travelling. Her language functions were normal, but learning and memory abilities, even after a two-year follow-up, were still grossly impaired. In this patient even the combined application of MRI and

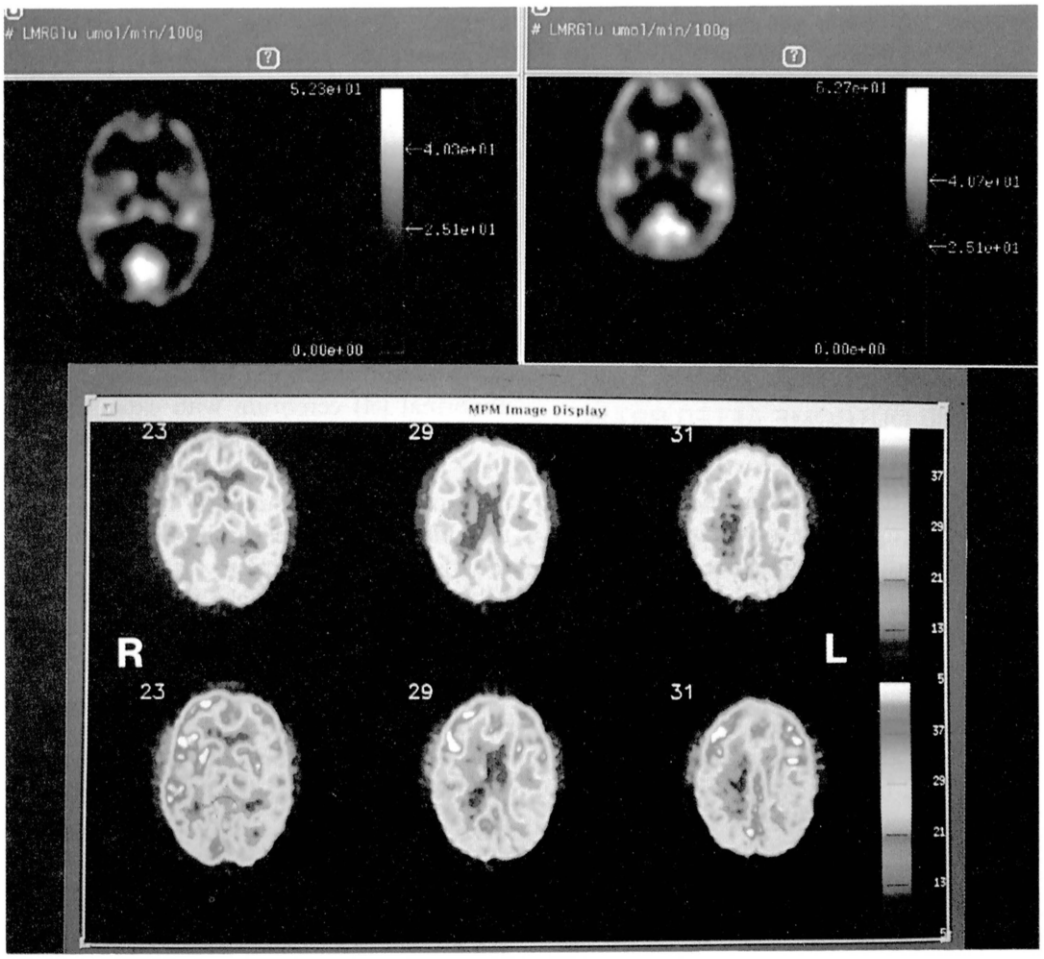

FIG. 1. PET scans of the brains of two patients with intelligence in the upper normal range. TOP: Both the left and right picture show normal cerebral glucose metabolism in a patient with no visible brain damage, but severe and long-lasting cognitive impairments. BOTTOM: PET images of glucose metabolism in a patient with left-hemispheric neuronal heterotopia. The upper row demonstrates the brain's metabolism under resting conditions and the lower row during activation. Increased glucose metabolism during activation (word generation) is seen both within areas of the normal cortex and within areas of the heterotopias. This patient (a medical student) had subtle neuropsychological deficits, and initially had been diagnosed as neurologically inconspicuous (see description in Calabrese *et al.*, 1994).

PET failed to reveal any topical or functional abnormality (Fig. 1 top). Again, the neuropsychological pattern, which had devastating psychosocial consequences in the long term, was not reflected in any of the imaging techniques applied.

