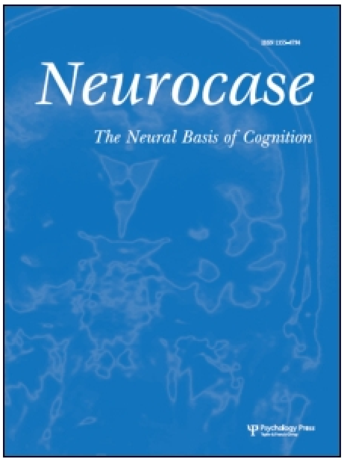

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A case study of long-term cognitive and social functioning following a right temporal lobectomy in infancy

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We present the rare case of an adult patient, FS, who had a right anterior temporal lobe resection during infancy to treat intractable epilepsy, and underwent a cognitive evaluation 19 years later. Given the paucity of literature on long-term outcomes for infants who receive neurosurgery for epilepsy, this case provides valuable information for both clinicians and patients. What little literature exists on infant and child surgical outcomes for epilepsy suggests a variable course, with several areas of possible cognitive and social difficulty. FS's assessment at the age of 21 revealed only mild difficulties with memory, sequencing, and visual imagery, and spared intellectual functioning, working memory, problem-solving and social cognition, along with a high level of socioeconomic functioning. Thus, the case of FS suggests that neurosurgery during infancy is not necessarily associated with large-scale cognitive impairment, and furthermore, that high levels of functioning both educationally and vocationally are possible after surgical treatment of epilepsy in infancy.

Keywords: Epilepsy; Infancy; Temporal lobe; Frontal lobe; Cognition.

INTRODUCTION

Very little is known about cognitive outcomes for individuals who have undergone large-scale neurosurgery at a very early age, as such events are extremely rare. Here we present data from a patient, FS, who underwent a right temporal lobectomy at just under 24 months of age, to treat intractable epilepsy. At the age of 21 years, despite having approximately one seizure per year and taking Topiramate, which is known to adversely affect cognition, FS exhibited remarkably intact cognitive abilities, despite some areas of difficulty. Her cognitive profile speaks to the resilience of the developing brain and its potential for plasticity.

Epilepsy and cognitive and social consequences

Chronic temporal lobe epilepsy has been associated with a number of cognitive impairments, including deficits in overall intellectual capacity, academic achievement, memory functioning, language, visuospatial skills, executive functioning and

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motor speed (Jokeit & Schacher, 2004; Oyegbile et al., 2004). These impairments are more likely and more pronounced if the onset of seizures is early in life, if the seizures are severe, and of high duration and frequency (Meador, 2002).

Deficits associated with epilepsy are not limited to cognitive functioning; there are also reports of enduring social deficits, although the literature is somewhat inconsistent. Anxiety, depression, psychosis and unusual personality traits such as moralism, humorlessness and paranoia have all been associated with temporal lobe epilepsy (Schulman, 2000). Frontal lobe epilepsy has also been associated with social cognitive deficits, in particular humour appreciation and facial expression decoding (Farrant et al., 2005), and frontal lobe involvement is common in temporal lobe epilepsy (Schulman, 2000). Damage to the right hemisphere may be particularly associated with social functioning deficits, according to a study comparing left and right hemispherectomy patients (Fournier, Calverley, Wagner, Poock, & Crossley, 2008).

Epilepsy surgery in adulthood

Neurosurgery is commonly used to treat epilepsy. The goal of surgery is to improve seizure control, since both falling over and tonic-clonic seizures can lead to secondary brain lesions and further cognitive impairment (Helmstaedter et al., 2004). Ideally, surgery would cause no further cognitive decline, and may even bring about cognitive improvement by enhancing the functioning of intact tissue (Helmstaedter et al., 2004). Nonetheless, research suggests that approximately 50–60% of surgery patients experience long-term declines in memory functioning post-surgery, regardless of the lateralisation of the tissue removal (Helmstaedter & Kockelmann, 2006; Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003). Seizure-freedom post-surgery has also been linked with better long-term outcomes, in particular, achieving full-time employment (Asztely, Ekstedt, Rydenhag, & Malmgren, 2007).

Epilepsy surgery in childhood and infancy

Children with epilepsy have been less frequently studied than adults (Ray & Kotagal, 2005), and even when children are studied, the inclusion of infants is rare. The lack of information about cognitive outcomes from such early life surgeries is likely due to the difficulty in studying such a population; pre- and post-surgery evaluations of cognition are difficult or impossible, making later life cognitive status difficult to link with the effects of surgery. In addition, cerebral changes early in life occur in a highly plastic environment, meaning that brain development may take a unique course, making it difficult to compare results from one person to another. That said, such information is useful for both neurosurgeons and parents of infants with epilepsy, when making decisions regarding treatment options.

