Investigating Cognitive Neuroplasticity in Single Cases: Lessons Learned from Applying Functional Neuroimaging Techniques to the Traditional Neuropsychological Case Study Framework

S. G. Romero, C. F. Manly and **J. Grafman**

Cognitive Neuroscience Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA

Abstract

We summarize two case studies as a context for discussing the use of neuroimaging as a convergent methodology in the study of neuroplasticity in single subjects. Throughout this paper we argue for a different approach for including neuroimaging in these types of study. Previous case studies of neuroplasticity in patients (ours as well as others reported elsewhere) have added neuroimaging to the traditional neuropsychological framework of comparing patient results with matched control groups, and synthesized results through descriptions of anatomical and behavioral dissociations. This type of approach is referred to as the comparison approach. We advocate a different approach that builds on findings from previous behavioral skill learning research. Specifically, we propose adding neuroimaging throughout learning or recovery of the ability of interest and making inferences from systematic changes in activation topography and intensity that occur within the context of predicted behavioral changes. We dub this approach the online approach. This approach should allow future investigators to circumvent many of the interpretation pitfalls that are common in comparison studies.

Introduction

Since the ground-breaking work with monkeys demonstrating adaptation to lesions in the central and peripheral nervous systems (Merzenich *et al.*, 1983), there has been a substantial gain in our understanding of the mechanisms underlying neuroplasticity in humans (Chollett *et al.*, 1991; Weiller *et al.*, 1993; Grafman and Christen, 1999). Much of this work has been enabled by modern functional neuroimaging techniques. Although functional neuroimaging studies offer some advantages over the use of behavioral methods in traditional neuropsychological studies (Humphreys and Price, 2001), there are important issues in design and interpretation that must be considered when using functional neuroimaging techniques.

The advantages of neuroimaging include the convergent evidence it provides concerning which brain areas are involved in spared or recovered cognitive processing. It may also allow for the tracking of functional changes during the recovery of, or compensation for, damaged processes. There are, however, unique challenges in using functional neuro-imaging techniques in single case studies.

This paper will address these issues and offer some suggestions for optimizing functional neuroimaging investigations of neuroplasticity in single cases. First, we outline results from two of our recent case studies. Then, using examples from our experience, we discuss in detail the issues that should be considered when using functional neuroimaging. Throughout this discussion we will develop and present an optimal approach for combining functional neuroimaging with behavioral measures in case studies.

The standard practice in neuropsychological studies (without functional neuroimaging) is to assess behavioral performance and anatomy separately and later synthesize these results through structural descriptions of spared or damaged tissue, comparisons with control groups, and behavioral dissociations. For example, an earlier study of patient GK (who is presented below) assessed multiple language functions following a massive left hemisphere stroke and interpreted the observed partial abilities in terms of spared right hemisphere processing (Rapcsak *et al.*, 1991). Note that this is a reasonable approach in the absence of functional neuroimaging data.

Correspondence to: J. Grafman, Cognitive Neuroscience Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Building 10, Room 5c205, 10 Center Drive, MSC 1440, Bethesda, MD 20892-1440, USA. Tel: +1 301 496 0220; Fax: +1 301 480 2909; e-mail: grafmanj@ninds.nih.gov

Functional neuroimaging techniques, however, would allow Rapcsak *et al.*'s interpretation to be empirically tested provided standard assumptions are met regarding inferences from functional neuroimaging results. These assumptions include the fact that most techniques measure blood flow as a correlate of neuronal firing, and that the authors use proper task design and statistical analysis. Although these issues are important to any functional neuroimaging study, they are peripheral to the present topic. Thus, they will not be discussed further here except to mention that they also must be considered when designing functional neuroimaging studies and making inferences regarding the resulting patterns of activation.

There are two ways to incorporate functional neuroimaging into case studies, especially in studies of neuroplasticity. The first is to add it to the traditional case study framework. In this case, comparisons are made with control participants, and activation differences in the single case are interpreted through comparison to a specific group of controls or to previous neuroimaging studies with unimpaired participants. We refer to this approach as the comparison approach.

The other approach, which we will discuss more fully, we refer to as the online approach. Although the online approach is not always feasible, we will argue that when possible, it is the preferred approach for neuroplasticity studies of single cases. In the online approach, neuroplasticity is assessed during learning or practice of the ability in question. In case studies, this means that progress is assessed across the relearning, recovery, or reacquisition of a damaged or deficient skill or task, both at the behavioral and neuronal levels. We will further argue that the online approach circumvents many of the inferential ambiguities of a comparison design. It also capitalizes on the extensive amount of behavioral research on skill learning and the general principles that operate across different tasks and skills.

Basic behavioral principles of skill acquisition

The online design assumes that any relearning that occurs after brain injury is the product of general behavioral and neural principles that also apply to learning in unimpaired participants. In this section we will focus our comments on a few key findings from the past 20 years of behavioral studies delineating the mechanisms of skill acquisition, and outline the main theories of skill learning which are based on these findings. In the next section we focus on the types of neuroplasticity that have been observed from studies of learning and recovery of function.

There are several prevalent findings in the skill acquisition literature. First, response times decrease with practice across a wide range of tasks, from cigar rolling to memory retrieval (Crossman, 1959). Regardless of the task, this speed-up can be well characterized by a general class of mathematical functions called power functions with a single fitted parameter [see Newell and Rosenbloom (1981) for an extensive discussion of the power law].

The second finding is that most acquired skills show good long-term retention (Proctor and Dutta, 1995). Usually this retention is demonstrated by some measure of savings (e.g. response time speed-up) that indicates that the original learning and the relearning during a retention test do not occur at the same rate. After training it is rare for there not to be some evidence of savings from training over the initial learning session.

Another finding that is well documented in the skill literature is that different forms of training can produce drastically different outcomes regarding the acquisition and retention of skills. In general, it has been found that factors which promote faster acquisition can sometimes interfere with long-term retention. Similarly, factors which optimize long-term retention of a skill do not expedite initial learning of a skill [see Schmidt and Bjork (1992) and Healy and Bourne (1995) for extensive discussions concerning these factors].

One final finding worth mentioning concerns the specificity of training that can be expected. In general, practice-related learning has been shown to be very specific to the items and tasks that are trained (Healy and Bourne, 1995). Transfer of training is rare and only occurs in very specific cases (Proctor and Dutta, 1995). These findings will be of great importance when designing online studies for the recovery of function.

Following early work by Bryan and Harter (1899) and later work by Fitts (1964), many of the modern theories of skill acquisition explain speed-up in processing as a progression through different learning stages. They differ, however, in what stages they propose, and we present three main theories to illustrate the breadth of theoretical positions which have been adopted. It should also be noted here that none of these represents a comprehensive theory of skill acquisition nor have all the factors and mechanisms involved in skill acquisition been fully worked out. Instead these theories should be viewed as a guide for designing online patient studies.

The ACT theory (Anderson, 1983, 1992) proposes a transition from a declarative form of knowledge to a procedural form. Declarative knowledge is 'what' knowledge; procedural knowledge is 'how to' knowledge. In the declarative stage, knowledge consists of facts that must be rehearsed, including situational characteristics and instructions. During practice, the learner develops task-specific procedures which do not require the active maintenance of declarative knowledge. Performance continues to improve as these procedures are refined or tuned to the practiced context. The ACT theory assumes that performance is subsumed by a single strategy or type of processing that becomes more refined.

In contrast, Logan (1988) and Rickard (1997) have suggested that sometimes acquisition involves a strategic switch from one type of processing to another. These theories suggest that initially, a multi-step algorithm is used to perform a task. With practice, direct links to memory are developed and eventually expert performance relies on memory retrieval. Logan assumes that both processes begin in parallel and the faster one produces the response, whereas Rickard assumes

that the two strategies must be processed sequentially. Because initially there is no memory representation for the task, the longer algorithm determines performance. As the task becomes more practiced and memory traces get stronger, performance will rely mostly on the faster memory retrieval process. Logan also assumes that each trial results in a separate or independent record in memory. Rickard assumes that a single representation or record is built up in memory for each item and is appended during practice.

Taken together, these results from behavioral studies of skill learning suggest that several considerations are necessary when designing online neuroimaging studies with single cases. First, the skill and tasks in question must be analyzed to assess to what extent strategy shifts can be expected, and, second, to what extent strategies may be processed in parallel. Third, the design of a proposed training regimen should be consistent with the goals and predicted outcomes of the study. Recovered functioning would be of only limited value if it was not long lasting. We now consider previous functional neuroimaging investigations of neuroplasticity.