However, for many of the more complicated situations the addition of methods allowing metabolic analyses (SPECT, PET) will increase diagnostic firmness from the anatomical side. And we still should not forget that modern electrophysiological techniques (brain mapping, evoked potentials) further add to the validity of brain damage related inferences. As the application of PET and SPECT for clinical usage is presently rather limited, we will concentrate in the following on the much more frequently used CT- and MR-based imaging techniques. Here, it is necessary first to detect generally the regions involved and then to use our knowledge of tissue conditions as a background for determining the affected zones with greater precision.

Though presently neuropsychological knowledge includes a huge range of background material on relations between brain damage and behavioural alteration, we still need to bear in mind that even after 'seeing' a lesion there is no immediate implication for the subject's behaviour. There are a number of factors which influence the behavioural outcome of brain damage, with the most frequently cited variables of

influence being the aetiology, size and locus of the lesion, and the age, education, intelligence, motivation and constitution of the patient.

Furthermore, we now have internalized what was previously formulated at various points of time, namely that we are only able to describe (or localize) deficits, but not functions (Goldstein, 1939) and that it is not possible to make direct inferences from the malfunctioning of a damaged brain to the (well-)functioning of an intact one (Chow, 1967).

BEHAVIOURAL AND GENETIC VARIABLES INFLUENCING THE OUTCOME AFTER BRAIN DAMAGE

As there is no point-to-point assignment between function and morphology, it is obvious that there will be a high inter-individual variance in outcome and prognosis between brain damaged patients with respect to their performance pattern along various personality and intellectual domains. Even if the damaged portions of the brain look similar, we cannot be sure that their functions are always equivalent. Our current methodology allows predictions only with respect to core defects, but not when the anatomical damage is incomplete (e.g. unilateral or affecting a cortical area or a nucleus only in part) or diffuse. Age, the pre-morbid intellectual status, gender, handedness, and cerebral dominance are the most direct factors, influencing the prognosis after brain damage.

Age

Age has been regarded as one of the major individual differences influencing prognosis (Teasdale *et al.*, 1979). There are some age-associated microanatomical and neurochemical changes which on the one hand limit self-restorative capacity after brain damage, while on the other hand the same age-dependent intrinsic alterations may make the organism more vulnerable to some external viral, toxic or other environmental agents (Bondareff, 1985).

We wish to mention here that the Kennard principle, stating that a brain lesion at an earlier age will lead to less behavioural deficits than a similar lesion in later life (Kennard, 1942), has been increasingly questioned (Corkin *et al.*, 1989; Isaacson, 1975; Schneider, 1979), and that consequently age-related changes and prognoses vary depending on a number of intervening variables (but see the work of Zuccarello *et al.*, 1985, who reviewed studies in which the Kennard principle was found to hold for brain-damaged children).

Abnormal pre-natal brain development is another example demonstrating substantial inter-individual variation. The cerebral organization on a functional level may vary substantially among such individuals. We recently described a 21-year-old female student referred to us for evaluation of epileptic seizures without family history (Calabrese *et al.*, 1994). She had a delayed language development until age five. Retrospectively, at the time of school admission speech testing revealed normal language functions; otherwise her general cognitive development seemed normal. Although the neurological examination indicated normal functions, MRI scans revealed a grossly abnormal left cerebrum with extensive heterotopias in the left temporo-parietal and frontal regions; the right cerebrum appeared normal. The actual neuropsychological examination indicated slight deficits not only in verbal learning and memory, but also in the visuo-spatial domain. Application of a dichotic listening test resulted in a strong left-ear advantage. In a subsequent PET study we could demonstrate both under resting and verbal activation that the functionally active Wernicke and Broca areas of this particular patient were situated in the right hemisphere (Fig. 1 bottom). This is another example demonstrating that a synoptic application of several brain imaging techniques together with comprehensive neuropsychological testing may reveal individual differences in information processing.

Education, gender and cerebral dominance

Similar to the above-given argument on psychosocial factors, the post-lesion outcome profits from a high pre-morbid intelligence and education (Aarabi, 1990; Grafman *et al.*, 1986). Even sex has been found to be of influence, as gender differences have been established for a number of perceptual and cognitive functions (Alesch *et al.*, 1991; Allen *et al.*, 1991; von Cramon, 1990; Kimura, 1987; Le Vay, 1991). This robust interaction between gender and specific abilities is reflected by a different brain, and in particular, cortical organization (McGlone, 1980). One of the most prominent theoretical accounts of lateralization differences was given in Buffery and Gray's (1972) female lateralization theory, which states that for males there is a higher degree of lateralization for speech function. Consequently, although structural damage appears equivalent on merely topographical and volumetrical grounds this gender-specific organization difference may explain differences in recovery dynamics and in language performance after brain injury.

