Brain and Cognition

Developmental outcomes after early prefrontal cortex damage☆

Paul J. Eslinger,[a],* Claire V. Flaherty-Craig,[a] and Arthur L. Benton[b]

[a] *Departments of Neurology, Neural and Behavioral Science, and Pediatrics, Laboratory of Clinical Neuropsychology and Cognitive Neuroscience, Penn State University, College of Medicine, Hershey Medical Center, P.O. Box No. 850, Hershey, PA 17033, USA*
[b] *Departments of Neurology and Psychology, College of Medicine, University of Iowa, USA*

Abstract

The neuropsychological bases of cognitive, social, and moral development are minimally understood, with a seemingly wide chasm between developmental theories and brain maturation models. As one approach to bridging ideas in these areas, we review 10 cases of early prefrontal cortex damage from the clinical literature, highlighting overall clinical profiles and real life developmental outcomes. Based on these cases, there is preliminary evidence to support distinctive developmental differences after: (1) dorsolateral, (2) mesial, and (3) orbital-polar prefrontal lesions, for more profound impairments after bilateral damage, and possibly for recovery differences after very early vs. later childhood lesion onset. Further case and group studies are needed to confirm reliable effects of specific lesion locations, the influence of age of lesion onset, and related experiential and treatment variables in determining adult outcomes. Rather than a single underlying deficit associated with early prefrontal cortex damage, we interpret the findings to suggest that it is the altered integration and interplay of cognitive, emotional, self-regulatory, and executive/metacognitive deficits that contribute to diverse developmental frontal lobe syndromes. The findings support the fundamental importance of prefrontal cortex maturation in protracted cognitive, social–emotional, and moral development.
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1. Introduction

Understanding the neurobiological bases of cognitive, social, and moral development is an immense challenge to the developmental neural and behavioral sciences. Many of the existing models of development have emerged from broad psychological constructs that are beginning to be evaluated in relation to neuropsychological and brain maturation processes as well as neurobiological and psychosocial influences. An interesting avenue of analysis that may contribute to bridging of ideas in this area concerns the available cases of early frontal cerebral damage. Investigations of the developmental effects and outcomes of these clinical cases,

both in the laboratory as well as in their life experiences, can constitute an important test of certain ideas and serve as fertile ground for identifying scientific hypotheses.

In the adult neuropsychology literature, the frontal lobes have been strongly implicated as an important neural substrate of executive aspects of cognition, social behavior, and moral conduct. Early descriptions of frontal lobe syndromes arose from several 19th century investigators, described in recent reviews and analyses (e.g., Benton, 1991a, 1991b; Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994; Macmillan, 2002; Tranel, Anderson, & Benton, 1994). Harlow (1848, 1868), Jastrowitz (1888), Welt (1888), and Oppenheim (1890) were particularly attuned to changes in social behavior, personality, and emotional regulation that occurred after frontal lobe pathology. Subsequent investigators continued to elaborate on the nature and extent of these enigmatic defects, their causes and management (e.g., Brickner, 1936; Eslinger & Damasio, 1985; Fuster, 1991; Grafman, 1995; Miller & Cummings, 1999; Stuss & Benson, 1986; Stuss & Knight, 2002),

firmly establishing a vital role for the frontal lobes, particularly the prefrontal cortex, in such processes. In addition, several studies have revealed that profound executive function and social–emotional defects can occur after early damage to the prefrontal region (e.g., Ackerly & Benton, 1948; see Eslinger, Biddle, & Grattan, 1997; Grattan & Eslinger, 1991; Tranel & Eslinger, 2000 for reviews). It is from these perspectives that we highlight and discuss observations on cognitive, social–emotional and moral development that have become available through study of patients with early frontal lobe damage. In some reports, there are psychological test data that shed light on cognition, emotional processes, and behavioral patterns that portray aspects of social and moral development. In others, there are illuminating descriptions of these individuals' real life experiences that help characterize many aspects of normal as well as altered development after early frontal lobe damage. Not all testing and developmental details can be adequately described and compared in a short manuscript, but we have strived to highlight sufficient aspects to give readers an overview of these clinical cases and their developmental course.