Neuroimaging studies of neuroplasticity

In general, there are four forms of neuroplasticity that have been observed. These four forms are referred to as homologous area adaptation, cross-modal reassignment, map expansion and compensatory masquerade (Grafman and Litvan, 1999). Homologous area adaptation refers to the emergence of a new cognitive process in a homologous region in the opposite hemisphere. Cross-modal reassignment refers to the reassignment of areas usually receiving input from one sensory modality to process information from another sensory modality. Map expansion refers to the growth of a functional area either with training or following the loss of input to an adjacent region. Finally, compensatory masquerade refers to the phenomenon by which a cognitive process appears to be normal or recovered due to a shift in processing to an atypical strategy.

Two types of previous neuroimaging study have provided some of the evidence for these forms of neuroplasticity. One type has focused on skill learning using unimpaired volunteers, and most of these have studied visuomotor skill learning. The second has focused on the recovery of function in patients with developmental or acquired lesions. In general, studies of skill learning demonstrate that training or practice leads to map expansion (Elbert *et al*., 1995; Schlaug *et al*., 1995), with an immediate effect on cortical activation that is specific to the trained items (Karni *et al*., 1995). Then as participants become expert, fewer resources are needed (Pascual-Leone *et al*., 1995) and experts exhibit more compact activation than novices (Krings *et al*., 2000).

Investigations of functional recovery have shown that deafferented cortical areas are recruited for cross-modal reassignment (Sadato *et al*., 1996; Bounomano and Merzenich, 1998). Conversely, it has also been shown that for a particular function (e.g. language processing), atypical,

auxiliary cortical areas are recruited when there is a lesion to a typical processing area (Chollet *et al*., 1991; Weiller *et al*., 1993; Nudo and Miliken, 1996). It is unclear what role these auxiliary areas play in the recovery of function. These areas might be involved in a compensatory masquerade or they could be involved in a simple homologous area adaptation (a new cortical area supporting the same cognitive strategy).

In language, for example, it is generally believed that unimpaired (right-handed) participants only use left hemisphere areas for certain forms of language processing [but see Binder (1997) and Weiller *et al*. (1997) for conflicting neuroimaging results]. However, patients with left hemisphere lesions in language areas seem to activate homologous right hemisphere areas to an extent that is correlated with damage in the left hemisphere (Karbe *et al*., 1998). A couple of neuroimaging studies have also demonstrated perilesional left hemisphere activations (Heiss *et al*., 1993; Price *et al*., 1995). What is not clear is how novel these supplemental areas of activation are in the patients. In other words, is the right hemisphere processing simply reactivation of symmetrical representations inhibited in unimpaired subjects during lateralization, or are these areas recruited and used by patients alone as a function of a newly emerging processing in the right hemisphere (Weiller, 1998)? Notably, these differences could just be due to cognitive strategy differences between impaired and unimpaired groups (i.e. compensatory masquerade). Similarly, it is not clear to what extent activation in perilesional areas reflects processing that is contributing to performance. Perilesional activations could just indicate attempted processing in partially functioning cortical areas that are no longer necessary or sufficient for the performance of a task. These uncertainties are directly related to the use of the comparison approach in these studies.

Two cases

The following cases are discussed with an emphasis on what guided our interpretation of the results. Our summaries of these cases are intended to provide a basis for the theoretical discussion of planning future case studies involving functional neuroimaging and neuroplasticity. Separate reports of the specific studies have been submitted independently for publication (Basso *et al*., submitted; Romero *et al*., submitted).

Case GK

GK, a 65-year-old male, was right handed prior to his strokes. He suffered two strokes, a massive left hemisphere stroke at the age of 45 years and a smaller ischemic lesion in the right frontal operculum at the age of 61 years. GK received extensive language training after the first stroke and progressed from global aphasia to resembling a Broca's type aphasic. His second stroke left his language abilities stable (Rapcsak *et al.*, 1991). GK has a right visual field hemianopia
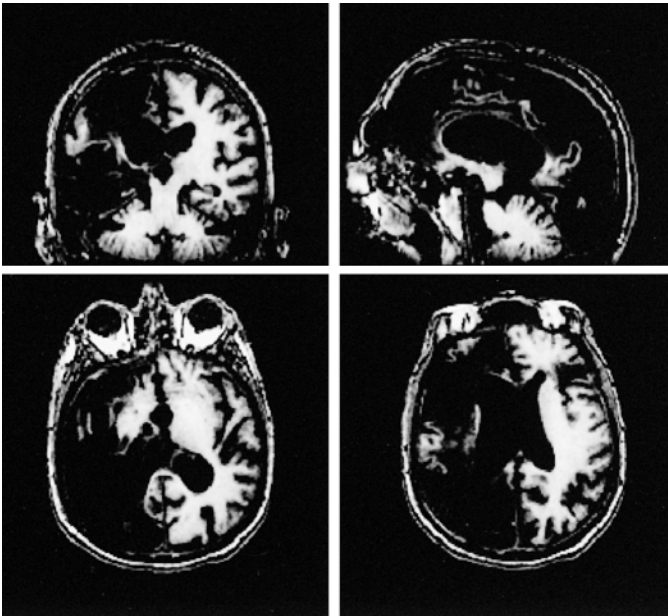
Table 1. Summary of GK's results on the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) and the Boston Naming Test

PALPA items	
19 Letter identification	100%
21 Letter discrimination	100%
23 Spoken–written letter matching	24/26 (92%)
24 Visual lexical decision with 'illegal' pseudowords	60/60 (100%)
25 Lexical decision imageability and frequency	112/120 (93%)
26 Visual lexical decision and morphology	45/60 (75%)
27 Visual lexical decision and spelling–sound regularity	59/60 (98%)
29 Letter length reading	24/24 (100%)
30 Syllable length reading	16/18 (89%)
31 Word reading	
Low imageability and low frequency	15/20 (75%)
Low imageability and high frequency	17/20 (85%)
High imageability and low frequency	19/20 (95%)
High imageability and high frequency	19/20 (95%)
33 Grammatical class reading	25/40 (62.5%)
36 Pseudoword reading	0/24 (0%)
47 Spoken word–picture matching	39/40 (97%)
48 Written word–picture matching	38/40 (95%)
51 Word semantic association	
Low imageability	8/15 (53%)
High imageability	11/15 (73%)
52 Spoken word–written word matching	23/30 (77%)
Boston Naming Test	
Total correct	33
Self correct	3
No response	9
Total errors	18
Semantic errors	15
Neologisms/jargon	0
Phonological errors	3

Fig. 1. Orthogonal view using neurological orientation (i.e. left is left) of GK's magnetic resonance image, with two axial slices. Relative to the center of the volume, the slices are 6.6 mm to the right and 5.6 mm anterior. The left axial slice is 20.2 mm inferior and the right axial slice is 3.0 mm inferior. The lesion encompasses the majority of the left hemisphere, although there is some spared tissue in the basal frontal lobe, uncus, globus pallidus, and a perirolandic region connected to the thalamus by a spared portion of the anterior limb of the left internal capsule.

and right-sided hemiplegia. Table 1 presents the results of our assessment of GK's language abilities with the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA; Kay *et al.*, 1992) and the Boston Naming Test (Kaplan *et al.*, 1978). GK was completely unable to read non-words and had trouble reading real words that were low frequency and low imageability. Overall GK's performance was consistent with a classification of deep dyslexia.

As alluded to above, we wanted to test the hypothesis that GK's recovered language abilities were the product of purely right hemisphere processing. Thus, we studied GK's recovered language abilities using a comparison approach.

We initially assessed the extent of GK's structural brain damage with a high-resolution (1.5 mm/slice) magnetic resonance imaging (MRI) scan. Although the damage to GK's left hemisphere was extensive, there were remaining islands of tissue with normal signal intensity in the left hemisphere. These areas were present in the perirolandic and sensorimotor cortex and also in the basal frontal lobe, uncus and globus pallidus. A portion of the anterior limb of the left internal capsule also showed comparable signal intensity to the internal capsule in the right and seemed to connect the thalamus with the spared left perirolandic region. A high-resolution T1-weighted structural MRI of GK's brain is displayed in Fig. 1. We assessed GK's metabolic activity with a resting (i.e. no sensory stimulation) positron emission tomography (PET) scan. In addition to the majority of the

right hemisphere, this study demonstrated normal metabolic activity in the spared left basal frontal and perirolandic regions.