Other personality factors

There are a number of other personality factors, such as extraversion/introversion, mood states and genetic

variants (Markowitsch, 1988) and demographic variables (Meier *et al.*, 1987) which are all of influence in determining the prognosis after brain damage. Personality factors may be of special influence in cases with progressive degenerative diseases (Alzheimer's, Parkinson's disease) as there is frequently an interaction between intellectual decline, altered mood, changed biorhythms and even psychotic states. Demographic variables may interact with other factors determining outcome after brain damage. High educational and socio-economic levels may favour a good prognosis after brain damage, even when the patient is already old. Taken together, the person as a whole constitutes a major factor in determining the outcome after neuronal injury and may outweigh many other factors, naively thought to be most crucial.

ANATOMICAL VARIABLES INFLUENCING THE PSYCHOLOGICAL OUTCOME

Current views on functional localization (or better on the ability to correlate brain structures or regions with behavioural manifestations) usually favour a moderate position emphasizing that specific sensory and motor functions are usually more strictly 'localizable' than complex behavioural acts such as thinking. However, we have learnt from PET activation studies that even these basic functions are prone to a high inter-individual variability and plasticity with respect to their cortical representation (e.g. Schlaug *et al.*, 1994). But even accepting an intermediate position, variables such as the lesioned volume, the lesioned locus, together with dynamic factors and consequences, such as metabolic changes and the origin of the lesion (e.g. closed head injury versus glioma), will influence and determine the prognosis of the individual.

We all know of the major hypotheses used to 'explain' the dynamic neuronal and behavioural changes after brain injury (von Cramon, 1990; Feeney and Baron, 1986; Kaas, 1991; Markowitsch *et al.*, 1985; Meyer, 1973; Rothi and Horner, 1983). Of these, spontaneous recovery of cognitive functions is very limited, both qualitatively and in time. Therapeutic interventions may accelerate the processes of reorganization or partial restitution, reduce the action of diaschisis, and may oppose the development of improper or non-economic behavioural strategies (von Cramon, 1990). Brodal (1973) gave a self-report on the dynamic consequences of a stroke on behaviour and by doing so provided a vivid example of the immediate and the long-term consequences of brain damage. His contribution suggests that focal damage may have remote effects as well (see also Szelies *et al.*, 1991).

Severe closed head injury

A particularly difficult example for revealing brain damage by neuroradiological examination is severe closed head injury. CT results without signs of abnormalities may lead to wrong conclusions (Snoek *et al.*, 1979; Snow *et al.*, 1986). For severe kinds of closed head injury with prolonged unconsciousness, a normal CT scan (in the absence of any mass lesion) may be regarded as an indicator of diffuse axonal injury (Gennarelli *et al.*, 1982). Thus, in spite of CT pictures without signs of abnormalities, there may be numerous disturbances in the long-term, for example in the fields of attention, learning and memory, problem solving and thinking, which argue for definite brain damage (e.g. Van Zomeren and Van den Burg, 1985). Furthermore, to make valid inferences on neurobehavioural consequences of severe closed head injury, possible corollary pathophysiological consequences (or secondary brain damage) have to be considered as well. Richardson (1990) mentioned as likely possibilities intracranial haematoma, brain swelling, raised intracranial pressure, ischaemic brain damage, infection and post-traumatic epilepsy.

Minor head injuries

For patients with minor closed head injuries and CT results without signs of abnormalities, there are often also no obvious focal neurological signs, though there is growing evidence that such individuals have a poor neuropsychological outcome (Rimel *et al.*, 1981), even long-term (Barth *et al.*, 1983). This assumption is further corroborated by Levin *et al.* (1987) who demonstrated in 85% of their patients who had MRI scans 44 additional intracranial lesions than previously found in CT scans. Thus, MRI may give substantial evidence for existing structural damage in subjects with minor or moderate head injury. As already mentioned, dynamic imaging may be superior to static in detecting possible functional abnormalities. This is clearly exemplified in a study of Ruff *et al.* (1994) who examined nine patients suffering minor traumatic brain injury with little or no evidence of CT- or MRI-proven brain damage, but with deficient neuropsychological performance. PET examination on the other hand confirmed for all nine patients the neuropsychological evidence.