1.1. Ideas on executive, social, and moral development

While the developmental psychology and neuropsychology literatures have acknowledged the importance of neurobiological factors such as brain maturation (e.g., Casey, Giedd, & Thompson, 2000; Eslinger, Grattan, & Damasio, 1992; Johnson, 1993; Kolb, Gibb, & Gorny, 2000; Segalowitz & Rose-Krasnor, 1992; Stuss, 1992; Thatcher, 1991), investigators have only begun to incorporate these factors into models of cognitive and social development. The role of the prefrontal cortex and its related networks, in particular, has been increasingly recognized as vitally linked to maturation of executive functions and social–emotional adaptation from childhood into adolescence and early adulthood in the developmental neuropsychology literature. For example, Welsh and Pennington (1988) defined executive functions (EF) as "the ability to maintain an appropriate problem-solving set for attainment of a future goal." They emphasized the central importance of: (1) planning and programming future actions, (2) maintaining these in mind until implemented (i.e., working memory), and (3) inhibition of other actions (Pennington, Bennetto, McAleer, & Roberts, 1996). Several of these elements are similar to proposals by Goldman-Rakic (1996), Constantinidis, Williams, and Goldman-Rakic (2002), Luria (1966), Fuster (1991), and Eslinger et al. (1992) who have emphasized the link to the prefrontal region as a crucial neural substrate. Denckla (1996) has proposed that the process of psychological development from childhood to adulthood can be understood as the "unfolding of executive functions." EF entails domain-general control processes for future-oriented actions that depend upon inhibition of prepotent responses, delay of responding, and verbally mediated rules to govern behavior. Rather than a hierarchical role for EF, she proposed that EF is at the center of elaborated cognitive operations. Barkely (1996, 1997) has emphasized the role of attention in development of EF and suggests that "an 'executive' response or function is a special case of an 'attending' behavior" that influences the likelihood of later events and actions. Similar in some ways to Shallice's (1988) notion of a supervisory attentional system, Stuss's (1992) hierarchical-feedback model of EF development, and Fuster's proposal of cross-temporal contingencies (1991), Barkley conceptualizes EF as mechanisms to bridge temporal and spatial gaps, sequences of action and altering the probability of later responses. Eslinger and colleagues (1996, 1997) have suggested that a core feature of EF development is emergence of a prospective archival working memory system with cognitive and social executors that serves to maintain goals, plans, and intentions that have motivating value over extended periods of time. This proposal shares some similarities to Grafman's (1995) managerial knowledge units as more stable and motivating representations of knowledge that sustain goal-directed behaviors as one matures toward self-directed, independent functioning in adolescence and adulthood. Physiological evidence has been marshalled in support of specific stages and sequences of frontal network maturation that continually elaborates upon and reorganizes cognitive, emotional and behavioral processes for broader adaptive capacities (Case, 1992; Thatcher, 1991). An important extension of developmental EF ideas has been the distinction between so-called "hot" and "cool" EF. Zelazo and Müller (2002) have identified cool EF as those subserving relatively abstract and decontextualized problem solving whereas hot EF involves affective processing in problem solving, with both linked to theory of mind and other social cognitive abilities. While such an approach has been articulated for cognitively and emotionally based empathy (Eslinger, 1998), application to a broader range of processing domains is needed. These diverse approaches and their constructs are increasingly yielding operationalized measures of working memory, inhibition, decision-making, problem solving, and social cognition that require a wider range of adaptive processing than tapped by general intelligence measures. While these have been somewhat successful for childhood and early adolescent age ranges, performance on many tests of purported frontal lobe functions reach adult levels in early to mid adolescence, suggesting that a broad spectrum of maturation has yet to be experimentally tapped (Levin et al., 1991; Passler, Isaac, & Hynd, 1985; Welsh, Pennington, & Groisser, 1991).

From the developmental psychology literature, some salient ideas from the seminal approach of Piaget (1968) may be potentially informative to the understanding of how early prefrontal injuries may alter maturation. For example, Piaget proposed that the child actively constructs original mental structures that become progressively elaborated through experience, including actions, consequences, and outcomes. Elementary forms of self-awareness and self-monitoring are also crucial to perceive intentional movements that influence objects, people and other aspects of the environment. Such processes and structures contribute to and underlie the fundamental basis of representational knowledge that eventually evolves into "working knowledge" that is dynamic and permits spontaneous, adaptive interactions with the world. The emphasis on construction of such mental structures would seem to be just as pertinent to social cognition and theory of mind capacities as the child formulates notions of intentionality, thought and emotional experiences occurring in others through various developmental phases as early as 18 months of age (e.g., Baron-Cohen, Tager-Flusberg, & Cohen, 1993). These may also be early forerunners of the psychological structures that underlie empathy, moral judgment, and other aspects of interpersonal behavior where brain maturation is critical. Flavell, Miller, and Miller (1993) emphasized that social cognition in particular requires some of the most complex inferential skills. Hence, investigating the effects of alterations to brain maturation may provide clues to developmental processes of how knowledge is acquired and organized.

