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Preserved speech abilities and compensation following prefrontal damage

(neuroimaging/positron emission tomography/aphasia/recovery/lesion)

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ABSTRACT **Lesions to left frontal cortex in humans produce speech production impairments (nonfluent aphasia). These impairments vary from subject to subject and performance on certain speech production tasks can be relatively preserved in some patients. A possible explanation for preservation of function under these circumstances is that areas outside left prefrontal cortex are used to compensate for the injured brain area. We report here a direct demonstration of preserved language function in a stroke patient (LF1) apparently due to the activation of a compensatory brain pathway. We used functional brain imaging with positron emission tomography (PET) as a basis for this study.**

How the human brain recovers function following injury remains one of the most puzzling scientific mysteries. In particular, the recovery mechanism(s) that allows speech function after injury to brain areas critical to language has been debated for more than a century (1–3). In the past, researchers have sought to understand speech production deficits by examining patients with brain damage and trying to determine what the patients cannot do. The logic applied in these studies is as follows: if a brain area is damaged and a person cannot perform certain speech tasks, then the damaged area, in some way, participates in the lost functions. However, this approach does not provide a powerful methodology for determining how patients might be performing any preserved and/or recovered functions.

Recent positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies in normal subjects have characterized the functional anatomy of several speech tasks (4–8). These studies provide a unique context for the study of patients with speech production deficits. Utilizing this context, we have developed an approach to the study of compensation following injury. The unique feature of this approach is to determine which brain area is damaged in a patient and identify tasks that are known to activate that area in neuroimaging studies of normal subjects. By testing the patient on these tasks, preserved performance can be used as a predictor of tasks likely being accomplished by compensatory brain pathways. Then, neuroimaging can be used to determine these compensatory pathways. As a final step, additional behavioral testing can be conducted to determine task capabilities potentially using the compensatory pathways.

We report here a case study, of patient LF1, where we used this approach. As a basis for this study, we relied on the finding that a relatively small area in the left-inferior frontal cortex near Broca's area has been activated across many production tasks in normal right-handed subjects (8, 9). Patient LF1 sustained an ischemic stroke that included this portion of left frontal cortex. Using the approach outlined above, we identified preserved speech capabilities in LF1 and then identified the pathway activated during one task relying on this preserved function.

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MATERIALS AND METHODS

Behavioral Methods. Standard neuropsychological evaluation was conducted by a trained neuropsychologist (J.S.).

For more specific cognitive assessments, behavioral sessions outside of the PET scanner were used to collect the data presented in Tables 1 and 2. For these sessions, LF1 sat in front of a computer and responded to words presented one at a time. For each task, a list of single words (or parts of words) was presented on a computer monitor, and LF1 either (*i*) read the words or (*ii*) generated additional words that were in some way related to the presented words. For most of the generation tasks, the trials were self-paced and 20 trials were included per block. However, for the word reading tasks and some of the words-stem completion tasks, the trials came at a regular interval of 3.5 sec. For the tasks involving auditory stimulation, the cues were read to LF1.

Behavioral testing during the PET scanning session was similar and used a task LF1 was found to do quite well (see *Results* and *Discussion*). For each of three scans, LF1 was visually presented 20 individual word-stems (e.g., "Cou") and instructed to say aloud word completions (e.g., "Couple"). Word-stems were presented for 3 sec on a computer screen (one per 3.5 sec). All word-stems were unique three-letter combinations and have been used in previous studies (10). Three fixation scans, in which LF1 looked at a central cross hair, served as reference control scans.

PET Methods. Standard PET scanning methods were used in conjunction with the ^{15}O-labeled water bolus injection technique (11–14). Images were acquired on a Siemens 953B scanner with 31 transaxial slices and reconstructed using a Butterworth filter (order = 5, half frequency = 0.4 cycle per cm). The use of this filter results in images smoothed to 17-mm full width at half-maximum. All images were normalized for global blood flow and transformed to a standard stereotaxic space using an estimate of the AC–PC plane obtained from a lateral skull x-ray (15). This procedure, which has been done routinely in normal subjects, proved effective for placing patient LF1 in stereotaxic space. Informed consent was obtained prior to scanning in a manner approved by the Human Studies and the Radioactive Drug Research Committees of Washington University.