Childhood onset of epilepsy has been associated with poorer long-term outcomes than later-life onset, including more cognitive deficits, abnormal neurological development, and smaller brain volumes (Hermann et al., 2002, 2006). The course of surgery in children with epilepsy appears to parallel adult outcomes, and may indicate a lower risk of memory deterioration, but more systematic research on long-term outcomes is needed to draw strong conclusions, given contradictory results within the literature (Lah, 2004).

One study investigating socioeconomic outcome in 60 children who underwent cortical resections in late childhood or early adolescence (M = 12.2 years, SD = 4.8), showed that seizure-freedom predicted better educational, vocational and interpersonal outcomes at follow-up (M = 7.6 years), although this group's level of functioning was still lower than expected for the general population (Keene, Loy-English, & Ventureyra, 1998). Other studies have shown similar deficits in child patients even when neurosurgery was successful with regard to seizure reduction. For example, researchers who examined cognitive outcome up to 2 years after temporal-lobe resection in child patients (M = 9.2 years of age) found no significant post-surgical cognitive improvements after cortical resections, even for those whose seizures were largely under control (Van Oijen et al., 2006). Another study examined 20 children between 7 and 14 years (M = 11.6, SD = 2.4) who became seizure-free following temporal lobectomies, and found that left-sided lobectomies were associated with verbal deficits, while right-sided lobectomies were associated with visual or figural deficits (Jambaque et al., 2007). Taken together, these studies suggest that for some child patients, there are long-term cognitive consequences of neurosurgery, despite good seizure control.

But what of patients who undergo surgery even earlier, in infancy? In infancy, epilepsy is more commonly associated with malformations than sclerosis (Bourgeois, 1998), increasing the chances of unusual brain development, and brain abnormalities have been linked to poorer cognitive outcomes (Hermann et al., 2006). In contrast, some research suggests that early onset is associated with better long-term cognitive outcomes (Griffin & Tranel, 2007), and may prevent much of the cognitive decline associated with epilepsy (Engel, 1999). So, again the picture is somewhat mixed. A study examining outcome in 31 children who had cortical resections of various types within the first 3 years of life (M = 18.3 months, range = 28 days to 36 months) found that, although the operation was largely successful in reducing seizures (i.e., 77% of children experienced a greater than 90% reduction in seizure frequency), neurological examinations 1 year post-surgery did not confirm any functional improvements in the seizure-free patients compared to their pre-surgery performance (Duchowny et al., 1998). Research that has examined more long-term consequences, however, has been more promising. Infants with intractable epilepsy (N = 15; M = 2.3 years, range = 5 months to 5 years) who underwent hemispherectomies were followed up approximately 4 years post-surgery were found to be seizure-free in 73% of cases, and there was no evidence of cognitive decline. The authors thus concluded that cognitive outcomes are better for infantile surgery as opposed to surgery later in childhood (Lettori et al., 2008).

There is a clear need for further research into neurosurgical interventions in infancy to determine the cognitive and social prognoses of these surgeries. After all, long-term cognitive and social functioning are some of the most important contributors of quality of life. Here we present a relevant case to contribute to this effort. FS is an important example of someone who had a right anterior temporal lobe resection during infancy, and was followed up at the age of 21. Her situation is unusual, both because of her very young age at surgery, and because of the opportunity to assess her cognitive and social functioning 19 years later.

PARTICIPANT

At the time of her assessment, FS was 21 years old and employed in an accounts-payable department while completing a training course after-hours to become a text editor. As an infant, she was diagnosed with epilepsy and experienced multiple seizures daily. At the age of 1 year and 8 months a calcified lesion was removed from her right temporal lobe. Because this surgery did not resolve her seizures, 4 months later, the remainder of her right anterior temporal lobe was removed. Following the surgery, FS was paralysed on the left side of her body for 7 days. Over the next 4 years, she underwent physiotherapy to regain mobility and strength, and speech therapy to re-learn speech sounds and develop her language skills.

