Chapter 5
Alexia Theory and Therapies: A Heuristic

Some of what we know about the normal reading system, and much of what we know about impaired reading, comes from the studies of brain-injured patients carried out within the framework of *cognitive neuropsychology.* The reading models we described in Chap. 1 were to a large degree developed to explain the patterns of breakdown of the reading process that have been observed following brain damage, although they are models of the normal reading system. Debates about which model is the best have also in many instances referred to the model's ability to simulate or explain the different reading errors observed in the alexias [1–5]. In Chap. 1, we focused on the models, and in Chaps. 3 and 4, we have described much of the empirical observations that the models both build upon and aim to explain. Many of these observations are from single case studies, some of which have had an immense impact on models of reading. In this chapter we take a step back and look at the foundations of cognitive neuropsychology and how its assumptions and methods relate to the studies of reading that have generated much of what we know about pure alexia and the central alexias. We will also address questions that relate not only to the cognitive neuropsychology of reading but to cognitive neuropsychology in general, and touch on some methodological issues. The aim of this rather elaborate presentation is to enable the critical and clinical assessment of the knowledge provided by neuropsychological studies of reading, particularly the single case research. We will then go on to present some general considerations regarding treatment of alexia and address some important issues that should be carefully considered when aiming to design intervention studies.

Cognitive Neuropsychology: Why Patients May Tell Us Something About How We Read

Cognitive neuropsychology has its roots in the "behavioral" neurology of the nineteenth century, with the diagram makers Broca, Wernicke, and Lichtheim and of course Dejerine, Hinshelwood, and Exner who were particularly interested in reading and writing. The diagrams of that early era are not at all that different from more

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modern models from cognitive neuropsychology, and many of them were quite sophisticated. And yet for a long time, this area of research was fairly silent; much of the twentieth century passed by before the enterprise of cognitive neuropsychology started. This happened for good reasons (see Selnes [6] for an overview): it was only when the "cognitive revolution" ended the era of behaviorism, and made it scientifically acceptable to study mental information processing, that the scientific study of "what deficits reveal about the human mind" [7] again became possible.

The study of reading processes and reading disorders has been central in the development of cognitive neuropsychology. Many will hold that the birth of cognitive neuropsychology was with Marshall and Newcombe's 1966 [8] paper on reading errors in an aphasic patient, followed up some years later by their seminal paper "Patterns of Paralexia" [9] (presented at the International Neuropsychology meeting in 1971 and then published in 1973; see Chap. 1). Another milestone was a scientific meeting dedicated to one of the forms of alexia suggested by Marshall and Newcombe – *Deep dyslexia* – in 1978 and the edited book resulting from this conference [10]. This book was not only concerned with deep dyslexia, but also contained chapters on surface dyslexia and beginning reading [11], analogies between speed reading and deep dyslexia [12], and acquired dyslexia in Japanese [13]. Indeed, many of the included papers have had an immense effect on the cognitive neuropsychology of reading: One is Shallice and Warrington's paper [14] where they suggested the conceptual distinction between peripheral and central alexias, a distinction still widely used. Another is one of the most influential case studies ever published in cognitive neuropsychology, the study by Schwartz et al. [15], showing that there are "word-specific print-to-sound associations." This study of a single patient who could read irregular words aloud that she did not understand (i.e., had no semantic representation of) is still cited as the main reason for having a direct lexical route in the DR(C) model (although the same pattern of performance has been observed in a very few other patients [3, 16, 17], see Chap. 4).

Not very long after this, Max Coltheart suggested that syndrome labels for acquired reading disorders like surface and deep alexia were not very useful. This was related to the number of "syndromes" made possible, for instance, by the Dual Route model of reading. There were at that time at least 11 components (boxes and arrows) in the simple Dual Route model, which would allow for an enormous number of unique patterns of impairment if each component could be damaged individually. Coltheart concluded that the usefulness of alexic syndromes to cognitive models of reading "is likely to be short-lived" (Coltheart [18], p. 370).

In contrast to the partially clinical aims of this book in describing diagnoses and treatment, cognitive neuropsychologists have traditionally not been interested in brain injury or brain-injured subjects per se. Rather, the study of how cognition can be affected by brain injury is seen as a unique opportunity to study the *functional architecture* of the normal cognitive system. This functional architecture is commonly visualized as a box-and-arrow model of the normal information processing system, specifying its modules or components and the flow of information between these modules. Thus, cognitive neuropsychology is traditionally considered a branch of cognitive psychology, rather than neuropsychology, where the focus has

been much more clinical. This division has become less visible in later years, where cognitive neuropsychology has also been applied in assessment, for instance, the creation of theoretically founded test batteries like *PALPA* [19], and model-based intervention and rehabilitation [20]. And contrary to Coltheart's predictions, syndrome labels like *surface dyslexia* are still used not only in the clinic, they also continue to be studied within cognitive neuropsychology proper.