Diffuse brain damage

Many cases with hypoxic brain damage (e.g. after heart attack) or some forms of encephalitis fail to result in detectable brain damage, though the patients are multiply deficient in everyday life (von Cramon, 1990; Parkin *et al.*, 1987; Volpe *et al.*, 1986; Volpe and Petito, 1985).

PET measures of glucose metabolism may reveal a number of divergent and individual variants of brain damage in patients with anoxic symptoms (De Volder *et al.*, 1990). PET outcome may be indicative of diffuse disseminating brain diseases such as the beginning of a primary degenerative disease (Alzheimer's disease) or in cases with so-called pseudodementia. Alternatively, there may be focal (monotopic or polytopic) brain damage which is ascertainable more readily. If, for instance, due to chronic arterial hypertension, numerous vascular microlesions (due to hypertensive 'microangiopathy') accompany the focal brain damage, then the principal syndrome or symptomatology may be blurred by accompanying basic disturbances such as cognitive slowness, and reduced abilities to attend and concentrate. In rare cases, the focal damage may lead to a full-blown pattern of neuropsychological abnormalities which before had been successfully compensated for (e.g. in cases with a combination of numerous lacunar infarcts together with ischaemic demyelinating white matter lesions, as in subcortical arteriosclerotic encephalopathy). Consequently, special attention has to be given to possible cumulative effects, manifesting after a lesion that is at first glance considered to be monotopic.

Aetiology

The aetiology of damage to the brain may be of considerable importance for a proper evaluation of immediate and delayed behavioural consequences. The most clear-cut distinction is between a sudden change (infarct, trauma) and a slow, but progressive change (degenerative diseases, sometimes tumours). Such patients may have developed a number of mechanisms of functional compensation so that their growing brain damage may be undetected for long time periods.

Time

Time *per se* may be of crucial importance not only with respect to the above given aetiological distinction, but also in general with respect to changes in behaviour and brain (Tamura *et al.*, 1991). Spontaneous recovery is one of the most cited terms used to explain changes occurring within the first months after brain damage. Generally, "the degree of initial deficit is a significant determinant of the subsequent amount of recovery and the residual deficits" (Dikmen *et al.*, 1983; p. 333).

Post-traumatic amnesia

The duration of post-traumatic amnesia (PTA) is regarded as an important variable in the determination of severity in closed head injury. A combination of PTA with coma scales has found widespread application in clinical practice (Van Zomeren and Van den Burg, 1985).

Lesion locus and extent

That lesion size *per se* is not the only determinant of the extent and degree of functional derangements, is obvious when considering some small target areas. Damage to the retinae may be quite small in size, but leads to an inability to use the many regions of the human brain implicated in visual analysis. Similarly, damage to small portions within the brain stem may result in a permanent comatose state. And even in the cerebrum, small strategic white matter lesions may have devastating consequences on intellectual functions (see, e.g. Massaro *et al.*, 1991).

Meta-analyses of brain damage and behavioural alterations lead to complex and unpredictable interdependencies as was shown by Irle (1987, 1990) for human and non-human data. And the analysis by Grafman *et al.* (1986) of possible relationships between brain tissue volume loss, lesioned locus and cognitive defects led them to conclude that volume was only of importance when a crude, global cognitive measure was used but not when a specific process was measured. The lesioned locus was only then of predictive value when the cognitive process was circumscribed and specific (e.g. face recognition).

Activation, mood, emotional conditions and brain state

Activation, mood, emotional conditions and brain state can interact in an unpredictable way (Allman, 1991; Auerbach, 1986; Peper *et al.*, 1991; Starkstein *et al.*, 1990). Depressive conditions may blur the performance level of a brain-damaged patient to a considerable degree (Allman, 1991; Starkstein *et al.*, 1990). Furthermore, hormone and neurotransmitter levels as well as nutritional habits certainly influence outcome after brain damage as they are already of considerable importance in subjects without brain damage (Benton *et al.*, 1994; Buchanan *et al.*, 1992).

FACTORIAL INTERACTION AS AN EXPLANATION FOR MISMATCHES

In the foregoing sections we mentioned several factors which *per se* may lead to inconsistencies between brain status as inferred by imaging techniques and behaviour as operationalized via neuropsychological tests. An interaction of the aforementioned variables is obvious. The following part illustrates in which way these interdigitated factors should be treated to

Table I. Possible relationships between neuropsychological and neuroimaging outcomes

Image status	Positive neuropsychology	Negative neuropsychology
Positive	Highest diagnostic concordance	Magnitude of psychological effect too small Inadequate psychological tools adopted Effective compensatory mechanisms on the behavioural or neural side Ceiling-effect in psychological test outcome Neuroradiological artifacts
Negative	Resolution problem Inadequate imaging method Time parameters of scanning Malingering by patient Floor effect in psychological test outcome Transient effects such as in transient psychogenic amnesia, psychogenic amnesia, transient ischaemic attack	'Null hypothesis'

minimize or at least to explain diagnostic inconsistencies. Table I summarizes possible sources of potential mismatch factors which should be considered in order to strengthen an interdisciplinary (e.g. psychological and radiological) diagnosis. Only those cases will be considered where either imaging or behavioural analyses are incongruent.