A high-resolution magnetic resonance image (MRI) scan of her brain taken 1 year prior to her assessment indicated evidence of a right anterior temporal lobectomy, with residual gliotic change extending into the right frontal lobe, according to the neurologist's report. There was also evidence of widening of the right Sylvian fissure and prominence of the extra-axial fluid spaces over the right frontotemporal region. The anterior portion of the right hippocampus had been excised, and the middle and posterior regions exhibited evidence of gliotic change. Figure 1 presents slices from this scan, illustrating the extent of damage.

At the time of testing, FS reported poor strength, flexibility and coordination on her left side. Her seizures were largely under control, occurring approximately once per year. FS was taking Topiramate daily, for both seizure control and headaches, and Depo-Provera for treatment of endometriosis. She reported no depressed mood either at interview, or on the Depression, Anxiety and Stress Scales, a self-report measure of mood (Lovibond & Lovibond, 1995). She denied use of recreational drugs or tobacco, and consumed alcohol very rarely.

FS reported memory difficulties, including problems remembering the details of movies despite retaining the overall gist, and problems retaining multi-stage instructions at work. She also reported a short attention span and difficulties with sequencing, explaining that she was unable to re-organise a list of instructions in her mind, forcing her to follow them in the order they were presented to her. Additionally, FS described an inability to conjure mental visual imagery, and a life-long difficulty with mathematics.

HYPOTHESES

Given the variability among epilepsy patients, and the limited amount of information available on the long-term consequences of epilepsy surgery in

TABLE 1

FS's neuropsychological performance. Scores are scaled, unless indicated with an *, in which case raw scores are presented. References for norms are included

Domain	*Function*	*Scale*	*Sub-scale*	*Score**	*%ile*	*Range*	*Reference*
Intellectual Ability							
	Current IQ	WAIS-III	Full Scale IQ	101	53	Average	Wechsler, 1997a
	Current IQ	WAIS-III	Verbal IQ	101	53	Average	Wechsler, 1997a
	Current IQ	WAIS-III	Performance IQ	100	50	Average	Wechsler, 1997a
	Current IQ	WAIS-III	Verbal Comprehension Index	110	75	Average	Wechsler, 1997a
	Current IQ	WAIS-III	Percepual Organization Index	109	73	Average	Wechsler, 1997a
	Current IQ	WAIS-III	Processing Speed Index	96	39	Average	Wechsler, 1997a
	Current IQ	WAIS-III	Working Memory Index	80	9	Moderately Impaired	Wechsler, 1997a
Verbal Comprehension							
	Verbal Comprehension	WAIS-III	Vocabulary	14	90	Superior	Wechsler, 1997a
	Verbal Abstract Reasoning	WAIS-III	Similarities	10	50	Average	Wechsler, 1997a
	Crystallized IQ	WAIS-III	Information	12	75	Average	Wechsler, 1997a
Visuospatial Function							
	Copying	Rey Complex Figure	Copy	34/36*	>16	Average	Meyers & Meyers, 1996
	Visual Comprehension	WAIS-III	Picture Completion	8	25	Average	Wechsler, 1997a
	Visual Construction	WAIS-III	Block Design	15	95	Superior	Wechsler, 1997a
	Visual Abstract Reasoning	WAIS-III	Matrix Reasoning	12	75	Average	Wechsler, 1997a
Attention / Concentration							
	Working Memory	WAIS-III	Digit Span	8	25	Average	Wechsler, 1997a
	Visual Attention	Trail Making Test DKEFS	Visual Scanning	9	37	Average	Delis, Kaplan, & Kramer, 2001
Processing Speed							
	Processing Speed	Stroop DKEFS	Colour Naming	4	2	Severely Impaired	Delis, Kaplan, & Kramer, 2001
	Processing Speed	Stroop DKEFS	Word Reading	5	5	Moderately Impaired	Delis, Kaplan, & Kramer, 2001
	Motor Processing Speed	WAIS-III	Digit-Symbol	11	63	Average	Wechsler, 1997a
	Motor Processing Speed	WAIS-III	Symbol Search	8	25	Average	Wechsler, 1997a
	Motor Speed	Trail Making Test DKEFS	Motor Speed	10	50	Average	Delis, Kaplan, & Kramer, 2001
Verbal Memory							
	Immediate Recall	WMS-III	Auditory Immediate	13	9	Moderately Impaired	Wechsler, 1997b
	Delayed Recall	WMS-III	Auditory Delayed	16	23	Below Average	Wechsler, 1997b
	Recognition	WMS-III	Auditory Recognition Delayed	14	91	Superior	Wechsler, 1997b
	Immediate Recall	RAVLT	List A, all 5 trials	50/75*	38	Average	Schmidt, 1996
	Short Delay Recall	RAVLT	List A, after interference	9/15*	38	Average	Schmidt, 1996
	Long Delay Recall	RAVLT	List A, delayed recall	7/15*	7	Moderately Impaired	Schmidt, 1996
	Recognition	RAVLT	Recognition, List A	14/15*	38	Average	Schmidt, 1996