Cognitive neuroscientists have been much more interested in the cerebral substrate of cognitive functions than cognitive neuropsychologists, and believe that knowledge about brain function from the neuronal to network levels can constrain theories of cognitive processes. At least for pure alexia and the models of visual word processing, the cross-fertilization between brain science and cognitive neuropsychology has been very fruitful. For the central alexias, the cognitive neuropsychological models still dominate both in research and in the clinical domains, where test batteries, designed to test the many modules identified in the language system at large, are influential in the work of many speech-language pathologists and neuropsychologists.

Basic Assumptions: A Critical Review

The Uniformity of the Functional Architecture

In cognitive neuropsychology, all patients, although they have different functional deficits, are assumed to perform with some damaged version of *the same (cognitive) system*, and this is why one can draw inferences about the cognitive system in general from studies of single cases. It is also the reason that group studies are rarely done in cognitive neuropsychology; one would not expect to find two patients with the exact same functional deficit, and thus grouping (to the traditional cognitive neuropsychologist) becomes meaningless. So there is an assumption of shared normal cognitive architecture between individuals, and at the same time an assumption that no two damaged cognitive systems are exactly the same. Any patient with damage to the cognitive system may, however, be admitted as evidence for or against a model: If the model can't explain a patient's pattern of performance, then the chances are the model is wrong. This idea of a shared or common cognitive system stands in contrast to what is often the starting point in clinical neuropsychology, where it is of utmost importance to take individual differences into account. If this did not happen, we could accidently diagnose people with poor IQ and low education as demented, or people with developmental dyslexia as *a*lexic. When the clinical neuropsychologist tries to assess which cognitive functions may have been affected by brain injury, the starting point is always a comparison either with a group of normal controls that are matched to some degree to the patient's age and education or with previous performance by the same patient. In traditional cognitive neuropsychology, it was comparatively rare to compare patients' performance to that of normal controls, and this has implications for the interpretation of many reported dissociations. If patient performance is not compared to controls, how do we know what is "normal

performance" and what is "impaired"? This problem was noted by Tim Shallice in his seminal book *From Neuropsychology to Mental Structure* [21]:

> It is a standard part of the clinician's assessment of a patient to compare the patient's behaviour with that of controls and of patients who may have similar lesions. The undertaking of group studies to establish norms and the obtaining of anatomical correlates are part of the clinician's routine practice. The daily use of this sort of information is foreign to ultra-cognitive neuropsychology, and this is a major problem [p. 215].

The question of a common functional architecture is particularly important in relation to reading and alexia. Reading is an ability that varies significantly between subjects: The type and mode of reading instruction, how much people engage in reading, and how fast and efficiently they do so vary between people of normal intelligence and without developmental reading disorders. As we discussed in Chap. 1, even readers that behaviorally perform at the same level may use different brain networks to perform the task [22]. In addition, the orthographies of different languages differ to a degree that makes it implausible that the exact same functional architecture of the reading system arises in different languages, even if they are written with the same letter set [23, 24] (see Chap. 1). This issue is rarely discussed in cognitive neuropsychological studies of reading. While the literature on reading acquisition often takes this aspect into account, cognitive neuropsychology seems to have treated this issue much more pragmatically: when patients are impaired following brain injury, they are severely impaired, and this cannot be explained by their premorbid reading skills. This is probably true, but the pattern of breakdown seen following injury may be related to premorbid skills and the patients' native language. For instance, when it comes to "compensating mechanisms" like the letter-by-letter reading observed in pure alexia, the availability and efficiency of such strategies may vary depending on premorbid reading skills, the language to be read, and possibly also general cognitive resources.