In the functional MRI study of GK's language abilities we used three tasks, single word reading (either words or pseudowords), lexical decision, and a visual detection task. Data were collected from GK and three age-, gender-, and education-matched controls. We used block design functional MRI in which the lexical decision and word reading tasks were compared with the visual detection task in separate runs. Runs with the reading task used words or pseudowords but not both in the same run. In each run, the reading task was alternated with the visual detection task, such that there were three blocks of each task per run. We point out for later discussion that GK could not read any pseudowords in our pilot testing.

Discriminative responses during scanning sessions were not possible because verbal responses produce movement artifacts and GK could not press a button with his right hand and the use of a button box (in the left hand) was also not possible. Instead, GK and the controls were instructed to do the tasks in their heads (i.e. read words, decide if a real word was presented or detect the visual stimulus), and then press the button in their left hand when they were done in each trial. This enabled us to collect response time data. We also collected data on the tasks outside the scanner, using verbal responses and the same response windows as during the scanning session so we could assess accuracy.

A custom gradient echo-planar imaging sequence (field of view = 24, acquisition matrix = 64 × 64, repetition time = 3000 ms, echo time = 40 ms, flip angle = 90°) was used to collect the functional volumes. Each volume consisted of 18 axial slices, 6 mm thick. Four dummy volumes were acquired at the beginning of each new run in order to reach a steady-state magnetization. A structural T1-weighted brain MRI was also collected for each subject and was used to overlay the statistical activation maps for anatomical identification.

The analysis was performed with SPM96 (Wellcome Department of Cognitive Neurology, London, UK). The images were realigned to the first volume of the first run. The controls' images were normalized into the reference system of Talairach and Tournoux (1988). Normalization of GK's images into this standard space could not be performed due to the size of the lesion involved and the presence of perilesional tissue. Images collected during the two runs that included each type of reading task (either word or pseudoword reading) were analyzed separately. All images collected during the two runs in which the lexical decision task was alternated with the detection task were also analyzed separately. All activation differences are reported relative to the detection task. We applied ANCOVA global normalization to remove global signal differences among runs. For the control group analysis, we combined the data for all three controls. Contrasts were specified as subtractions. Because we expected *a priori* to find left inferior frontal gyrus and left inferior temporal gyrus activation in the control group, we tested this hypothesis by thresholding the resulting statistical maps with a Z-value = 3.09 ($P < 0.001$). Cluster analysis was performed only for GK with a test both for spatial extent and Z level with a threshold of $P < 0.05$.

In the scanner, the controls were slower at reading words or making lexical decisions than in the visual detection task. The controls were also slower at reading pseudowords than words. Additionally, the controls' accuracy was above 95% for all tasks (measured outside the scanner). In the scanner, GK was slower for word reading than for lexical decision, but was as fast in the lexical decision task as in the visual detection task. Outside the scanner, GK was unable to read any pseudowords but was 93% accurate in reading words and 95% accurate in making lexical decisions.

Activation was found in the left inferior temporal gyrus when the controls were reading words relative to the detection task and there was activity near Broca's region when the controls read pseudowords relative to the detection task. For the lexical decision task (compared with the detection task), the controls exhibited activation in the bilateral inferior frontal gyrus, and in the left orbitofrontal and occipital regions as well as the right cerebellum. No reliable activation was detected when GK was reading pseudowords relative to the detection task, but reliable activation was found in the right hemisphere for (real) word reading relative to the detection task. Specifically, activation was found in the right middle temporal gyrus, motor and pre-motor areas, and right cerebellum. Additional activation for GK (during word

reading relative to the detection task) was also found in residual tissue in the left inferior frontal lobe. For lexical decision, GK exhibited significant activation in the right inferior frontal gyrus. In concordance with other neuroimaging studies (e.g. Binder, 1997), the matched controls exhibited reliable activation mainly in the left inferior temporal gyrus for reading real words in relation to the control task and also near Broca's area in the left hemisphere when reading only pseudowords in relation to the control task. For lexical decision (relative to the control task), the controls exhibited activation in bilateral inferior frontal gyri. Direct comparisons between GK and the controls were not possible because GK's images could not be normalized. These differences in patterns of activation suggest that GK's recovered language abilities are due to plastic neuronal changes in the right hemisphere.

Our study of GK was more informative than traditional neuropsychological case studies because of the addition of functional neuroimaging data. GK's results generally support the hypothesis that his recovered language abilities are the product of right hemisphere processing enabled either through homologous area adaptation or compensatory masquerade. We cannot, however, differentiate between the homologous area adaptation and compensatory masquerade hypotheses because we cannot be definitive regarding GK's cognitive strategies in these tasks. Similarly, we cannot rule out the possibility of perilesional contributions, especially involving the basal frontal and perirolandic regions. These two difficulties are directly related to the comparison approach used for this study. It is important to note that even if activation changes are due to a strategy shift, this may be a typical compensatory change in the recovery of cognitive function. Just as a strategy shift might be typical in the acquisition of a cognitive skill for unimpaired participants, patients may need to relearn skills by starting again with a resource-intensive strategy and then switch to a more efficient strategy. Conversely, patients may just depend on a resource-intensive strategy that may or may not have been used during the original learning of the skill in question. We will discuss this issue in more depth below.

Case JS

In our study of this patient we were interested in investigating the possible cognitive and neural etiology of developmental dyscalculia [see Romero *et al*. (submitted) for a full report on this study]. At initial presentation, JS was an 18-year-old right-handed male with no neurological history, except a diagnosis of developmental dyscalculia in elementary school. During his initial evaluation, JS demonstrated a normal full-scale IQ with substantial scatter: above average scores on all of the non-numerical subtests and very poor performance on the arithmetic and coding subtests. On the Key Math Diagnostic Arithmetic Test (Connolly *et al*., 1976), JS scored at the 79th percentile for understanding basic arithmetic concepts, at the 42nd percentile for using numbers in applied
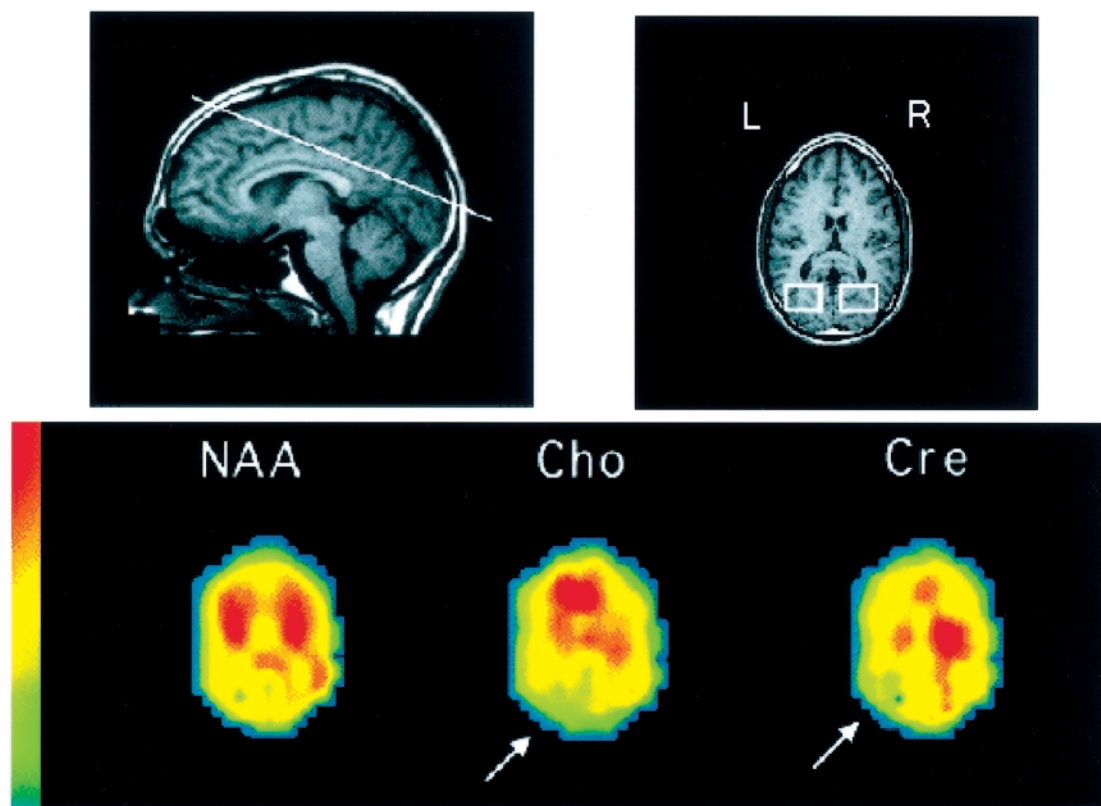
Fig. 2. Top-left presents a T1-weighted sagittal scout image of JS's anatomical magnetic resonance image. The white line indicates the slice used for the color-scale spectroscopy data in the lower panel. The white boxes in the top-right panel indicate the placement of the regions of interest in the posterior temporoparietal lobes for analysis of the spectroscopic data. The bottom panel presents color maps for the levels of *N*-acetyl-aspartate (NAA), choline (Cho) and creatine (Cre). Regions of low metabolite signal intensity are represented in green and blue. Regions of high metabolite signal intensity are represented in yellow and red. The arrows indicate areas of decreased Cho and Cre in the left posterior temporoparietal lobe. There was also a mild (non-significant) focal decrease in NAA.