During three PET scans, LF1 performed word-stem completion tasks (see *Behavioral Methods*) which were compared,

Abbreviations: PET, positron emission tomography; fMRI, functional magnetic resonance imaging.

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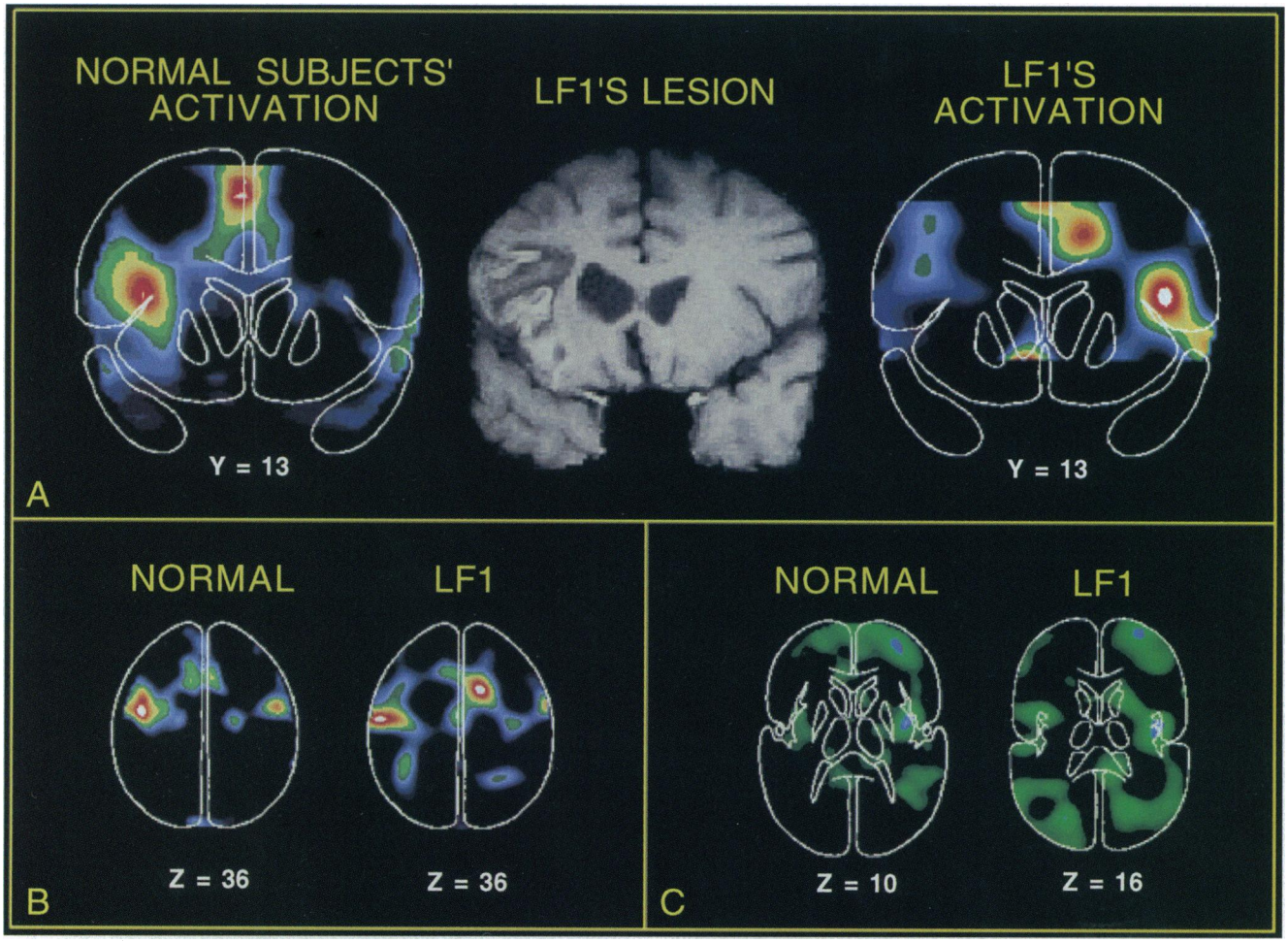