Piaget also described how the concrete, operational thinking phase of middle childhood incorporates operations that organize successive steps, seriation of events, and various types of groupings for objects, knowledge and actions into new combinations. While he emphasized such processes in the development of knowledge and human mathematical abilities, these fundamental cognitive processes may also relate to the organization of social cognition such as the structured event complexes and managerial knowledge units proposed by Grafman (1995). These combinations of actions allow one to define and organize multiple behavioral possibilities into schemas or mental models that can serve as guidelines or algorithms for regulating behavior over stretches of time, space and context in order to achieve more complex goals in a sustainable fashion. Such cognitive operations, though still minimally understood, would appear to be one of the fundamental building blocks for executive functions. Along with these cognitive contributions to social and moral development, Piaget also emphasized how "Cooperation among individuals coordinates their points of view into a reciprocity which assures both the autonomy of the individual and the cohesion of the group." This is particularly evident in the middle childhood years. It is

during this time that the early forms of moral feelings evolve from highly structured obedience to rules to the emergence of a greater breadth and depth of moral feelings that arise as a function of cooperation and the beginning of mutual respect between persons. Piaget provided as an example the difference between children 4–6 years of age playing a game, each according to their own uncoordinated rules, and children 7–12 years of age beginning to agree on rules and "controlling each other in such a way as to maintain equality before a single rule." Thus, this transition from individual rules to common rules that are the result of social agreement, allows people to succeed in a much more regulated types of competition and group activity. This, in turn, can pave the way for construction of more abstract notions such as honesty, cheating, fair play, and justice. These constructs become based on a sense of equality and fairness. Knowledge about intentionality of others (i.e., theory of mind) is particularly critical for moral judgments (Flavell et al., 1993). In a sense, the context and goal of actions (rather than the actions alone) begin to override judgment of what is fair and just. From a standpoint of moral knowledge and development, the abstraction of certain common and universal principles that apply to social behavior emerge and begin to guide judgment and behavior. With the emergence of this broader interpersonal perspective and sense of social cooperation, children develop an increasing autonomy of social–moral reasoning and judgment, coinciding with a sense of progressive egalitarianism.

Piaget postulated the transition from pre-operational to concrete operational thinking as characterized by the emergence of "role-taking" skills. Many social theorists (Flavell, Botkin, & Fry, 1968; Flavell et al., 1993; Selman, 1971) have identified role-taking as one of the cornerstones for social and moral development. An important interpersonal process that is relevant here is empathy, considered the extension of role-taking into the domain of role-enacting, involving cognitive as well as emotional experiences in response to the mental/emotional state and experiences of others.

Empathy has been operationalized in a number of ways over the past 30 years, most recently formulated from common behavioral referents by Hogan as part of an overall cognitive/behavioral developmental theory of moral character (Grief & Hogan, 1973; Hogan & Dickstein, 1972). Emphasizing stages in the refinement of moral conduct, Hogan's five dimensions are focused on moral knowledge, socialization, empathy, autonomy and ethical attitude (Hogan, 1973, 1975). With little distinction between social and moral rules, Hogan's perspective is both distinct and complementary to that of Kohlberg, whose moral judgment model is less concerned with actual behavioral aspects and more with the level of reasoning implicit within ethical decision-making processes (Kohlberg, 1973; Kohlberg & Kramer,

1969; Rest, Turiel, & Kohlberg, 1969). Both Hogan and Kohlberg have extrapolated Piaget's developmental stage approach to the social–moral realm with notable success, as indicated by the significant body of research investigating the mediating role of cognitive development in both moral reasoning and social behavior (e.g., Kennedy, Felner, Cauce, & Primavera, 1988; Markoulis, 1990; Murke & Addleman, 1992; Mwamwenda, 1991; Rest et al., 1969; Selman, 1971; Tomlinson-Keasy & Keasy, 1974).