settings (e.g. making change), but lower than the first percentile for computational ability (i.e. addition, subtraction, multiplication and division). In contrast, JS scored above the 95th percentile on the Raven Progressive Matrices test of spatial reasoning (Raven, 1958). Further pilot testing revealed that JS had great difficulty in single digit multiplication tasks: verification (e.g. $4 \times 7 = 21$ true or false?) and production (e.g. $4 \times 7 = ?$). JS needed to use a paper and pencil for the majority of the problems in both tasks. Thus, his mean response times ranged from 7.1 to 11.3 s and 6.9 to 12.7 s for verification and production, respectively. JS was 87% accurate for verification and 73% accurate in the production task. JS did perform relatively normally in a pilot numerical comparison task (e.g. select the larger number: 54, 59). In this task, JS exhibited the numerical distance effect in response times, such that he was reliably faster in choosing the larger of the two numbers when the numerical distance between them was larger, and slower when the two presented numbers were numerically closer together.

Based on a previous study of patients with developmental dyslexia (Rae *et al.*, 1998), we first neurologically assessed JS with structural MRI and magnetic resonance spectroscopy (MRS). Although the structural MRI was independently read by two experienced neuroradiologists as normal, the MRS scans demonstrated a focal deficiency in the left inferior

parietal lobe (see Fig. 2) of three metabolites that are correlated with neuronal density (Levy *et al.*, 1999). This finding is entirely consistent with earlier lesion studies and with functional neuroimaging studies with unimpaired participants that implicate the left parietal lobe in numerical processing (Grafman *et al.*, 1982; Grafman and Rickard, 1996).

The MRS finding suggested two possible explanations for JS's numerical difficulties, one involving plasticity. They could be due to: (1) a typical network for number processing that is missing a particular mechanism in the inferior parietal areas; or (2) the migration of these processes to atypical cortical areas or the recruitment of new cortical areas following damage to the typical processing area (i.e. homologous area adaptation or map expansion). Thus, we wanted to use functional MRI to assess the location of numerical processing in JS's brain. We chose to use the numerical comparison task for this part of the study. Based on previous research and theoretical models regarding number processing, we expected that the brain areas used for the numerical comparison task would also be used for single digit arithmetic (McCloskey *et al.*, 1985; Viscuso *et al.*, 1989; McCloskey and Lindemann, 1992).

We used a comparison approach for this experiment by collecting data from JS and five age- and education-matched

control participants. Brain activation associated with number processing was assessed in all participants by contrasting brain activation on the number comparison task with that elicited by three different control tasks in a block design functional MRI study. We used three control tasks because previous functional neuroimaging studies of the task had yielded variable findings that may have been attributable to the different control tasks used between the studies (Dehaene *et al.*, 1996; Chochon *et al.*, 1999; Rickard *et al.*, 2000). In one control task, font comparison, the participants were presented with the same numbers as those used in the number comparison task and the task was just to decide if the two numbers were presented in the same font (e.g. 53 **54**). In the second control task, the detect ones task, the participants were presented with a string of four numbers and had to indicate if the string contained the number 1 (e.g. 7813). In the final control task, the participants were presented with two pairs of symbols (e.g. ✳✳ ✳✳) and had to indicate if the two pairs were the same (i.e. the same symbols in the same order). These three control tasks were alternated twice per functional run in a pseudo-randomized manner. The same functional and structural scanning sequences as those used for GK were used in this study.

All data pre-processing and statistical analysis was performed using SPM96. Each participant's data were pre-processed as follows. First, all the functional images from every run were realigned to the first image acquired during the first run. Then, the high-resolution anatomical image for each participant was spatially normalized to the Talairach atlas (Talairach and Tournoux, 1988) using only affine transformations, and these normalization parameters were applied to all of the realigned functional images. Spatial smoothing was applied to the realigned, normalized functional images with a three- dimensional, 10 mm full width at half maximum Gaussian kernel.

The statistical analysis was first performed separately for each individual and then again on the group data for the controls. For each analysis, temporal smoothing and mean magnetic resonance signal normalization (ANCOVA) were applied. For the group analysis we used a voxelwise significance threshold of 0.001 corrected for multiple comparisons to $P < 0.05$ with the standard SPM96 spatial extent correction. For the single subject analyses a voxelwise threshold of 0.005 was corrected for multiple comparisons to $P < 0.1$ (spatial extent correction) due to the lower degrees of freedom available in these analyses. Contrasts were defined as simple subtractions comparing the number comparison task with each of the three control conditions.

In the group analysis of the controls there were two main areas of activation: (1) a bilateral parietal region including the left superior parietal lobe, left precuneus and right precuneus extending from Talairach $z = 48$ to Talairach $z = 72$; and (2) an area in the left medial frontal gyrus. Similar to these findings, the single subject analysis for JS resulted in significant activation in the left superior parietal lobe extending from $z = 60$ to $z = 76$ as well as activation

in the right paracentral lobule directly bordering on the precuneus extending from $z = 48$ to $z = 76$. The comparison of the peak activation results between the control participants and JS suggests that the number comparison process for both is located in the same parietal location. However, if we compare the spread of activation, JS did not exhibit activation in the more inferior areas of the parietal lobe but the controls did. Furthermore, JS exhibited activation in the more superior areas of the parietal lobe but the controls did not. Although such a subtle shift cannot be quantified statistically, these descriptive results suggest a possible shift in JS's number comparison processing to more superior areas away from the areas that the MRS scan indicated as being deficient. This evidence supports the inference that map expansion has occurred in JS.

Discussion

The two cases discussed above have shed light on the issues involved in adding functional neuroimaging as a convergent method in the study of neuroplasticity in single cases. In the past, neuropsychological case studies have only included behavioral assessments and, when possible, structural imaging. Recently, however, it has been possible to add functional neuroimaging to these studies, but this technique has been utilized within the traditional framework of comparing patients with controls. These studies can be more informative than studies including only behavioral methods, but we believe that there is a better way to incorporate functional neuroimaging into studies of recovery of function. Due to convergent neuroimaging and behavioral findings, our studies of GK and JS were slightly more informative than they would have been had we used only behavioral methods. As we have pointed out, however, these studies are not without some ambiguity in the interpretation of the functional neuroimaging results that are directly tied to the use of the traditional comparison approach. Specifically, GK's recovered language processing could be the product of either homologous area adaptation or compensatory masquerade, or some combination of the two that might also include processing by perilesional areas. Similarly, it is difficult to quantify a spatial shift of processing in JS with the comparison approach. We will now turn our attention to discussing the methodological issues involved in using functional neuroimaging in patient studies based on our particular experience with these two patients as well as reports in the literature, striving along the way to point out many of the advantages to using an online approach for future studies.

Practical issues to be considered

Statistical power and task selection should be the first considerations in any neuroimaging design with a single case. There are a couple of reasons to consider them. Because the field of human brain mapping is relatively new, the cognitive process of interest may not have been targeted in

previous imaging studies, and it can be difficult to predict the success of a new design. In such cases it is tempting to throw the proverbial 'kitchen sink' at a case to be sure of finding something interesting. We suggest instead that investigators look for the fewest task combinations that will yield interesting results. Instead of several tasks and several controls, we suggest that investigators use one task of interest and as few control tasks as possible.