Shallice [21] also noted that it is common *not* to report clinically important background information about patients studied within cognitive neuropsychology, and this is a major problem too: If we don't know where the lesion is, how many lesions there are, or whether there are concomitant visual field defects or language problems, it is very difficult to question the conclusions drawn by the authors reporting a particular patient. The same holds for what type of testing is done and how; to be able to replicate the tests and interpret and criticize the results, we need to know what they were and how they were done. This may seem all too obvious, but here is an example: It has commonly been assumed that patients with pure alexia can read numbers normally. In the review mentioned in Chap. 3 [25], we went through the literature to see if this was really the case, armed with good definitions of dissociations and the statistical procedures to match them. It turned out, however, that neither definitions nor statistics were the main problem; it was the lack of data presented in the papers: under the heading of "possible dissociations" (which is not a strictly defined term), we could merely note that "Findings that may indicate a dissociation between performance with letters and digits are reported in (…) 44 patients (…). For 33 of these, the original papers lack the details necessary to reach any

conclusions about the type of dissociation, either because tasks with letters and digits are not comparable ($N=5$), or, more often, because too few details are given about assessment methods and stimuli ($N=28$) [p. 2286] [25]". To be fair, many of these studies did focus on other issues than the relation between letter and number processing, but the lack of data corroborating the claims of impaired and preserved functions was striking nevertheless.

Modularity and Subtractivity

Two different, but related assumptions in cognitive neuropsychology concern *functional modularity* of the cognitive system and *anatomical modularity* in the brain. It is assumed that the functional architecture of cognitive processes is a configuration of modules: These are the boxes in the traditional box-and-arrow models derived from cognitive neuropsychology and represent information processing systems or subsystems. Such functional modules can be defined in different ways, but most will agree that for a function or cognitive component to be seen as modular, it should have at least a few of the characteristics suggested by Fodor [26]. He proposed that a module should, "to an interesting extent" (but allowing for degrees), be domain specific, innately specified, informationally encapsulated, hardwired (i.e., associated with specific, localized neural systems), fast, autonomous (i.e., automatic), and "not assembled" which means not made up of more elementary subprocesses. These were not offered as strict criteria as much as guidelines, and Fodor never made any explicit claim that a module should have all or even most of these attributes, he just stated that they commonly did [26, 27]. For reading, this is important, as reading is certainly not innately specified, and it is still a matter of debate whether the components (for lack of a better word) of the reading system are domain specific or hardwired, but most will agree that when successfully learned, reading is fast and to large extent automatic. The components of the reading system are, however, generally considered as modules by cognitive neuropsychologists, and this holds even for the components (or boxes) of interactive models like the Dual Route Cascaded (DRC) model (see Chap. 1) [28].

So we can study the functional architecture of cognition because it consists of modules, but cognitive neuropsychologists would not get very far if this functional modularity did not correspond to anatomical modularity, which is the notion that cognitive modules are represented in relatively specific areas of the brain. It is imaginable that a cognitive module could be subserved by brain tissue distributed throughout the brain, but if this were so, focal brain damage would never affect a single module, and cognitive neuropsychologists would get very little information from studying patients with brain injury.

This is related to the *subtractivity* or *transparency* assumption. The performance of a brain-injured individual is assumed to reflect the workings of the normal cognitive system minus one or more modules. So modules can be "subtracted" away by brain injury, but new modules will not be added by damage to the brain. This is not

to say that patients do not use strategies to compensate for their lost or damaged function(s), but it does mean that this compensation is done with modules or functions that the patient possessed before the injury, and which all other normal cognitive systems possess.

Dissociations

Coltheart [27] supplied a shorter and perhaps more precise definition of a module: "A cognitive system is modular when and only when it is domain specific [p. 114]." This is related to the idea of *separate modifiability* [29, 30]: Systems A and B are modular with respect to each other if and only if they can be changed independently of each other. One way of changing them could be by brain injury, so that if system A can be affected by injury to the brain without affecting system B, and system B can be affected by another injury (typically in another patient) that does not affect system A, then systems A and B can be said to be modular.

This is exactly the principle of *double dissociation,* a central principle in cognitive neuropsychological research. To show that two systems, components, or modules are indeed independent (domain specific or separately modifiable), we need to demonstrate this empirically. This cannot be done by mere association: there are numerous observations of associated deficits in the neuropsychological literature, for instance, between deficits in reading and writing. Studying such patients with alexia and agraphia could lead to the view that there is a common module for reading and writing. This conclusion or hypothesis would, however, be refuted by a single patient showing a deficit in reading but with intact writing; a patient showing a dissociation. From this *single dissociation* then, one could draw the conclusion (or hypothesize) that there is a module for reading. It would not be advisable to conclude that there is also a separate module for writing; to support such a conclusion (or hypothesis), we would need to find a patient who was impaired at writing but had intact reading. Then we would have a *double dissociation*, which constitutes strong evidence for the independence of processes or modules if (and in our opinion only if) the tests are sensitive, performance is compared to normal subjects, and statistical analyses are done.