Although Kohlberg and Hogan emphasized a subject's justification for a moral judgment, information processing approaches involve an assessment of the actual rules applied to make social–moral judgments (Schultz & Schleifer, 1983). What information does a person process and how does a person manipulate it to arrive at a judgment? Still others emphasized key interactions among Piagetian, information processing and social–emotional contexts in social and moral decision-making (e.g., Flavell et al., 1993). Kohlberg's approach has been based on the presentation of moral dilemmas, which are complex situations without a single or clear solution. By contrast, information processing approaches provide straightforward cases in an effort to elucidate the moral reasoning rules applied to solve them. From a developmental standpoint, approaches that rely on presentation of lengthy narratives and a complex verbally mediated response may clearly underestimate children's social–moral reasoning abilities (Darley & Schultz, 1990).

Many of the skills that are implicit in social and moral development are reminiscent of executive function processes, which are often associated with the prefrontal cortex and include self-awareness, inhibition, cognitive flexibility, generating different response possibilities, and utilizing representational knowledge. Study of children with prefrontal cortex damage, therefore, may be particularly informative about brain maturation influences on social and moral development.

The following are brief summaries and analyses of the available descriptions of cognitive, social, and moral development in several cases with early prefrontal cortex injury (see Table 1 for summary highlights).

1.2. JP: The case of Ackerly and Benton (1948)

JP is one of the most informative cases available in the literature on human prefrontal lobe damage because of the congenital nature of the damage and the long period of prospective and follow-up study. Formal clinical services and testing of JP began when he presented to the Louisville Mental Hygiene clinic for evaluation and treatment in 1926, at 13 years of age. In retrospect, the authors were able to establish that JP learned to walk and talk by about one year of age and appeared to have normal developmental milestones and general intelligence. However, by 2–3 years of age he had a marked tendency to wander long distances, without fear of being lost or incurring punishment. On a number of occasions he was retrieved by police who found him far from home. Another feature of his early childhood behavior was his "Chesterfieldian" manners, to the point of being over-polite and ingratiating towards adults. This excessive courteousness had a shallow quality to it and persisted throughout much of his adolescence and early adulthood.

His early school experiences indicated difficulties from day one. In reviewing the rich descriptions offered by the authors, it is not too difficult to infer that impairments in inhibition, attentional regulation, working memory, delay of responding, and sequencing led to pervasive interpersonal difficulties. JP engaged in many behaviors that made him unpopular with schoolmates. These included boastfulness, bossing of younger children, stealing money, masturbating in school, and interpersonal impairments so extreme that he was described as "heartily disliked" and having "extremely poor" social adjustment. Curiously, adults could be "charmed by his courteous, ingratiating manner. Even professional workers were not at first immune to his bland, 'innocent' manner as suggested by the impression of the interviewing psychiatric social worker that despite the miserable history, he was a 'normal' boy for whom much could be done through supervision and psychotherapy." However, these behavioral and adaptive impairments proved intractable and continued throughout follow-up study, leading Ackerly and Benton to characterize the impairments as an arrest of development and a *primary social defect*.

It was not until JP was 20 years of age that he received detailed medical and neurologic evaluation. He was admitted to the psychopathic ward of the Louisville General Hospital for repeated stealing of cars of relatives and neighbors. Exploratory surgery at this time lead to the diagnosis of "cystic degeneration of left frontal lobe, absence of prefrontal lobe on the right, chronic arachnoiditis, adhesions on the anterior cranial fossa." EEG studies at 24 and 28 years of age were interpreted as "showing no positive evidence of abnormality." These results, within the more comprehensive history taken on JP, supported a congenital process of "cortical degeneration or destruction due to brain abscess." Estimated location of frontal lobe damage was reconstructed from the neurosurgical report and is represented in Fig. 1.