Visual Memory						
Immediate Recall	WMS-III	Visual Immediate	10	2	Impaired	Wechsler, 1997b
Delayed Recall	WMS-III	Visual Delayed	11	3	Impaired	Wechsler, 1997b
Short Delay Recall	Rey Complex Figure	Immediate Recall	23/36*	38	Average	Meyers & Meyers, 1996
Long Delay Recall	Rey Complex Figure	Delayed Recall	22/36*	24	Below Average	Meyers & Meyers, 1996
Recognition	Rey Complex Figure	Recognition Total Correct	21/24*	34	Average	Meyers & Meyers, 1996
Executive Function						
Phonemic Fluency	Verbal Fluency DKEFS	Letter	6	9	Moderately Impaired	Delis, Kaplan, & Kramer, 2001
Semantic Fluency	Verbal Fluency DKEFS	Category	7	16	Below Average	Delis, Kaplan, & Kramer, 2001
Cognitive Inhibition	Stroop DKEFS	Inhibition	1	1	Impaired	Delis, Kaplan, & Kramer, 2001
Concrete Problem Solving	Tower Test DKEFS	Total Achievement Score	9	37	Average	Delis, Kaplan, & Kramer, 2001
Abstract Problem Solving	WCST	Categories Completed	6*	>16	Average	Heaton et al., 1993
Task-switching	WCST	Perseverative Errors	6*	99	Superior	Heaton et al., 1993
Sequencing						
Sequence following	Trail Making Test DKEFS	Number Sequencing	9	37	Average	Delis, Kaplan, & Kramer, 2001
Sequence following	Trail Making Test DKEFS	Letter Sequencing	10	50	Average	Delis, Kaplan, & Kramer, 2001
Task-switching	Trail Making Test DKEFS	Number-Letter Switching	10	50	Average	Delis, Kaplan, & Kramer, 2001
Working Memory	WAIS-III	Arithmetic	6	9	Moderately Impaired	Wechsler, 1997a
Working Memory	WAIS-III	Letter-Number Sequencing	6	9	Moderately Impaired	Wechsler, 1997a
Narrative Sequencing	WAIS-III	Picture Arrangement	5	5	Moderately Impaired	Wechsler, 1997a
Social Cognition						
Mental Inference	Mind-in-the-Eyes	Total Score	25*	34	Average	Baron-Cohen, Wheelwright, Hill et al., 2001
Empathy	IRI	Perspective-taking	34*	99.9	Superior	Davis, 1980
Empathy	IRI	Empathic Concern	23*	82	Average	Davis, 1980
Empathy	IRI	Personal Distress	7*	31	Average	Davis, 1980
Social Skills	Autism Spectrum Quotient	Social Skills	3*	38	Average	Baron-Cohen, Wheelwright, Skinner et al., 2001
Communication Skills	Autism Spectrum Quotient	Communication	4*	14	Below Average	Baron-Cohen, Wheelwright, Skinner et al., 2001
Visual Imagery						
Imagination	IRI	Fantasy	9*	12	Below Average	Davis, 1980
Imagination	Autism Spectrum Quotient	Imagination	6*	1	Impaired	Baron-Cohen, Wheelwright, Skinner et al., 2001
Imagination	NEO PI-R Openness	Fantasy	13*	7	Moderately Impaired	Costa & McCrae, 1992