One reason why double dissociations are much more powerful than single dissociations is that the simplest interpretation of a single dissociation is that one task is just more difficult than the other. Perhaps reading is just easier than writing? Given that this is a plausible interpretation, there is little evidence for independence or modularity in a single dissociation. If, however, the opposite pattern can also be observed (and given the basic assumptions of a common functional architecture across individuals), this means that task difficulty cannot explain the results and provides a stronger argument for independent modules.

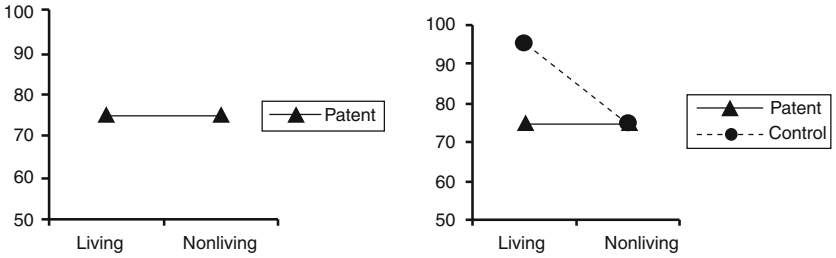
Shallice [21] discusses three types of dissociations which enable different inferences to be drawn from them. A *trend dissociation* is seen if a patient performs abnormally on two tasks, but performs *markedly better on* task A than on task B, without reference to a control group. A trend dissociation does not provide any strong evidence for modularity, but it may be useful in generating hypotheses: based

on this observation, we could hypothesize that task A and B are performed by different modules, and then hope to find another patient showing a clearer dissociation. It is of course a problem to define what "markedly better performance" is if performance is not compared to controls. One plausible example is if a patient were to produce the same words in writing and speech, and the patient was incapable of naming out loud, but much better (but not perfect) at written naming. In such a case, most would agree that the performance in writing is markedly better than in speech, although no one would know just how much better.

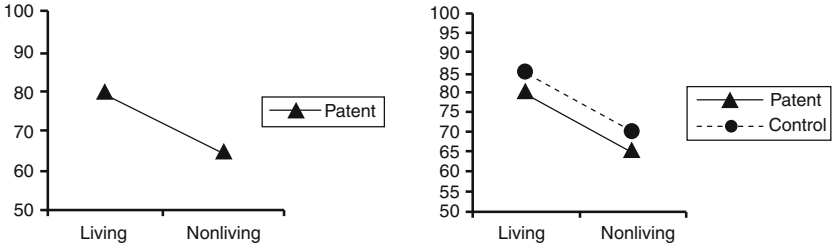
A *strong dissociation* is seen if a patient performs abnormally on two tasks, but task A is performed *very much better* than task B. This could either be with reference to a control group (so that for task A the patient is, e.g., 2 standard deviation (SD) below the mean of the control group, and for task B the patient is, e.g., 5 SDs below the control mean), in which case it is sometimes called a *robust dissociation* [21]. Traditionally, it has also been considered evidence for a strong dissociation if a patient performs abnormally on one test, where normal controls can be expected to perform at ceiling level, and is impaired on another. The strongest evidence for separate modules or systems is a *classical dissociation*, which is seen if a patient performs normally (i.e., within the normal range compared to controls) on task A and is impaired (i.e., significantly outside the range of normal controls) on task B.

What is important to keep in mind here is that what the cognitive neuropsychologist is trying to show is that the pattern observed in the patient would not be observed in the normal population. This means that if we can show that everyone is better at writing than reading, a "selective" deficit in reading following brain injury would not be very informative. This is why relating the patient's performance to normal controls becomes very important. Imagine a word list where normal controls read only 75 % of the words correctly and another where everyone scored 100 %. If a patient then should score 72 % on one list and 98 % on the other, this would not be evidence of any kind of dissociation, but we would only know this if we had the normal data. Returning to the hypothesis mentioned previously, that number reading can be spared in pure alexia, we did not find any classical dissociation supporting this notion [25]. We did notice, however, that all the trend and strong dissociations reported went in the same direction: Patients were always reported to be better with numbers than letters. What we did, then, was to test normal subjects in a task where letters and digits were difficult to see (they were presented very briefly, and then masked). The results showed that our normal subjects were better at identifying digits than letters in this task, which strongly indicates that for some reason digits are just a little easier to perceive or recognize than letters. The best explanation for the finding that some pure alexic patients perform better with numbers than letters, then, is that there is a difference in difficulty between the two tasks and not separate modules responsible for letter and digit reading.