There are a number of observations with regard to JP's social and moral development that are relevant to current models within developmental neuropsychology and psychology. From a very early age, JP showed no evidence of fear or anxiety in wandering long distances from home and being lost. This point has been emphasized by Benton (1991a, 1991b), who indicates that even

Table 1
Summary of cases of childhood frontal lesion

Case	Author (yr)	Chronological age of lesion onset	Age at time of study	Area of neuroanatomic involvement	IQ	Primary deficits	Strengths
JP	Ackerly (1964) Ackerly and Benton (1948) Benton (1991a, 1991b)	Congenital	12 yr	Extensive bilateral prefrontal	S-B IQ = 92 Army Alpha IQ = 100	Application of socialknowledge. Sustaining friendships. Planning, impulse control. Social self-regulation. Learning from experiences. Abstraction beyond ''materials in view.''	Initiation. Conversational language. Elementary cognitive abilities. Socially engaging at times
GK	Price, Daffner, Stowe, and Mesulam (1990)	Perinatal	28 yr	L > R frontal cortex and white matter to caudate	WAIS-R VIQ = 102 PIQ = 90 FSIQ = 96	Serious behavioral problems from 8 years of age. Impulse control and social self-recognition. Sustaining friendships. Criminal behavior. Learning from experience.	Initiation. Gregarious. Elementary cognitive abilities
ML	Anderson, Bechara, Damasio, Tranel, and Damasio (1999, 2000)	3 months	23 yr	Right prefrontal cortex Mesial, polar, lateral, and lateral orbital regions. Anterior cingulate damage Brodmann's areas 10, 9, 46, 8, 12, 24, and 32	WAIS-R VIQ = 94 PIQ = 104 FSIQ = 98	Problems began at 5 years of age. Inattentive, impulsive and poor judgment. Low academic achievement. Showed little to no anxiety, fear and empathy. Unable to live on own, manage finances and social relationships.	Average intellectual and academic skills. Pleasant manners and socially outgoing.
FD	Anderson et al. (1999, 2000)	1 yr 3 months	20 yr	Bilateral frontal polar, anterior orbital and right mesial orbital damage. Brodmann's areas 11, 10, 9, 46, and 47	WAIS-R VIQ = 85 PIQ = 98 FSIQ = 90	Problems began at 3 years of age. Disruptive behavior at home and school. Arrests for shop-lifting. Verbally and physically abusive. Frequent lies. Did not respond to punishments, therapy or medications. Lack of empathy and self-evaluation.	Initiation. Elementary cognitive abilities
MJ	Eslinger et al. (1997)	3 yr	8, 14, and 16 yr	Right dorsolateral prefrontal cortex in region of the middle frontal gyrus; Brodmann's area 9 and partially 46	WISCIII VIQ = 96 PIQ = 95 FSIQ = 95	Early social and attentional changes with disinhibition and impulsive responding. Later testing revealed relative difficulties in visuospatial aspects of executive function tasks and poor organizational strategies 13 years after illness. Social problems have continued in adolescence with few friendships, conflicts with siblings, and minimal perception and sensitivity to emotional states of others. Views social world largely with indifference	General intellect. Speech and language skills. Academic achievement. Autonomy and initiative in independent activities has maintained p/t jobs while in school. Animal friendly