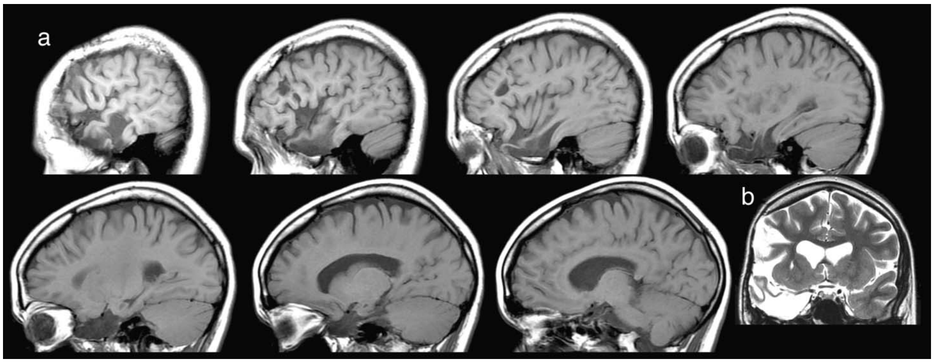

Figure 1. Slices from an MRI structural scan of patient FS conducted at 20 years. Part A shows sagittal slices from a T1 high resolution sequence, visualizing the extent of a right temporal resection. Part B shows a coronal slice from a T2-weighted fast spin echo sequence, illustrating right frontal tissue abnormalities (left is right).

infancy, it was difficult to predict what difficulties FS may have, beyond the difficulties she was reporting and those that commonly accompany temporal lobe epilepsy, taking Topiramate and Depo-Provera. Consequently, we administered a comprehensive battery of tests assessing the domains of intellectual ability, attention and concentration, processing speed, verbal and visual memory, executive functioning, sequencing ability, social cognition and visual imagery.

METHODS

Neuropsychological testing was conducted over two separate sessions, 3 weeks apart. The tasks administered are listed in Table 1, categorized by functional domain. The source for each task's norms is also listed in Table 1. Standard neuropsychological measures including the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III, Wechsler, 1997a), the Wechsler Memory Scales – Third Edition (WMS-III, Wechsler, 1997b), the Rey Auditory Verbal Learning Test (Rey, 1993; Schmidt, 1996), the Rey Complex Figure Test (Meyers & Meyers, 1996; Rey, 1993), the Wisconsin Card Sorting Test (WCST, Heaton, Chelune, Talley, Kay, & Curtiss, 1993), and the Delis-Kaplan Executive Function System (DKEFS, Delis, Kaplan, & Kramer, 2001) were administered, and will not be described in detail here. Measures less commonly used in neuropsychological assessments are described below.

Social cognition measures

The ability to infer the mental states of others was assessed using the Reading-the-Mind-in-the-Eyes Test-revised (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001a), which requires participants to indicate which of four mental state terms applies to a target picture that depicts the eye-region of an individual. It is sensitive to subtle differences in the ability to ascribe mental states, and is separate from general intelligence (Baron-Cohen et al., 2001a). We also administered the Interpersonal Reactivity Index, a self-report measure of empathic ability (IRI, Davis, 1980, 1983), and the Autism-Spectrum Quotient (ASQ, Baron-Cohen et al., 2001b), a self-report measure of autism-spectrum-like behaviours. The Social Skills and Communication subscales were used to examine her social functioning.

Visual imagery

In light of FS's self-reported difficulty with imagination, we examined three self-report scales of visual imagination. The IRI's Fantasy subscale appears to measure one's capacity to imagine oneself as a part of fiction (Mar, Oatley, Hirsh, dela Paz, & Peterson, 2006). The Autism-Spectrum Quotient includes an Imagination subscale, which we deemed relevant to visual imagery. Finally, we included the Openness to Experience scale of the NEO Personality Inventory – Revised (NEO PI–R, Costa & McCrae, 1992), specifically the Fantasy subscale, which includes questions like: 'I have a very active imagination'.

RESULTS

All of FS's scores on formal testing are presented in Table 1, including raw or scaled scores, percentile measures, and the range in which her performance fell.

Spared cognitive and social functions

FS's cognitive profile was characterised by spared function in most areas. Specifically, her current Full Scale IQ fell within normal limits. Her performance on measures of verbal comprehension and visuospatial function were within the average range. When measures of working memory and attention were limited to those with no sequencing components (as with Digit Span), her performance was normal, and her visual attention was average. On simple sequencing tasks, in which she had to apply an over-learned sequence (Trail-Making Test), her performance was normal. Her problem-solving abilities on both concrete and abstract problem-solving were intact. She performed normally on an objective, mental-inference task, and her self-reported empathic ability was within normal limits. She exhibited no deficits on any measures of recognition memory.

Impaired cognitive and social functions

FS exhibited mild to moderate difficulties with verbal fluency, and moderate to severe difficulties with processing speed and cognitive inhibition on the D-KEFS version of the Stroop test. On complex sequencing tasks, when she was required to organise information by imposing a sequence on it (Letter–Number Sequencing, Arithmetic, Picture Arrangement), she was moderately impaired. She reported mild to severe impairment on scales assessing her ability to engage in visual imagery, and reported mild difficulties with communication skills on the Autism-Spectrum Quotient. Her memory performance was variable, with moderate to severe impairment on immediate learning of verbal and visual information, evidence of normal retention at short delays, and mild to moderate difficulties with delayed recall.