FIG. 1. PET data are displayed for normal subjects and for LF1 performing the stem completion task. MRI data for LF1 are also displayed. All PET data are without threshold with increasing intensity of color reflecting the greatest change in PET activation [white = increased rCBF, blue = decreased rCBF]. The right hemisphere is displayed on the right. Labels below each image represent the corresponding plane in the Talairach and Tournoux (1988) atlas (17). LF1's data revealed several predictable large responses. These responses were in areas similarly activated by normal subjects except that the prefrontal response was right-lateralized instead of left-lateralized. (*A*) (*Left*) PET data from normal subjects show left-inferior prefrontal cortex and anterior cingulate activation *increases*, extending into SMA. (*Center*) MRI data from LF1 reveal a lesion in the area of left-inferior prefrontal cortex. The lesion extends into frontal opercular insula but does not extend dorsal to the inferior frontal sulcus or anterior to the central sulcus. Raw rCBF images of LF1 (not shown) also indicate the lesion includes the portion of cortex activated by normal subjects. (*Right*) LF1's PET data show a right-lateralized activation in an area nearly homologous to the left-lateralized area activated by normal subjects. These data were collected across three separate PET scans. (*B*) Shown are horizontal sections of *increases* in PET activation. Both normal subjects (left section) and LF1 (right section) activate motor, premotor, and anterior cingulate/SMA with greater left-lateralized activation in motor cortex. (*C*) Shown are horizontal sections of *decreases* in PET activation. Both normal subjects (left section) and LF1 (right section) show activation reductions in right prefrontal cortex and right insular cortex suggesting that an insular pathway is suppressed. LF1's activation reductions are localized slightly superior to similar activations in the normal group image.

using subtractive methodology, to three fixation reference task scans. Such PET data reflect local changes in blood flow which are known to correlate with neural activity (14). The primary analysis of the PET data consisted of taking regions based on the left-lateralized prefrontal activation observed during word-stem completion in normal subjects (all right-handed and between the ages of 18 and 35) (10) (see Fig. 1) and determining the magnitude of that region's activation in the normal subjects and for LF1. The coordinates for the left region were obtained from an averaged image of all available normal subjects. A right-lateralized region was defined as the reflection of the left-lateralized region. The regions of interest were 14-mm spheres centered on the peak activation within left-prefrontal cortex and the exact homologue on the right side. Similar procedures involving this kind of regional analysis have been used previously (8, 10, 16).

The regions were first examined using the averaged image of the normal subjects. Then, to more closely examine the behavior of the regions, each of the normal subjects was examined individually and compared to LF1 (see Fig. 2). For the normal subjects' individual activations, within-subject averaged images were used that comprised four variants of the word-stem completion task. These variants were all similar in that subjects completed the stems to form words, and each variant was independently found to produce robust activation within the same left-prefrontal area (10, 16). Averaging across the variants increased the signal-to-noise properties of the normal-subject images. Using these data, t values were obtained for the right and left regions for each normal subject. These values were compared to the value obtained for LF1.

Additional activations outside of prefrontal cortex are reported for LF1 which correspond to the peak locations of the activations. The t values (and P values, uncorrected for multiple comparisons) correspond to activations within 14-mm spherical regions defined on these peak locations.

RESULTS AND DISCUSSION

LF1's Case History and Neuropsychological Findings. LF1, a familial right-handed 72-year-old retired professional, was

Table 1. Cognitive testing of LF1: Initial testing

Cognitive task	Example: Of visual cue	Example: Of correct response	LF1's performance, %
Word reading			
Nouns	House	House	100
Verbs	Fly	Fly	100
Low-frequency exception	Deaf	Deaf	95
Low-frequency regular	Grape	Grape	100
Read noun after 3-sec delay	House	House	100
Word generation			
Verbs for nouns	House	Build	15–30
Nouns for verbs	Eat	Cake	40
Synonyms	Baby	Infant	40
Opposites	Hot	Cold	60
Rhymes	Foil	Boil	0
Word-stem completion	**Cou**	**Courage**	**85–90**

For each of the word reading and word generation tasks that LF1 completed, an example of a cue that he viewed is shown. Typical responses expected of normal subjects are also shown. For example, for the "verbs for nouns" task LF1 saw words such as "House" and tried to come up with verbs like "Build." The word-stem completion task (in boldface type) was performed surprisingly well considering the location of LF1's lesion.

brought into the hospital after waking up with speech difficulties and general confusion. Clinical evaluation, including computerized tomography and MRI, revealed a stroke damaging portions of left-inferior frontal cortex. MRI did not reveal lesions in any other brain areas including the temporal lobes (Fig. 1).