When neuropsychology fails to confirm structural damage

The positive assumption. Although in most cases where structural brain damage is evident from neuroimaging there are also overt behavioural deficits present, in some cases this relationship does not hold. We will first assume the structural lesion to have neuropsychological consequences. In this case one source of inconsistency may be explained by the fact that a given psychological effect is too small in magnitude to be detected by a given test. This is a source of mismatch which has to be dealt with by adjusting the neuropsychological tools according to the kind of investigation. This should be best done by using valid, reliable and standardized tests with suitable norms, avoiding ceiling effects (see Mayes and Warburg, 1992 for these criteria in the memory test domain). Another important factor to be considered is the motivational disposition of the subject under study. Especially when assessing neuropsychological deficits via questionnaires and checklists (visual inattention, memory, etc.) one should have in mind the problem of so-called under-reporting (Hickox and Sunderland, 1992), which beside self-monitoring deficits is also partly caused by lack of motivation. To make things more difficult, and to show how cause and effect are inter-twined in the study of brain–behaviour relationship, it is important to mention that motivational deficits *per se* are a common consequence of brain damage. Finally, we also have to question the adequancy of the neuropsychological tool adopted.

The negative assumption. If we now assume that the structural affection is indeed not accompanied by neurobehavioural deficits, this could be explained by a range of adaptational factors which may be effective in compensating for lost abilities after brain damage (i.e. neural plasticity, substitutional functions, etc.). Another potential factor to explain why morphological changes do not always result in neuropsychological deficiencies may be sought in the time course of the acquired lesion (see above; e.g. tumor versus trauma). Thus, a non-conspicuous neuropsychological test result may be due to a 'serial-lesion-effect' which — provided the single lesions are separated long enough in 'time and space' — would leave enough time for synaptical and cellular reorganization processes to operate (Stein, 1987). Mismatch data from multiple sclerosis patients could be explained by this mechanism. The serial-lesion argument is also suited to highlight the role of so-called 'nodal-points' of cognitive information processing (Markowitsch, 1988). This is exemplified by a follow-up study on a patient who after his right-brain infarction of the anterior thalamus had no detectable neuropsychological anomalies, although two years later he suffered from persistent anterograde amnesia after a further, left anterior-thalamic, infarction (Calabrese, 1996). This case should illustrate that there will be relatively little compensatory power when some anatomical structures, thought to be relevant in information processing, are bilaterally destroyed. Again, the picture is far more complicated by the fact that both mechanisms (neuronal reorganization after serial lesions and sudden breakdown of a function due to affection of nodal points) may take place in the same individual.

This example can be used to point to problems in matching structure and function more generally. It is a frequently described fact that one and the same kind of measurable brain damage may or may not lead to functional impairments of a given kind, thereby questioning the possibility of structure–function relationships (Markowitsch, 1984). This puzzle can, however usually be solved when all major factors, determining structure–function bonds, are taken into account (von Cramon and Markowitsch, 1992; Markowitsch, 1988). Such factors have been mentioned above (e.g. age, education, gender, emotional and motivational status of the individual, type, kind, locus and aetiology of brain damage); additional examples are uni- versus bi-laterality of brain damage, bilateral symmetry and completeness of a damaged area, nucleus, or nuclear or areal configuration, involvement of white matter, strategic place of the damage (e.g. possibility of resulting in a disconnection syndrome). A complete consideration of these factors will, at least in theory, allow a precise determination of structure–function relationships.