DISCUSSION

On the whole, FS's cognitive and social abilities were remarkably spared, given her anterior lobectomy and the structural abnormalities in her right frontal cortex. Her intellectual function was within normal limits, her language comprehension abilities were in the superior range, and her high-level problem-solving abilities, social perception, and empathic ability were all within normal limits. Her recognition memory was within the high average range, suggesting that information was being encoded, and with the aid of cues, she was able to retrieve learned information. Another important strength for FS was her insight and awareness of her difficulties; she was able to clearly describe each of her areas of difficulty prior to testing. FS has recovered extremely well from her brain surgery, perhaps aided by the high level of plasticity of the human brain during early development.

This is not to say that FS has no difficulties at all, but rather that her difficulties are restricted to a small number of domains. It is also important consider her cognitive profile in the context of her Topiramate prescription. A number of neuropsychological deficits are found in people taking Topiramate, including mental slowing (Blum et al., 2006; Gomer et al., 2007) which is a frequent cause of discontinuation of the medication (Bootsma et al., 2008), impaired concentration and short-term memory (Froscher et al., 2005; Gomer et al., 2007; Lee, Jung, Suh, Kwon, & Park, 2006), impaired verbal fluency (Blum et al., 2006; Gomer et al., 2007; Lee et al., 2006; Romigi et al., 2008) and speech (Froscher et al., 2005), as well as difficulties with cognitive inhibition as measured by the Stroop test (Blum et al., 2006).

In addition, FS has a diagnosis of endometriosis, which is associated with pain and depression (Rodgers & Falcone, 2008), for which she takes Depo-Provera, a medication that has side-effects such as dizziness, headaches and nervousness (Murray, 2002), all of which may lower cognitive performance. To our knowledge, little research has been conducted on the direct cognitive consequences of either endometriosis or Depo-Provera.

Another possible factor besides her neurosurgery that may contribute to her cognitive status is that FS has experienced some seizures over the course of her life post-surgery. Although this patient clearly exhibits some impairments, these impairments should be interpreted in the context of factors other than surgery that might have influenced her test performance. Other patients who undergo a similar surgery but do not continue to experience seizures, and thus do not take Topimirate or other drugs for other conditions (e.g., Depo-Provera), may well exhibit an even more intact cognitive profile. As well, all things considered, it is likely that her cognitive performance is better than what would be predicted had no surgical intervention been undertaken, and her seizures continued at the rate she was experiencing pre-surgery. A body of evidence suggests that severe seizure disorders that begin early in life and require aggressive treatment are risk factors for poor cognitive outcome in epilepsy (Asztely et al., 2007; Helmstaedter et al., 2004; Lah, 2004)

FS's compromised ability to impose a sequence on stimuli is more likely to be related to the integrity of her frontal lobe than that of her temporal lobe (Romine & Reynolds, 2004). Order information has consistently been associated with the dorsolateral prefrontal cortex in both animal and human lesion studies (Marshuetz, 2005), as well as fMRI studies with humans with (Sirigu et al., 1996) and without brain damage (Crozier et al., 1999; for a review see Mar, 2004).

One interesting observation is that FS self-reported a somewhat impaired capacity for imagination across two measures, but exhibited intact mental inference abilities and self-reported normal or superior empathic and social cognitive abilities. Understanding others, or theory-of-mind, and imagination have been linked theoretically (Buckner & Carroll, 2007; Mar & Oatley, 2008). There is also meta-analytic evidence based on neuroimaging data that a single network that represents imaginative processes (self-projection or scene-construction) supports theory-of-mind processing (Spreng, Mar, & Kim, in press). This patient, however, appears to exhibit a dissociation between the two, similar to a recent study that provided evidence for a potential functional dissociation between autobiographical memory (which may involve imagination) and theory-of-mind in two patients (Rosenbaum, Stuss, Levine, & Tulving, 2007). Clearly, more work in this area is required to clarify this issue.

In conclusion, the case of FS provides heartening evidence that early surgical intervention for epilepsy, specifically anterior temporal lobe resection, does not necessarily lead to large-scale cognitive and social impairments as measured on long-term follow-up. While some difficulties are expected in adulthood, many important functions are spared, and high levels of functioning, including good educational attainment and gainful employment are possible.

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