Neuropsychological testing began 1 month after the stroke. At this time, LF1 was well oriented, attentive, and interested in the testing procedure. LF1 exhibited little spontaneous speech but could respond to simple questions. When he spoke, his speech often contained normal grammar and syntax. He could repeat words, read words, and name most objects (34 of 36 correct on confrontational naming). LF1 had difficulties on many complex speech production tasks and tasks sensitive to perseveration errors [e.g., Wisconsin Card Sorting Test and Stroop Test (18)]. LF1 showed remarkably preserved abilities in other areas. LF1 scored in the top 1 percentile on nonverbal tests of block design and visual reproduction, indicating he was an extremely intelligent individual with a premorbid IQ likely to be above 120. LF1 was severely impaired on the Thurstone verbal fluency task (18), a task requiring the generation of multiple words beginning with a single letter. This fluency impairment did not extend to a nonverbal design fluency task (19). Overall, LF1 presented as a mild nonfluent aphasic, scoring in the normal range on most subtests of the Boston Diagnostic Aphasia Exam. Follow-up testing 6 months after injury revealed milder, but still significant, speech impairments.

Cognitive Testing. To determine LF1's preserved and impaired speech abilities, a series of speech production tasks was administered. The results are shown in Table 1. Consistent with neuroimaging studies that have shown only minimal left-inferior prefrontal cortex activation during highly automated speech tasks (7, 20), LF1 could successfully read words. In contrast, LF1 failed on more demanding speech generation tasks, several of which are known to activate left prefrontal cortex in normal subjects (4, 5, 7). He was severely impaired at generating verbs given nouns, nouns given verbs, synonyms, opposites, or rhymes. Given the constellation of tasks that LF1 could not do, it appeared that his inability to generate words was not restricted to a single class of words. LF1 was asked to write verbs for presented nouns, which he also could not do (5%), indicating that his impairment generalized to multiple output modalities.

LF1 was, however, able to access words given partial words as cues. In this task, word-stems were presented (e.g., "Cou", "Hou") and LF1 generated word completions (e.g., "Couple", "House"). This was a surprising finding because normal subjects reliably activate left-inferior prefrontal cortex while doing this task (10, 21). Thus, word-stem completion presented itself as a candidate task that LF1 was completing using a compensatory brain pathway.

Functional Neuroimaging Results. Having isolated an island of preserved function, we next used PET functional neuroimaging techniques to determine which brain areas were active while LF1 performed the word-stem completion task. We hypothesized that LF1 might have been using brain areas in the right hemisphere to compensate. Past research, using both lesion-behavior analysis and imaging techniques, has suggested that the right hemisphere may perform atypical language function following stroke or when disconnected from the left hemisphere by resection of the corpus callosum (22–27). Alternatively, LF1 could have been using an insular cortex pathway to compensate. Raichle *et al.* (7) demonstrated that an insular pathway can be used for more automatic speech tasks in normal subjects, and past patient research has supported the possibility of multiple routes for speech production in aphasic patients (28). Perhaps LF1, who could do well-automated speech tasks such as word repetition, generalized the use of this pathway. This insular pathway is normally deactivated (right > left) while normal subjects perform the word-stem completion task while left prefrontal cortex is activated (10).

LF1 was scanned three times while performing the word-stem completion task. Compared to fixation reference conditions, activations similar to normal subjects (10) were observed in anterior cingulate cortex ($x, y, z = -3, 31, 12$; peak = 6.8%; $P < 0.05$), left motor cortex ($x, y, z = -59, -11, 40$; peak = 8.2%; $P < 0.03$), anterior cingulate extending into SMA ($x, y, z = 15, 9, 40$; peak = 12.6%; $P < 0.01$), left-lateral extrastriate cortex ($x, y, z = -37, -65, 1$; peak = 10.6%; $P < 0.05$), and medial extrastriate cortex/cerebellum ($x, y, z = 3, -61, 2$; peak = 7.5%; $P = 0.06$). Coordinates (x, y, z in mm) correspond to the stereotaxic coordinates of the Talairach and Tournoux brain atlas (17).