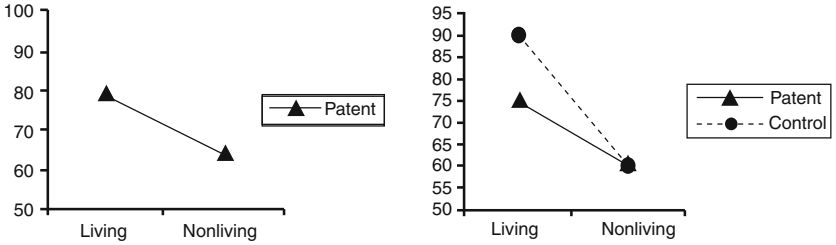
This point is very nicely illustrated with regard to the so-called category-specific recognition deficits (the observation that some patients can recognize natural objects but not man-made objects and other patients showing the opposite pattern) in Fig. 5.1. In this example it becomes very obvious that data are actually impossible to interpret if they are not compared to a control group; what looks like a dissociation may not be (or may go in a different direction), while data that do not look like



Example 1: Patient 1 appears to show no category effect, but referencing to control data reveals a living deficit



Example 2: Patient 2 appears to have a nonliving deficit, but this disappears when referenced to controls



Example 2: Patient 3 appears to have a category deficit for nonliving, but referencing to control data reveals a living deficit

Fig. 5.1 Hypothetical examples of patient performance on two tests (recognition of living and nonliving items) [31] (Reprinted with permission from Elsevier). In the *left column* is the patient's performance, and in the *right column* this performance compared to a control group, clearly illustrating that without reference to a control group, we have no way of knowing which test results represent a dissociation or in which direction it may point

a dissociation at all may represent one; all depending on the performance of normal subjects in the same task.

Traditionally, many of the tests used in cognitive neuropsychology, both the published test batteries and experimental tests devised to investigate a given hypothesis, are tests where normals would be expected to perform at ceiling level. This means one of two things, both of which are problematic: Either (1) there is little or no normal variation in performance (all normal subjects can read the words or name the objects in question). In this case, it is impossible to know if there are processing differences between tasks and stimulus types in the normal population, because the task is too easy for us to tell. Or (2) there is normal variation on the tasks, but we do

not know how performance varies as we have no control data. We mentioned above that abnormal performance on two tasks, where performance on task A is very much better than task B, may, according to Shallice's (1988) original definition, constitute a strong dissociation even without reference to normal controls if normals would be expected to perform at ceiling level in both tasks. But what if normals would also show a difference between tasks if we just made both tasks a little more difficult (by presenting the stimuli quickly or by making them do the task as fast as they can)? This would mean that the difference observed in the patient can also be observed in the normal population, and thus there is no dissociation at all. This is what we found for letters and digits, and presumably there are other observations in cognitive neuropsychology that can be explained in the same way. This is also why we are inclined not to accept a strong dissociation without reference to a control group as meaningful evidence regarding the functional architecture of the reading system (or any other cognitive function), although they may be valuable in generating hypotheses.

A Note on Test Methods

A common argument for using simple tests with patients is that they are patients, and we typically test them in the domains where they are impaired. So if we were to use more difficult tests, we would find that the patients could not do them at all or would get very few items correct. This would both preclude error analysis, which has been very important in the study of reading since Marshall and Newcombe [9], and it would frustrate the patient. There is at least one way that this can be overcome, however, and that is by giving the patients the same simple tasks but measuring the time it takes to perform them and then using this reaction time as the data to compare with normal subjects. This is done in many recent studies, and some also use composite measures that take both errors and reaction times into account [32]. Considering the importance of reaction times in the peripheral alexias, it is curious that this measure is rarely used with central alexic patients. For these patients, error patterns and the relative sparing or impairment of reading nonwords and irregular words are of course important. It remains an open question, however, if these patients are indeed normal in reading the "unimpaired" category of words when response times are measured.

In the clinic it may still make sense to let patients perform quite simple tasks in order not to frustrate them unnecessarily, but both in cognitive studies looking at potential dissociations of functions and in treatment studies aiming to measure the effect of treatment, sensitive measures are very important. Also, as most alexia syndromes (or symptom clusters) are defined by patterns of impaired and preserved functions, it is important to use comparable and sensitive tests. In the case of a patient that cannot read any nonwords aloud but reads exception words with ease and clearly understands them, the diagnosis may be quite clear (phonological alexia), but this does not happen all that often (see Chap. 4). Rather, patients are commonly impaired across the board, but their reading of some words may be disproportionally affected. In these cases a comparison with normal subjects is very

important, both to pinpoint the main deficit in the patient and in finding tasks where the performance is relatively preserved (although not necessarily normal). To decide how to proceed with treatment, one may not need to document a clear classical dissociation, but it will be helpful to know with some confidence which aspects of reading are more impaired.