The logic behind this suggestion assumes that scanning time is limited. We believe that maximizing statistical power for a simple design is more useful than collecting few data in numerous conditions. To select a good simple design, it may be necessary to do extensive piloting. Behavioral piloting with the patient is necessary, but neuroimaging piloting with control participants should also be carried out prior to scanning the patient. It may be tempting to choose the flexibility of an event-related functional MRI design rather than a block design. However, block designs usually have much more statistical power than event-related designs (Aguirre *et al*., 1999). Furthermore, block designs are potentially better suited for skill training designs because practice–block is usually the unit of analysis when fitting power functions to reaction time data.

The ideal of a simple, focused, and powerful design might be hard to obtain. Yet we believe it should always be kept in mind. For example, when planning our study of JS, previous functional neuroimaging data for the number comparison task were mixed, and there were questions about the appropriate control task (Deheane *et al*., 1996; Rickard *et al*., 2000). So, we used three control tasks in our study. This resulted in fewer conditions for each task in each scanning run. In this case it could have affected power, but given the earlier ambiguities we believed it was a reasonable trade-off. Further-more, we thought the effect on power would not be too adverse because we could use short presentation times for these tasks (1200 ms). Thus, a large number of trials could be used in each block.

Two additional related issues concern functional neuro-connectivity and, because functional neuroimaging techniques depend on blood flow, the possibility of arterial reorganiza-tion. These are especially important when there seems to be perilesional activation. When perilesional activation occurs, it is best to assess whether the tissue is still functional and connected to undamaged regions. Also, following stroke or other acquired lesions, there may be arterial reorganization (Liu, 1988; Krupinski *et al*., 1994) and apparent perilesional activation might be due to an arterial artifact rather than any neural reorganization. Just as neuroimaging results with unimpaired participants can show artifacts due to a draining venous flow in an area of interest, results with patients can exhibit artifacts due to an artery in an unusual place (due to arterial reorganization). Assessing the connectivity of functionally related regions is fairly straightforward; reason-able inferences can be made using PET or diffusion magnetic resonance (Pajevic and Pierpaoli, 1999). Assessing arterial

changes post-lesion is more troublesome, and involves procedures that carry some risk (i.e. arteriography).

It is important to note that even if these issues are addressed there still may be problems with making inferences regarding perilesional activation in comparison designs. For example, in our study of GK's recovered language abilities we were able to determine that there were spared areas of functional tissue in his left hemisphere, some of which were connected to the rest of the brain, but we could not be sure that they were contributing to the processing in question.

Task selection

Some investigators have advocated that functional neuro-imaging of patients only be carried out with tasks they can perform above chance (Price and Friston, 1999). In general we agree, but there are cases where it can be fruitful to include tasks that cannot be performed above chance. We believe that the use of such tasks will be useful in cases in which later behavioral improvement is coupled with systematic changes in activation, and these changes can take many different forms. For example, in an online design it may be necessary to scan the patient during a task that they are initially unable to perform but where improvement is anticipated. Behavioral data from this first session may be nearly uninterpretable. On the other hand, if the patient is expending systematic effort, but unable to produce the desired behavioral output, the corresponding pattern of activation may reflect much of the necessary processing with the exception of a deficient and crucial mechanism. If this same patient improves behaviorally after training, there should also be systematic changes in the activation pattern, reflecting either an improvement in the crucial mechanism or a new and effective compensatory strategy. The interpretation of such changes can be guided by predictions based on studies of plasticity in skill learning (e.g. systematic expansion of a crucial cortical sector map) in normal subjects. (See the example in the following paragraph for a more concrete example.)

A more complex, but more informative, design is also possible using an additive factors approach. This can be done using task analysis to break a larger task or skill down into component processes (i.e. perceptual, motor, and various cognitive components) and then designing tasks that require differential contributions from these components during per-formance to see which tasks the patient can and cannot perform above chance. Then a small set of tasks is selected, each differing from the next by a single component process. The patient is scanned with these tasks (including some that cannot be performed) throughout training or recovery. This allows interpretations to be based on converging empirical evidence. It is not difficult to imagine, for example, the case in which the processing of interest involves subcomponents A, B, and C. These components can be assessed by tasks X, Y, and Z, respectively. The patient may be unable to do the processing of interest but is able to perform relatively well

in some subset of tasks. Using neuroimaging to track the changes in the task of interest as well as the three sub-component tasks will allow for inferences about which subcomponent's improvement leads to training-related gains. More specifically, say the patient can perform neither the processing of interest nor task Y but is able to perform tasks X and Z. It may be the case that with training, the patient develops the ability to do both task Y and the processing of interest. At the same time, a new area of activation becomes apparent or an existing area exhibits systematic change during scanning. In this case it could be inferred that subcomponent B typically is supported by the lesioned area and also that the reorganization of an area or recruitment of a new area has occurred to produce the recovered processing in question.

A simpler design, which does not break down the task into component processes, would only allow for tracking coupled changes in behavioral outcome and the associated neural plasticity without knowing the specific cognitive component process that had been improved by practice. In the simpler design, however, it may be too difficult to differentiate between recovery that is due to a strategy shift (i.e. compensatory masquerade) and recovery that is due to the reorganization or reassignment of a crucial mechanism (i.e. map expansion or homologous area adaptation). Finally, it is important to note that this is an oversimplified and ideal example; any assumptions regarding pure insertion in additive factors designs must be satisfied in the same way as expected in any previous use of additive factors studies using only behavioral measures. Given the past success of using additive factors methodology in behavioral studies of cognitive pro-cessing, we believe useful inferences are possible from less clear-cut situations as well.

In contrast, the additive factors approach used in a comparison design does not allow for strong inferences. For example, our study of GK's language function included a pseudoword reading condition that we knew he could not perform. It was included to compare any activation from this task with activation found during the reading of real words to see if there was any activation in common. Following additive factors logic, we hypothesized, one of two alterna-tives could be at play in GK's reading abilities. First, it could be the case that reading words and pseudowords utilizes overlapping processes except that pseudoword reading also requires some additional processing that GK was no longer able to perform. In this case, we would expect to see similar activation patterns whether GK was reading pseudowords or real words (with the exception of some additional areas needed for reading pseudowords). Alternatively, two distinctive mechanisms or processes could be utilized for reading the different types of stimulus. In this case we would expect that GK's activation pattern would be different in the two reading conditions. The results support the latter of these possibilities. Again, however, due to the comparison approach it is difficult to make strong inferences in this case because we were not looking at dynamic changes, just differences between a single case and a control group. An online approach

would allow us to be certain about the processing role of both the perilesional activation and the homologous area activation. Furthermore, tracking strategies in this study would have allowed us to determine if GK's recovered function was due to homologous area adaptation or compen-satory masquerade.

Finally, it may be the case that the patient will not be able to perform the task of interest but will be able to perform a similar task that requires some of the same processing. In this case we believe that it is reasonable to use a simplified task if it can be theoretically and/or empirically supported. For example, it was not possible to scan JS on his most impaired task (single digit multiplication) because his response times were often 30 s or more (i.e. outside the temporal window useful in functional MRI). Instead, we used the numerical comparison task, on the theoretically and empirically supported expectation that both tasks involved intersecting cognitive processes (i.e. the representation of numerical magnitudes).

Tracking cognitive strategies

The final practical issue we want to address involves strategy switches, which have also been troublesome for interpreting behavioral studies of skill learning. In our overview of current skill learning theory, we mentioned that skill learning might involve improvement in a single process or depend on the switch from a resource-intensive strategy to another more efficient one. The same is true for recovery of function in patients through compensatory masquerade. This possibility warrants attention in planning an online study of neuronal plasticity. Specifically, changes in activation patterns could be due to recruitment of new areas that compensate for defective processes or could be due to a strategy shift. This issue is directly related to the three theories of skill leaning that were discussed above. Specifically, the acquisition of a skill can be associated with the speed up or consolidation of a single process or could be the product of a strategy shift from a resource-intensive algorithm to a more efficient strategy such as memory retrieval. Recovery of processing may follow a similar path or may be enabled by a backward shift in processing from memory retrieval to a more resource-intensive process (e.g. Hittmair-Delazer *et al.*, 1994). If recovery does involve strategy shifts, issues regarding any possible parallel processing of strategies will become important and data regarding cognitive processing may greatly aid in the interpretation of patterns of activation. There are two ways to handle this issue. Patients can be specifically instructed to use a particular strategy and then behavioral measures can be used to verify the use of the prescribed processing. Alternatively, strategy reports can be collected from the patient. For a discussion on ways of tracking strategies, see Ericsson and Simon (1993) or any of the skill theories discussed previously.