In addition, LF1 showed significantly increased activation in a right-lateralized region homologous to the left-lateralized area activated by normal subjects ($P = 0.01$) (Fig. 1). The peak activation of 7.6% (SE = 1.7%) was localized to $x, y, z = 40, 13, 16$ in right-inferior prefrontal cortex in LF1 as compared to $x, y, z = -37, 20, 11$ for normal subjects. The location of this activation was in frontal-opercular cortex at or near Brodmann's areas 44 and/or 45, medial to Broca's area. This

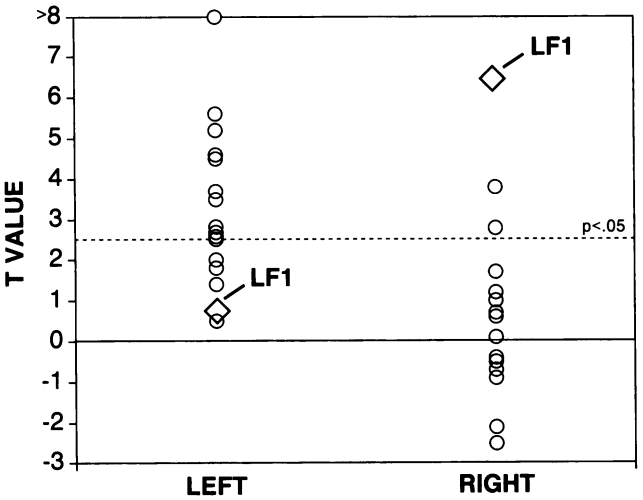

FIG. 2. *t* values for right and left prefrontal regions are displayed for each of 16 normal subjects and LF1. A dashed line represents a $P < 0.05$ cutoff for determining whether activations were significant in normal subjects. Many normal subjects showed significant activation on the left side, while only 2 of 16 showed significant activation on the right side. Moreover, LF1 showed activation only on the right side. His right response produced a *t* value [$t(2) = 6.4$, $P = 0.01$] considerably larger than that of any of the normal subjects.

activation was determined to be reliable using an unbiased region derived from normal subjects.

These findings suggest a pathway similar to that of normal subjects was activated except that, instead of left prefrontal cortex, LF1 activated right prefrontal cortex. LF1 also showed no activation of right insular cortex (rCBF change was negative) suggesting that he, like normal subjects, was not using this insular pathway as might have been hypothesized from the work of McCarthy and Warrington (28) and Raichle *et al.* (7) (Fig. 1).

We next addressed whether results similar to LF1's could be observed in subjects without left prefrontal damage. Mean activation in the right prefrontal region was examined in a group of 16 normal subjects. Activation in this right-lateralized region was near zero (<1% rCBF increase) indicating that, on average, normal subjects do not activate this area during stem completion. Moreover, examination of this region in the individual subjects showed that the largest activation produced a *t* value substantially less than that of LF1 (Fig. 2). The confidence interval at the 99% level for these normal subjects included a range far lower than the activation observed in LF1, either for magnitude or for within-subject *t* value. Furthermore, only two of the normal subjects showed peak activations that were slightly >4%. Thus, none of the normal subjects produced right prefrontal activation that was comparable to LF1 in either magnitude or reliability strongly suggesting that his functional anatomy was compensatory.

LF1 could complete the word-stem completion task 1 month after his injury, which suggests that this compensatory pathway was not a product of long-term neural reorganization. The finding that two normal subjects showed some minimal right prefrontal activation suggests a possible origin for LF1's compensation: perhaps some normal subjects, although predominantly using left prefrontal cortex, have a weak right prefrontal representation as well.