Studies reporting dissociations based on different patterns of below ceiling performance without reference to controls are very rare in newer literature, as journals now commonly demand both control data and statistical tests to publish case reports. Such studies are however numerous in the literature (and include many of the studies reported in Chaps. 3 and 4) which is why it is important to know that the conclusions drawn from these studies might not be as strong as they seem at first glance. This is not to say they have not been useful in generating plausible hypotheses and models of reading, but perhaps the models would have looked a bit different, had other criteria been applied. Both experimental and statistical techniques have evolved in the last 40 years and will continue to do so. For the future scientists interested in reading, then, it would be very useful if experimental and statistical details were reported to a degree that makes it possible to replicate (or not) results from our present, and with the benefit of hindsight perhaps discard some of the current work on reading and alexia.

Statistical Methods for Cognitive and Clinical Neuropsychology

The issue of statistically comparing a patient's test results to controls', or to available norms, has in the past been done in a variety of ways. However, in the last 15 years, there has been a significant development of statistical methods for cognitive and clinical neuropsychology, much thanks to John Crawford and his colleagues [33–37]. They have put much effort into developing methods for comparing single cases to small control groups while controlling the possibility for type I errors (finding a deficit where there really was none) [38]. Also, they have devised tests for detecting significant strong or classical dissociations in test performance [39, 40], comparing two patients with reference to controls [41], as well as statistical tests that control for covariates (like age or education) [42]. These methods have proven extremely useful, not least because most of their proposed statistical tests come with small, freely available computer programs that do the actual calculations (see http://homepages.abdn.ac.uk/j.crawford/pages/dept/psychom.htm). Much because of this, "single case research is alive and well and more rigorous than ever [p. 1151] [43]," as pointed out in a recent review of methods for single case neuropsychology. Crawford et al.'s methods are very useful when doing research, but they are also usable in the clinic, as outlined in a recent textbook in clinical neuropsychology [44]. Here, many of the practical problems facing clinicians when they want to evaluate the abnormality of one or more test scores are discussed. The problem of detecting changes in neuropsychological performance in individual patients, an important issue both when dealing with possible degenerative disorders and with effects of rehabilitation, is also considered, and possible solutions offered.

Case Series and the Way Ahead?

So case studies are more rigorous than ever and, at the same time, studies of case series are becoming more common both in cognitive neuropsychology in general, and in the study of reading. Roberts et al.'s [45] study of severity in pure alexia is an example of this, where both similarities and differences are taken into account in order to try to understand the "bigger picture" of what pure alexia is and isn't and how it may reflect on the normal architecture of the visual or reading system. The patients in this study were grouped according to the severity of their reading deficits, and correlation analyses were run to see if this corresponded to their performance in other tasks like object naming. One problem with this study, which is commonly used as an argument against group studies in cognitive neuropsychology, is that test scores were averaged over participants, and individual scores in the key experiments are not presented. In group studies and case series, associations become at least as interesting as dissociations, as systematic relationships (correlations) between factors can be investigated. The large series of patients with semantic dementia, reported by Woollams et al. [3], provide a nice example. They investigated whether there is a systematic relationship between the severity of semantic impairment and accuracy in reading exception words (see Chap. 4), a question that cannot be handled in a single case study. A notable feature of this work was that the empirical data from the patients were accompanied by a computational simulation of the results within the Triangle model of reading (and indeed, the prediction that surface errors should arise from semantic deficits was derived from this model). Although the conclusions of this study have been challenged [4], the important point here is that case series studies often come hand in hand with computational modelling work, aiming to simulate both the hypothesized normal process and the impaired or degraded system [46, 47]. In these cases, case series bring about evidence from two sources, rather than one.