Table 2. Summary of all possible results from comparison and online designs for studying neuroplasticity in single cases. Each outcome is presented with possible confounds to be considered during the design phase as well as the type of plasticity finding that such an outcome can be used to support

Possible outcomes	Possible confounds	Possible plasticity finding
Comparison approach		
No performance or activation differences	Power	No
No performance differences but activation differences	Pre-morbid strategy difference, perilesional activation	All except map expansion
Performance differences but no activation differences	Power, perilesional activation	All except map expansion
Performance and activation differences	Perilesional activation	All except map expansion
Online approach		
No behavioral improvement and no activation changes	Power, inadequate training	No
No behavioral improvement with activation changes	Inadequate training	All types
Behavioral improvement and no activation changes	Power	Unclear
Behavioral improvement and activation change	None	All types
Behavioral deterioration and activation change	None	All types but maladaptive
Behavioral deterioration and no activation change	Inappropriate training	Unclear

Substantive issues to be resolved

The critical issue in using functional neuroimaging in single case studies of neuronal plasticity is to produce a design in which the results will be unambiguous. Hence, investigators should consider possible outcomes during planning. We define a comparison approach as any study that compares experimental results from a patient or group of patients with unimpaired control participants in the same experimental tasks. The following critiques hold regardless of whether the comparisons are quantified by a statistical test or are more descriptive in nature. In contrast, online studies dynamically track behavioral and activation changes across partial or full recovery of a skill. This section outlines the full range of possible outcomes for both the online and comparison approaches. A summary of these outcomes is presented in Table 2 and warrants two general comments. First, notice that even if all the possible confounds can be addressed with a particular outcome in a comparison design, it is still difficult to make a case for plasticity in the form of map expansion. Imaging the patient only once and comparing the patient's activation profile with a control group makes it difficult to compare the size or spatial extent of activation across participants. In contrast, online designs allow for inferences regarding these possibilities. The second general comment concerns the ability to understand perilesional activation. In comparison designs, perilesional activation is quite troublesome, but in online designs we can predict that there will be activation changes in these areas to the extent to which they are involved in the patient's performance. We will discuss these issues in more detail below.

Comparison approach outcomes

We begin our discussion of possible outcomes by focusing on comparison approaches. There are four outcomes, produced by all combinations of significant or null behavioral or neuroimaging results. First, there could be neither performance nor activation differences between the patient and the controls. Assuming adequate power, this would suggest that processing is not affected by the lesion. It is

rarely an interesting result, so investigators are unlikely to design a study in which this is a possible finding. We include it here for completeness.

Second, there could be null performance differences but significant activation differences between the patient and the controls. This outcome does not necessarily imply plasticity or functional recovery. Activation differences could be due to a strategy difference (either pre-morbid or compensatory) between the patient and the controls that makes the patient's performance appear normal. Thus, strategy report measures should be collected to try to rule out this interpretation. Activation differences could also be due to a general blood flow artifact caused by arterial reorganization.

A recent study (Price *et al.*, 1999) focused on a patient with a lesion which included a left frontal area which was activated in unimpaired controls making semantic similarity judgements. The patient was not obviously impaired in the task and activated a similar network of areas as the controls, except for the damaged left frontal area. The authors argued that these results suggested that the left frontal area is superfluous for this task. However, without pre-morbid or recovery data from the patient or some sort of strategy report, the possibility remains that compensation strategies were developed following the lesion. It is well documented that most, if not all, of the recovery of function occurs in the first 6 months post-insult (Choi *et al.*, 1994; Katz *et al.*, 1999; Nudo and Friel, 1999; Thulborn *et al.*, 1999; Kertesz, 2000). Thus, it could be the case that the patient's ability was due to neural reorganization that occurred prior to testing. Although this study was not specifically focused on the recovery of function, it demonstrates many of the uncertainties that are inherent to a comparison design. See the discussion above for a similar problem in our own comparison study of patient GK regarding the interpretation of perilesional activation.

The third outcome is significant performance differences but null activation differences between the patient and the controls. Several interpretations are possible. First, the patient could be using a different strategy but recruiting the same neuronal network. Present research on plasticity and skill

learning has yet to address the relationship between strategy selection and activation patterns. Second, the neuroimaging design might have insufficient statistical power for a single case. A group analysis of neuroimaging data (from the controls) is more powerful than a single subject analysis (for the patient). Third, the patient may be using a typical but damaged network which is not processing with normal efficiency or the damaged network may have undergone some reorganization (i.e. map expansion). This may be the case with JS, but it is difficult to make such a quantitative argument with a comparison study. Specifically, with JS the peak of activation seems to be the same for him and the controls but the geometric center of JS's region of activation seems to be shifted superiorly. This finding suggests that the neural topography of this simple numerical processing shifted over time to use territory (i.e. superior parietal cortical region) that is typically used for more complex numerical processing (cf. Rickard *et al*., 2000). Unfortunately, it is difficult to test this difference statistically or to make strong claims about the shift being due to plasticity unless it is possible to observe this change with repeated activation studies. We believe that online designs will enable this type of inference because any shift in processing should result in a detectable shift in the pattern of activity.

The fourth outcome is significant performance and activation differences between the patient and the controls. The simplest interpretation is that different processes are used by the patient, which may or may not involve map expansion, homologous area adaptation or compensatory masquerade. It would be difficult to make strong inferences in favor of any type of plasticity without strategy data from both the patient and the controls. Even with strategy data, arterial reorganization artifacts could lead the investigator into spuriously thinking that a perilesional area is crucial to the recovered processing when it is not involved. The most troublesome problem with making inferences in this case is the fact that there are no data regarding pre-morbid behavioral and neural activation baselines for the patient to demonstrate and quantify any change that may have occurred in the single case. Without any data prior to injury concerning how the patient performed on these tasks and what cortical areas were involved, comparisons cannot be made concerning how much change may have occurred at both the cognitive and neural levels.

Online studies

Now we turn to online studies. There are six possible outcomes, produced by all combinations of significant or null neuroimaging results and improvement, deterioration, or no change in behavioral performance. Some outcomes are troublesome, but one in particular allows strong conclusions regarding neuronal plasticity.

The first outcome is no behavioral change and no activation changes across training. This reflects one of the risks of the online design, although in some cases one might infer that

the task or skill involved cannot be recovered. Null results might also be due to training that was too short or otherwise ineffective. Careful thought should be given to the training regimen and again it may prove useful to consult previous investigations from the behavioral skill learning literature regarding the factors that affect training and the extent to which transfer of training can be expected. Of course, it should be noted that completely null results could just be due to low statistical power.

Second, there might be null performance changes but significant activation changes. Given that behavioral measures are usually more powerful, this outcome might seem implausible. However, skill learning theories allow learning in the absence of performance improvement at the beginning of skill acquisition and during strategy changes, both times when the processes for more effective performance are being set up. Interpretation depends on the particular change in activation patterns, although to make any case for plasticity, it would be necessary to argue that there would have been behavioral changes had training continued. That is to say that practice was too short to allow for improvement, but this argument would have to be considered in relation to the particular training program. If the training was carried out for a significant period this would be a difficult argument to make. If the changes in activation excluded any new areas or areas different from those found in previous studies (or from controls), it would suggest a subtle reallocation of processing resources indicating possible map expansion but perhaps not a strategy shift or compensatory masquerade. On the other hand, if a completely different pattern of activation emerged, it might be easier to argue for compensatory masquerade because it seems more likely that new (i.e. non-homologous) areas would be recruited when an atypical strategy is being employed. In either case it is important to assess possible strategy shifts. At present there are few data suggesting how a cognitive strategy change is manifested in the brain. In general, early studies regarding this issue suggest that cognitive strategy differences are accompanied by activation intensity differences between areas in a distributed cortical network underlying a skill, as well as differences in the set of areas that make up these networks (Burbaud *et al*., 2000; Reichle *et al*., 2000). These findings are consistent with earlier results from dichotic listening experiments (e.g. Gordon, 1980), from other studies regarding goal instantiation (Koechlin *et al*., 2000), and from some work looking at cortical changes in the motor cortex with the serial reaction time task (Pascual-Leone *et al*., 1994; Zhuang *et al*., 1997). Furthermore, as the relationship between neuronal changes and skill learning is better delineated, we will be able to make better predictions regarding the possible outcomes of online designs.

The third outcome is significant behavioral improvement but null activation changes. Low statistical power is most likely to lead to this outcome. Although it may be possible for behavioral change to occur without concomitant activation

changes, there is no evidence for such a finding in the early neuroimaging studies of skill learning.