Behavioral Constraints on LF1's Compensatory Pathway. A natural question regarding the nature of LF1's compensatory pathway surrounds the domain of his preserved abilities. Although he could perform well on the word-stem completion task, he could not complete many other speech generation tasks. One difference between the word-stem completion task and tasks LF1 performed poorly was that LF1 was not supplied any words on the word-stem completion task. This difference caused us to hypothesize that LF1's word access difficulties might reside in an inability to purge or inhibit words once accessed. For example, when generating verbs for nouns, a whole word is given as a cue (e.g., "Dog") and the task is to say aloud a related verb (e.g., "Bark").

Perhaps LF1 failed at this task partly because he was unable to efficiently purge the word "Dog" and not because he could not retrieve "Bark." This could explain many of the previous results. On all reading tasks that he successfully performed, LF1 was given a word and asked to output *that* word. On the stem completion task, LF1 was not given a word but, rather, given a cue to help retrieve a word. On each generation task LF1 failed, a whole word was given and LF1 was asked to retrieve a *different* word. Typical neuropsychological fluency tasks, on which LF1 was severely impaired, require retrieving and producing multiple words in sequence.

To test the hypothesis that LF1 was impaired in purging accessed words, two new sets of word generation tasks were developed (see Table 2). The first set consisted of several tasks that provided cues for retrieving words but did not supply words themselves. The second set of tasks was designed to build upon the stem completion task (which LF1 could do) but change the task so that competing words were accessed as part of the cue. The results are shown in Table 2.

Consistent with the hypothesis that LF1's word generation difficulties reside in an inability to purge words once accessed, LF1 could do all of the tasks in set 1 and none of the tasks in set 2. Most striking was the finding that LF1 could generate single word-stem completions (e.g., given "Cou" he could say "Couple") but could not generate two words on the same task (e.g., given "Cou" he could say "Couple" but then he could not come up with "Cousin").

In this respect, LF1's compensatory pathway allowed him to access and output words but only in a limited manner. He did not have the flexibility to purge or inhibit already accessed

Table 2. Cognitive testing of LF1: Determination of LF1's access difficulties

Cognitive task	Example of cue	Example of correct response	LF1's performance, %
Set 1 tasks: Generation tasks that did not supply a word as a cue			
Word-stem completion	Cou	Couple	85–90
Single-letter word generation	G	Great	100*
Words from syllables	Auditory "pur"	Perfect	90
Set 2 tasks: Generation tasks that supplied competing words as part of the cue			
Whole word-stem completion	Courage	Couple	25
Words with same beginning	Auditory "purchase"	Perfect	0
Two word-stem completions	Dri	Drive, then Drink	20†

These tasks were formatted similar to the tasks in Table 1 except that two of the tasks presented auditory cues.

*On this task, LF1 produced several proper nouns as responses.

†LF1 was able to produce the first words in most cases (85%) but was unable to produce the second words.

words. This impairment might reflect an inability for his compensatory pathway to suppress more dominant responses while still allowing him to access words in noncompetitive situations (29).

Conclusions. We demonstrated that a stroke patient, LF1, activated a right-inferior prefrontal brain area during word-stem completion. This area is not typically activated by normal subjects performing word-stem completion and appears to be used by LF1 to compensate for his damaged cortex. These findings provide a starting point for future research. The right prefrontal pathway LF1 used during speech production may be strongly activated only when damage has occurred to left-lateralized brain areas more efficient for speech production. This area may be used during other kinds of tasks in normal subjects but is nonetheless sufficient to accomplish limited speech function in the damaged brain. If findings similar to LF1's are seen in other aphasic patients, these results can explain why aphasia is frequently incomplete and partial recovery can occur.

The approach we used to make these observations in LF1 can be used to study recovery of speech function in a wide range of patients as well as to study recovery outside the domain of speech function. In this respect, the most important aspect of the work on LF1 is not his particular findings but rather the explication of the approach used. Of central importance is that we sought to document his preserved speech functions, instead of trying solely to determine his impairments. This approach led us to a set of tasks in which it was likely that LF1 was using a compensatory brain pathway for performance. Functional neuroimaging was used to identify this potential compensatory pathway.

Our ability to favorably influence the recovery process will depend upon a more complete understanding of the neurobiological basis of speech production in normal subjects, the effects of injury, and possible routes to recovery. Functional brain imaging potentially provides an important tool for this work at all of these stages.

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