Some cognitive case series select patients based on anatomical rather than behavioral criteria [48, 49], bridging cognitive neuropsychology and cognitive neuroscience. If the presence of a lesion in a given area or region of the brain is used as a selection criterion, then the characterization of brain–behavior relationships should get more precise, which could possibly also inform our understanding of the cognitive processes involved. Consider the case of the visual word form area, which is found lesioned in most patients with pure alexia. Given that these patients have been selected based on symptoms (alexia) rather than the location of their lesion, it is still an open question whether there are patients out there with lesions in this area that do not have pure alexia (although there are indications, that this may indeed be the case [50]). Also, looking at the data from the PLORAS [51] study presented in Chap. 4, it becomes obvious that group studies have certain advantages. It seems clear from the data in this study (see Figs. 4.5 and 4.6) that the typical central alexic syndromes are clinically very rare, something we would never know if we were to judge the literature on single cases with acquired reading disorders. This is mostly a consequence of the theoretical interests of cognitive neuropsychology having dominated the research on acquired reading disorders, at the cost of clinical descriptions of more complex or

mixed cases. These complex cases may not inform cognitive theories, but they represent an important clinical challenge. We commented in Chap. 3 that most studies of rehabilitation of "pure alexia" did actually not present very pure cases, and we presented this as a problem. However, if most cases of alexia with relatively minor affection of other cognitive functions are not really pure, then perhaps treatments should to a larger degree actively target these mixed conditions.

In Chaps. 2 and 4, we presented some data from larger studies with wide selection criteria and a large number of patients. These studies find strength in the number of patients and the variability between them, rather than in selective deficits studied in depth, and we think that such studies may be even more important in the future. This does not mean that single case studies or dissociations are no longer interesting, and the debate about the relative weight that should be put on associations and dissociations will probably go on [3–5, 52]. For clinical and maybe even theoretical purposes, however, it may be time to broaden the horizon and characterize the true variability in the clinical presentation of reading disorders. This may not inform cognitive models to any interesting extent, but it could potentially inform our approaches to rehabilitation.

Can We Teach Patients How to Read?

It should be clear by now that patients have taught us quite a bit about how we – literate subjects – read. The amount of time and effort that patients with acquired reading disorders have invested in research projects over the last 40 years has been immense. And patients continue to participate in research, most of them knowing that the lessons we can learn may not benefit them personally. They hope, as do we, that in time we may understand both normal and impaired reading to a degree that can aid in the remediation of these disorders. Theories of reading have been developed and refined from the late 1800s until the present, but with the exception of hemianopic alexia, the treatment options for acquired reading disorders are not many nor are they well documented. One reason for this could be that once the ability to read is lost or impaired, it is not possible to relearn. This is probably partly true: It is very unlikely that alexic patients, in the chronic phase, will learn to read as fluently as before their injury. It is also true, however, that there is much we have yet to try, and there are some therapies for alexia that seem at least somewhat promising. So how do we proceed from here?

While a comprehensive review of therapy methods is beyond the scope of this book, there are some important lessons to be learned in the literature that should inform future reading rehabilitation studies. We will address these as a series of questions that someone designing an interventional study should be asking themselves.

What Should the Study Design Look Like?

Whether investigating single subjects or groups, there needs to be some form of control that the therapy can be compared to. This will obviously be related to the hypothesis being tested. If it is a mechanistic hypothesis ("we predict that

phonological cueing will improve reading in alexic patients better than semantic cueing"), then the form of the control should be obvious from the hypothesis. If the aim is more pragmatic and is related to clinical efficacy, then the issue is not so clear-cut. Given that behavioral therapies are, by definition, complex interventions, coming up with a control or "sham" therapy is not easy and may end up scuppering the study. In order to create a sham therapy, one needs first to deconstruct the interventional therapy and identify which parts are therapeutic and which are, to borrow a pharmaceutical term, inert. This can be tricky as it is not always obvious from the beginning which parts of therapy are actually therapeutic. As an example: in a large occupational therapy trial on outdoor mobility, the results were affected by including one of the key ingredients (an activity diary) in the "sham" group [53]. Indeed, the MRC group, who defined what a complex intervention is, suggests that in such cases standard clinical care is the better control, "Comparing the new intervention with standard treatment, if there is one, is more informative than comparing it to placebo [p. 29] [54–56]."