The fourth and best outcome is behavioral improvement and significant activation changes. As we have advocated, this would be the clearest demonstration of neuronal plasticity and is the main advantage of the online approach. Furthermore, training-related changes in imaging results would permit the identification of areas that are important in functional recovery. Systematic imaging changes should also delineate the extent to which there are consistencies in the recovery of patients with similar injuries as well as consistencies in recoveries that are observed in patients with different types of lesion and in different cortical areas. It is important to note that strategy reports will again be necessary to make strong inferences regarding what type of plasticity has occurred. For example, strategy reports will be crucial for differentiating between cases of compensatory masquerade and map expansion or homologous area adaptation involving the same cognitive strategy (i.e. same cognitive strategy carried out by different cortical processing areas). As we have alluded to previously, this outcome also allows investigators to sidestep issues of perilesional activation and arterial reorganization. For example, if a perilesional area is involved in recovered processing, it should show training-related changes. More generally, to the extent that areas are necessary (or at least useful) for processing in a certain domain, there should be learning-related changes in these areas in the form of correlations with behavioral data, or, better yet, significant trend components in activation data (across and within scanning sessions) that are similar to those found in the behavioral data. Although activation changes associated with the learning of new skills have been demonstrated, activation changes related to training in a highly learned skill have not been established, but training-related behavioral changes are known to occur. We speculate that if activation changes do occur during further training of established skills, it may be possible to assess the differences between the areas necessary for unimpaired processing and those used in recovered function, as suggested by previous studies using comparison designs (Price *et al.*, 1999).

The last two outcomes are behavioral deterioration with or without activation changes. The interpretation is similar to the corresponding outcomes with behavioral improvement, but special attention should be paid to these maladaptive changes, which may indicate possible mechanisms of interference with the recovery of function. For example, maladaptive changes might be due to the recovery of another biologically more important function affecting performance in the process of interest (e.g. the crowding hypothesis; Teuber, 1974).

In summary, we have outlined two current lines of investigation using functional neuroimaging to study neuronal plasticity: skill learning and the recovery of function in patient populations. Our own case studies, two of which we described, have shown many of the advantages of applying neuroimaging techniques to the study of single cases, as well as some concerns. We have advocated a systematic way to study functional reorganization or recovery in patients, blending the results from the behavioral skill learning literature and from early neuroimaging studies of the brain mechanisms involved in skill learning. In both cases presented here, the online framework may have circumvented or overcome many concerns in these studies that reflect current issues regarding drawing inferences from neuroimaging data about the mechanisms of neuronal plasticity. In the study of patient GK, the online approach might have allowed us to differentiate if his recovery was due to homologous area adaptation or compensatory masquerade. Strategy reports would have allowed us to assess whether his recovery was due to the same cognitive strategy used by the unimpaired controls. The online approach might also have delineated the extent to which GK's perilesional activation was involved in his recovered processing. Dynamic changes in perilesional activation across GK's recovery would have provided strong evidence that his abilities were not the product of only right hemisphere processing.

In our study of patient JS, the online approach might have allowed us to quantify statistically the subtle map expansion that we have speculated about. With JS, the online design would be much harder to implement because of the developmental nature of his deficit. Early detection might have been entirely impossible. It may, however, be possible to document JS's inability to learn these facts with an online design, and this is a topic for further research with developmental cases. Finally, it is important to note that it would be entirely possible with an online design to document subtle map expansion with patients who have other etiologies.

Although functional neuroimaging has already greatly aided the neuropsychological study of neuronal plasticity related to the recovery of function in patients, we have just begun to scratch the surface of what is possible with these techniques. More clever experimental designs with these techniques will continue to further our ability to make inferences regarding neuronal plasticity in the study of patients. We present the online approach as a step towards this goal.

References

Aguirre GK, D'Esposito M. Experimental design for brain fMRI. In: Moonen CTW, Bandettini PA, editors. Functional MRI. Berlin: Springer, 1999: 369–80.

Anderson J. Knowledge representation. In: The architecture of cognition. Cambridge: Harvard University Press, 1983: 45–84.

Anderson JR. Rules of the mind. Hillsdale: Lawrence Erlbaum, 1992.

Binder J. Functional magnetic resonance imaging. Language mapping. Neurosurgery Clinics of North America 1997; 8: 383–92.

Bryan WI, Harter N. Studies on the telegraphic language: The acquisition of a hierarchy of habits. Psychological Review 1899; 6: 345–75.

Buonomano DV, Merzenich MM. Cortical plasticity: From synapses to maps. Annual Review of Neuroscience 1998; 21: 149–86.

Burbaud P, Camus O, Guehl D, Bioulac B, Caille JM, Allard M. Influence of cognitive strategies on the pattern of cortical activation during mental subtraction. A functional imaging study in human subjects. Neuroscience Letters 2000; 287: 76–80.

Chochon F, Cohen L, van de Moortele PF, Dehaene S. Differential contributions of the left and right inferior parietal lobules to number processing. Journal of Cognitive Neuroscience 1999; 11: 617–30.

Choi SC, Barnes TY, Bullock R, Germanson TA, Marmarou A, Young HF. Temporal profile of outcomes in severe head injury. Journal of Neurosurgery 1994; 81: 169–73.

Chollet F, DiPiero V, Wise RJS, Brooks DJ, Dolan RJ, Frackowiak RSJ. The functional anatomy of motor recovery after stroke in humans: A study with positron emission tomography. Annals of Neurology 1991; 29: 63–71.

Connolly AJ, Nachtman W, Pritchett EM. Key Math Diagnostic Arithmetic Test. Circle Pines, MN: American Guidance Services, 1976.

Crossman RRFW. A theory of the acquisition of speed-skill. Ergonomics 1959; 2: 153–66.

Dehaene S, Tzourio N, Frak V, Raynaud L, Cohen L, Mehler J et al. Cerebral activations during number multiplication and comparison: A PET study. Neuropsychologia 1996; 34: 1097–106.

Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased cortical representation of the fingers of the left hand in string players. Science 1995; 170: 305–7.

Ericsson KA, Simon HA. Protocol analysis: Verbal reports as data. Cambridge: MIT Press, 1993.

Fitts PM. Perceptual-motor skill learning. In: Melton AW, editor. Categories of human learning. New York: Academic Press, 1964: 243–85.

Gordon H. Degree of ear asymmetries for perception of dichotic chords and for illusory chord localization in musicians of different levels of competence. Journal of Experimental Psychology: Human Perception and Performance 1980; 6: 516–27.

Grafman J, Christen Y, editors. Neuronal plasticity: Building a bridge from the laboratory to the clinic. Berlin: Springer, 1999.

Grafman J, Litvan I. Evidence for four forms of neuroplasticity. In: Grafman J, Christen Y, editors. Neuronal plasticity: Building a bridge from the laboratory to the clinic. Berlin: Springer, 1999: 131–9.

Grafman J, Rickard TC. Acalculia. In: Feinberg TE, Farah MJ, editors. Handbook of neuropsychology. Amsterdam: Elsevier, 1996: 415–31.

Grafman J, Passafiume D, Fagliono P, Boller F. Calculation disturbances in adults with focal hemispheric damage. Cortex 1982; 18: 37–50.

Healy AF, Bourne LE Jr. Learning and memory of knowledge and skills. Thousand Oaks: Sage, 1995.

Heiss WD, Kessler J, Karbe H, Fink GR, Pawlik G. Cerebral glucose metabolism as a predictor of recovery from aphasia in ischemic stroke. Archives of Neurology 1993; 50: 958–64.

Hittmair-Delazer M, Semenza C, Denes G. Concepts and facts in calculation. Brain 1994; 117: 715–28.

Humphreys GW, Price CJ. Cognitive neuropsychology and functional brain imaging: Implications for functional and anatomical models of cognition. Acta Psychologica 2001; 107: 119–53.

Kaplan EF, Goodglass H, Weintraub S. The Boston Naming Test. Boston: Lea & Febiger, 1983.

Karbe H, Thiel A, Weber-Luxenburger G, Herholz K, Kessler J, Heiss WD. Brain plasticity in poststroke aphasia: What is the contribution of the right hemisphere? Brain and Language 1998; 64: 215–30.

Karni A, Meyer G, Jezzard P, Adams MM et al. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature 1995; 377: 155–8.

Katz N, Hartman-Maeir A, Ring H, Soroker N. Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. Archives of Physical Medicine and Rehabilitation 1999; 80: 379–84.