When neuropsychological findings are not mirrored by results from neuroimaging

If we now look from the neuropsychological perspective — provided the aforementioned caveats are considered in the adopted tests and questionnaires — then a negative neuroimaging result despite detectable cognitive-behavioural deficits may also stem from different methodological flaws in neuropsychology and neuroimaging. In some cases the underlying pathological process may be undetected either because it is not yet demarcated, or simply due to resolutional restrictions of the adopted scanner. Sensitivity to partial volume effects has also to be taken into consideration. This point was exemplified by a study of Pfefferbaum *et al.* (1993) in which the authors found that the increase in cerebrospinal fluid volume was greater in older than in younger alcoholic patients. Although CT and MRI produced similar absolute ventricular volumes, the MRI estimates for sulcal volumes were larger. Another argument refers to the adequacy of the angulation method. There may be problems in imaging brain regions close to particular bone configurations (e.g. basal frontal lobes), or a scanner may have a limited window so that some (horizontal) portions of the brain are not scanned. This point is of special importance in the longitudinal evaluation of static images where the variability of a morphological structure may depend on differences in the orientation of the scanning axis (Rauch and Jenkins, 1996). Although such mismatches may be equalized in group studies, they clearly limit the reproducibility of single-case measurements.

Of interest in this respect are also patients after anoxic or hypoxic states who may, depending on the duration of the hypoxia, show various degrees of functional deficits, frequently in the absence of measurable brain damage (Parkin *et al.*, 1987). Sometimes, there is an enormous recovery when these patients are treated in a proper sequence with several strategies. We employed behaviourally oriented psychotherapeutic methods in parallel to cognitive training procedures in a patient after cardiac decompensation; this combined treatment, given over one and a half years, resulted in nearly complete recovery from an initially shy, retreated, and strongly memory-impaired condition (Calabrese and Markowitsch, 1995). Though it is difficult to generalize from a particular case, this example demonstrates that a proper selection of compensatory strategies and consequent treatment may lead to unpredictable degrees of functional recovery.

Neuropsychological deficits which would suggest a definite hemisphere-specific involvement not supported by static-imaging techniques, may be corroborated by dynamic imaging methods (e.g. Baumgartner and Regard, 1993). This relationship has been observed in several PET studies in which bilateral cortical and subcortical metabolic depression was detected after unilateral subcortical lesions (Szelies *et al.*, 1991). Thus the mismatch would merely stem from an over interpretation of a partly inadequate or insufficient imaging technique.

On the neuropsychological side one should also keep in mind the problem of floor effects when using evaluation methods which lack reference scores for the subject under investigation. This problem is often encountered in the evaluation of memory in very young patients (Beardsworth and Bishop, 1994) or older adults (Clegg and Warrington, 1994) and may lead to the occurrence of false positives (this point is discussed extensively in Gathercole *et al.*, 1993). A positive neuropsychological finding in the absence of evidence of a corresponding neuronal substrate may indicate that the behavioural consequence is of psychogenic origin. The fluctuation and diffuseness of the condition and an affect-related symptomatology with predominant disturbances in the autobiographical domain all may speak for a psychogenic origin. Although for such cases a re-evaluation of both the neuropsychological and the brain status after an adequate period may resolve the diagnostic dilemma, it has to be pointed out that the underlying pathology may be haemodynamic or of metabolic origin and therefore may be studied better by dynamic imaging (e.g. Calabrese *et al.*, 1994).

Lastly, we have also to consider forensic aspects; an exaggerating defective neuropsychological status without any hints of structural damage should alert us to the possibility of malingering, especially if there are medico-legal litigations for compensation among several involved parties (Richardson, 1990). For cognitive functions there are a few tools which may be helpful in detecting impostors. Bernard *et al.* (1993a) used the Wechsler Memory Scale – revised to establish about an 80% accuracy in detecting malingerers. The malingering pattern was characterized principally by a poorer or better performance in four easy immediate recall tasks, and in addition a poorer or better performance in three delayed recall tasks. Additional testing with a visual and a verbal test increased the accuracy to 86 or 88% (Bernard *et al.*, 1993b). The use of priming tasks may also provide a valid help in detecting impostors (e.g. Brandt, 1992; Kopelman, 1995).

CONCLUSION

The examples given above have demonstrated that neuroimaging techniques may sometimes fail to uncover lesions, may sometimes lead to wrong inferential conclusions with respect to the kind, locus and extent of lesions, and do not allow a schematic generalization with respect to the patient's prognosis. While we wish to emphasize the importance of these facts for a proper treatment of the brain-damaged individual, we are far from devaluing conventional neuroimaging in general. This contribution should alert neurologists and neuropsychologists to pitfalls and weaknesses which are inherent in every specific and individual kind of brain damage and which have to be treated by proper neuropsychological analysis. Brain imaging techniques are of major importance for routine diagnosis of the brain, but they cannot replace clinical examinations ranging from interviews to neuropsychological tests.

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