Having decided on a form of control, should the same subjects pass through the therapy and control blocks? If it is a single-subject study, then the answer is "yes," with the minimum of one, but preferably two or more baseline measures before the patient undergoes the therapy block. This is to deal with several issues: (1) test–retest, because the patient(s) may benefit from practice on the tests; (2) regression to the mean, because patients with "extreme" test scores will tend towards the average the next time they are tested, unless the test being used is perfectly precise; [57] and (3) "spontaneous recovery" (or worsening if a dementia patient), because the baseline may be varying for nonrandom reasons. The mechanisms behind spontaneous recovery are complex and largely clustered towards the time of brain injury [58], but they can occur at any time. So it is useful to deal with these potentially confounding issues by optimally designing the study. What if this is a group study? Well, there are two main options: (1) randomly allocating each subject to either a treatment or nontreatment group (Cochrane reviews and grant reviewers appear to prefer this option) and (2) using a form of crossover design (so that all subjects pass through therapy and control blocks, but the order in which they do so is randomized). The main problem with the first option is that the two groups may become accidently biased on some key variable or other (e.g., severity). A good way around this is to use minimization when randomizing [59]. The main problem with the second option is that carryover effects can muddy the picture, that is, patients going through a therapy block may improve, and then this improvement may remain in the second control block. Statistically this can be dealt with by looking at rates of change (the score may remain higher in the control block following a therapy block, but the rate of change should remain static or fall slightly). This can still be an issue if the therapy is so effective or the patients so mild that ceiling effects come into play. In general, we prefer crossover designs, as almost all patient studies suffer from the problem that between-subject variability is much greater than within-subject variability [60]. This reduces the power of studies that cannot control for this and puts them at risk of being unable to reject the null hypothesis for an intervention that is actually having a beneficial effect.

Should the Therapy Be Directed Towards Individual Items or Rule Learning?

This will obviously depend on the therapy-related hypothesis. As we saw in Chap. 4, some rule-based learning techniques do work, and one would thus expect them to generalize to non-trained stimuli. In general though, the evidence, for reading at least, mirrors naming therapy in aphasia which seems to be item specific. This is perhaps no big surprise, but it does mean that the outcome measures need to be looked at carefully. Several of the larger group studies have fallen foul of this. By choosing standardized tests of reading ability, they have biased themselves away from finding an effect; for if the training is item specific, and those items do not appear in the standardized test, then the study is almost bound to fail. On the other hand, even if therapy is item specific, one would hope that this would have a beneficial effect on the patient's reading experience (otherwise why bother?), and standardized tests are often used to try and capture this. In a study that relies on repetitive exposure to a training set of words, good practice would be to include tests of item specificity (one could use the same words but in a different font if one wanted to show that it was truly an item rather than identity priming effect), perhaps with matched controlled items to look for generalization; but also to measure reading ability/subjective experience of reading on more standardized outcome measures.

A quick word of warning about training on surrogate material: Marlene Behrmann trained patients with prosopagnosia on a series of virtual 3D objects called Greebles [61]. These are computer-generated images that resemble faces and can be manipulated more systematically than real faces. Families of Greebles can be created that resemble each other on certain features, and these can be used to train people to recognize a novel Greeble as belonging to a particular family, akin to retaining the rules that allow one to read nonwords. The patient needed a huge amount of training, up to ten times more than normal subjects, but did eventually learn some of the Greeble "rules." Unfortunately this came at a cost, and the patient actually got worse at human facial recognition (which was the target of the therapy); they concluded, "The findings indicate potential for experience-dependent dynamic reorganization in agnosia with the possibility that residual neural tissue, with limited capacity, will compete for representations."

How Much Therapy (Dose) Should Be Given?

The simple answer is lots! As pointed out at the very beginning of the book, reading appears effortless (thankfully), but this is because it is a skill that has been built up over decades of learning and continued practice. Language learning is not something that can be easily rushed. There is not much data on isolated learning to read a second language (as most people do this in the context of learning to speak a second language), but evidence from the American Foreign Service Institute, summarized in Omaggio's book [62], suggests that even to get to the most basic level of

proficiency (level 1 of 4), in the easiest of second languages (e.g., French given English) takes 240 h of practice. This is multiplied by a factor of two for a "hard" language, with each level of proficiency costing a further doubling of time on task. This is in normal learners who have a brain that is optimized for learning, so even more may be required in patients who, following their stroke, may have a reading impairment *and* a reduced capacity to learn. This will vary across subjects as we saw in Chap. 4 where, in a case series of two, one subject required three times as much training as the other [63]. In practice, most studies do not get to the 10 h of therapy mark (although some case studies do), but there is evidence that this level of practice is required to improve picture naming in aphasic patients [64]. This lesson is, however, still not learned: a recent high-profile study of speech therapy reported no significant effect of targeted speech therapy compared to a control of "social contact without communicative therapy" following an average of only 18 h of therapy in total [65]. The most efficient way to a high enough dose is to rely on intensity, but stroke patients, particularly in the post-acute phase, cannot always put up with therapy delivered at high intensity [66]. The reader will know by now that we prefer computer-based therapy where possible, as this allows the patient to control when and where to do the training. And, most importantly, because computer based therapy has been shown to work in hemianopic [67], pure [68], and central alexia [69].

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