Kay J, Lesser R, Coltheart M. Psycholinguistic Assessment of Language Processing in Aphasia (PALPA). Hove: Lawrence Erlbaum, 1992.

Kertesz A. Behavioral and cognitive disorders. In: Baskin DS, Yatsu FM, editors. Prognosis of neurological disorders. New York: Oxford University Press, 2000: 610–22.

Koechlin E, Corrado G, Pietrini P, Grafman J. Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. Proceedings of the National Academy of Sciences 2000; 97: 7651–6.

Krings T, Topper R, Foltys H, Erberich S, Sparing R, Willmes K et al. Cortical activation patterns during complex motor tasks in piano players and control subjects. A functional magnetic resonance imaging study. Neuroscience Letters 2000; 278: 189–93.

Krupinski J, Kaluza J, Kumar P, Kumar S, Wang JM. Role of angiogenesis in patients with cerebral ischemic stroke. Stroke 1994; 25: 1794–8.

Levy LM, Reis IL, Grafman J. Metabolic abnormalities detected by 1H-MRS in dyscalculia and dysgraphia. Neurology 1999; 53: 639–41.

Liu HM. Neovasculature and blood–brain barrier in ischemic brain infarct. Acta Neuropathologica 1988; 75: 422–6.

Logan GD. Toward an instance theory of automatization. Psychological Review 1988; 95: 492–527.

McCloskey M, Lindemann AM. MATHNET: Preliminary results from a distributed model of arithmetic fact retrieval. In: Campbell JID, editor. The nature and origins of mathematical skills. Amsterdam: Elsevier, 1992: 365–409.

McCloskey M, Caramazza A, Basili A. Cognitive mechanisms in number processing and calculation: Evidence from dyscalculia. Brain and Cognition 1985; 4: 174–96.

Merzenich MM, Kaas JH, Wall J, Nelson RJ, Sur M, Felleman D. Topographic reorganization of somatosensory areas 3b and 1 in adult monkeys following restricted deafferentation. Neuroscience 1983; 8: 33–55.

Newell A, Rosenbloom PS. Mechanisms of skill acquisition and the law of practice. In: Anderson J, editor. Cognitive skills and their acquisition. Hillsdale: Erlbaum, 1981: 1–55.

Nudo RJ, Friel KM. Cortical plasticity after stroke: Implications for rehabilitation. Revue Neurologique 1999; 155: 713–7.

Nudo RJ, Milliken GW. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. Journal of Neurophysiology 1996; 75: 2144–9.

Pajevic S, Pierpaoli C. Color schemes to represent the orientation of anisotropic tissues from diffusion tensor data: Application to white matter fiber tract mapping in the human brain. Magnetic Resonance in Medicine 1999; 42: 526–40.

Pascual-Leone A, Grafman J, Hallett M. Modulation of cortical motor output maps during development of implicit and explicit knowledge. Science 1994; 263: 1287–9.

Pascual-Leone A, Nguyet D, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. Journal of Neurophysiology 1995; 74: 1037–45.

Price CJ, Friston KJ. Scanning patients with tasks they can perform. Human Brain Mapping 1999; 8: 102–8.

Price C, Warburton W, Swinburn K, Wise R, Frackowiak R. Monitoring the recovery of aphasia using positron emission tomography. Journal of Cerebral Blood Flow and Metabolism 1995; 15(Suppl. 1): 696.

Price CJ, Mummery CJ, Moore CJ, Frackowiak RSJ, Friston KJ. Delineating necessary and sufficient neural systems with functional imaging studies of neuropsychological patients. Journal of Cognitive Neuroscience 1999; 11: 371–82.

Proctor RW, Dutta A. Skill acquisition and human performance. Thousand Oaks: Sage, 1995.

Rae C, Lee M, Dixon R et al. Metabolic abnormalities in developmental dyslexia detected by ^{1}H magnetic resonance spectroscopy. Lancet 1998; 351: 1849–52.

Rapcsak S, Beeson PM, Rubens AB. Writing with the right hemisphere. Brain and Language 1991; 41: 510–30.

Raven JC. Standard progressive matrices. London: H.K. Lewis & Co., 1958.

Reichle ED, Carpenter PA, Just MA. The neural bases of strategy and skill in sentence–picture verification. Cognitive Psychology 2000; 40: 261–95.

Rickard TC. Bending the power law: A CMPL theory of strategy shifts and the automatization of cognitive skills. Journal of Experimental Psychology: General 1997; 126: 288–311.

Rickard TC, Romero SG, Basso G, Wharton C, Flitman S, Grafman J. The calculating brain: An fMRI study. Neuropsychologia 2000; 38: 325–35.

Sadato N, Pascual-Leone A, Grafman J, Ibanez V, Deiber M, Dold G et al. Activation of the primary visual cortex by Braille reading in blind subjects. Nature 1996; 380: 526–8.

Schlaug G, Jancke L, Huang Y, Steinmetz H. In vivo evidence for structural brain asymmetry in musicians. Science 1995; 167: 699–701.

Schmidt RA, Bjork RA. New conceptualizations of practice: Common principles in three paradigms suggest new concepts for training. Psychological Science 1992; 3: 207–17.

Talairach P, Tournoux J. A stereotactic coplanar atlas of the human brain. Stuttgart: Thieme, 1988.

Teuber HL. Why two brains? In: Schmitt FO, Worden FG, editors. The neurosciences: Third study program. Cambridge: MIT Press, 1974: 71–4.

Thulborn KR, Carpenter PA, Just MA. Plasticity of language-related brain function during recovery from stroke. Stroke 1999; 30: 749–54.

Viscuso SR, Anderson JA, Spoehr KT. Representing simple arithmetic in neural networks. In: Tiberghien G, editor. Advances in cognitive science, Vol. 2: Theory and applications. New York: Wiley, 1989: 141–64.

Weiller C. Imaging recovery from stroke. Experimental Brain Research 1998; 123: 13–7.

Weiller C, Ramsay SC, Wise RJS, Friston KJ, Frackowiak RSJ. Individual patterns of functional reorganization in the human cerebral cortex after capsular infarction. Annals of Neurology 1993; 33: 181–9.

Weiller C, Chollet F, Frackowiak R. Physiological aspects of functional recovery from stroke. In: Bogousslavsky J, Ginsberg M, Hennerici M, editors. Cerebrovascular disease. Oxford: Blackwell, 1997: 2057–67.

Zhuang P, Toro C, Grafman J, Mangonotti P, Leocani L, Hallett M. Event-related desynchronization (ERD) in the alpha frequency during development of implicit and explicit learning. Electroencephalography and Clinical Neurophysiology 1997; 102: 374–81.

Investigating cognitive neuroplasticity in single cases: lessons learned from applying functional neuroimaging techniques to the traditional neuropsychological case study framework

S. G. Romero, C. F. Manly and J. Grafman

Abstract

We summarize two case studies as a context for discussing the use of neuroimaging as a convergent methodology in the study of neuroplasticity in single subjects. Throughout this paper we argue for a different approach for including neuroimaging in these types of study. Previous case studies of neuroplasticity in patients (ours as well as others reported elsewhere) have added neuroimaging to the traditional neuropsychological framework of comparing patient results with matched control groups, and synthesized results through descriptions of anatomical and behavioral dissociations. This type of approach is referred to as the comparison approach. We advocate a different approach that builds on findings from previous behavioral skill learning research. Specifically, we propose adding neuroimaging throughout learning or recovery of the ability of interest and making inferences from systematic changes in activation topography and intensity that occur within the context of predicted behavioral changes. We dub this approach the online approach. This approach should allow future investigators to circumvent many of the interpretation pitfalls that are common in comparison studies.

Primary diagnosis of interest

Tumour, stroke, developmental disorder

Author's designation of case

GK, JS

Key theoretical issue

● Functional neuroimaging in single case studies

Key words: neuroplasticity; skill learning; functional magnetic resonance imaging; neuroimaging

Scan, EEG and related measures

fMRI; PET; TMS; MR spectroscopy; MR diffusion

Standardized assessment

GK: Psycholinguistic Assessment of Language Processing in Aphasia (PALPA), Boston Naming
JS: Key Math Diagnostic Arithmetic Test, Raven Standard Progressive Matrices

Lesion location

● GK: majority of left hemisphere
   JS: no lesion (i.e. developmental case)

Lesion type

GK: stroke
JS: developmental disorder

Language

English