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SC2	Daigneault, Braun, and Montes (1997)	3 yr 5 months	7 and 8 yr	Left prefrontal, extensive deep white matter damage to head of caudate	?tul=0>WISC III VIQ = 82–88 PIQ = 96–107 FSIQ = 87–96	Poor attention, initiation and self-regulation. Mental inertia prominent. Perseverative. Impaired creative and sustained processing. Emotionally dependent. Requires constant encouragement.	Not impulsive. Benefitted from structure and cues. Pleasant and compliant attitude. Friendly.
PL	Marlowe (1992)	3 yr 11months	6 yr 1 months	Right prefrontal cortex Brodmann's areas 8, 9, 46, 10 and subjacent white matter	WISC-R VIQ = 119 PIQ = 132 FISQ = 128	Self-regulation in complex social environments. Novel problem solving in real world. Visual perceptual organization. Learning from experience. Impulse control, frustration tolerance	Utilization of verbal mediation and rehearsal. Initiation. Memory and language abilities, but declined measured intellect
MH	Price et al. (1990)	4 yr	24 yr	Bilateral frontal lesions after head trauma	WAIS VIQ = 78 PIQ = 83 FSIQ = 78	Impulse control with assaults. Sustained friendships. Sexual promiscuity. Planning. Academic achievement. Judgment and learning from experience.	Bravado. Memory, language and visual perceptual abilities
DT	Eslinger et al. (1992) Grattan and Eslinger (1991, 1992)	7 yr	33 yr	Left prefrontal cortex Brodmann's areas 8, 46, and 32, white matter underlying areas 45 and 24. Bilateral low cerebral blood flow in prefrontal regions (L > R)	WAIS-R VIQ = 85 PIQ = 80 FSIQ = 83	Arrested social, emotional and moral development. Sustained attention and concentration. Cognitive flexibility. Organization of complex information for cognitive processing. Using feedback to guide behavior. Planning, judgment, and cognitive estimation	Initiation. Elementary cognitive abilities. Conversational languageJC
	Eslinger et al. (1997, 1999, 2000)	7 yr	7, 12, and 16 yr	Right prefrontal cortex including dorso-, mid- and infero-lateral regions; Brodmann's areas 9, 10, 44, 45, 46, and 47 and subjacent white matter Minor damage to dorsal premotor cortex (area 6), and anterior insula	WISC III VIQ = 112–125 PIQ = 90–112 FISQ = 101–121	Acute deficits of left hemispatial neglect, constructional apraxia, spatial scanning and distractibility. 4 year follow-up revealed resolution of hemispatial neglect and constructional apraxia but executive function deficits in attentional control, visuospatial working memory, cognitive flexibility and strategic learning. An acquired attention deficit was evident along with mild personality and social behavior changes. 8 year follow-up showed further cognitive improvements and typical social–emotional maturation in adolescence. Attentional difficulties, impulsive responses, and mild social cognition changes still evident	General intellect. Verbal working memory. Language-based skills. Problem solving. Initiation, empathy Stable friendships. Positive family role
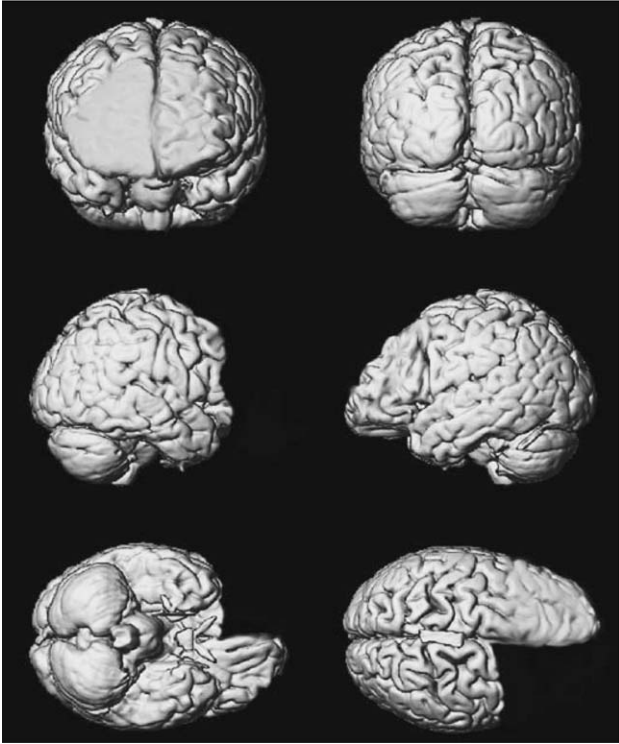
Fig. 1. Reconstruction of congenital frontal lobe lesion in JP based upon neurosurgical report.

with severe punishment, JP never altered this behavior. The role of anxiety, fear and somatic states in contributing to learning and decision-making processes that underlie behavior has recently been emphasized by Damasio and colleagues (1991) and related to neural mechanisms mediated in part by the ventromedial frontal lobe. On the other hand, Piaget (1968) emphasized that self-awareness and self-evaluation by the young child leads to an elementary sense of success or failure from their actions, which is often tied to obedience to rules. When such awareness and evaluation is integrated with affective states, anticipatory anxieties and other somatic states, both cognitive and somatic cues may serve in part to guide future actions. JP's lack of concern for such consequences and marked absence of anxiety were noted by Ackerly and Benton. JP was never heard to be self-critical, and appeared to have little insight to serve him in reflecting upon and utilizing his experiences. He did not seem to intentionally plan to take advantage of others but his rudimentary social skills and lack of concern for consequences often landed him in trouble. Situations that led to acting-out and criminal behavior (e.g., mistreating others, stealing a car or money) were the result of losing some advantage over others or coming across an opportune circumstance rather than premeditation.

It is clear that JP could not effect the transition from individual rules to common rules that result from social

agreement. From a very early age, JP appeared to have no empathy or sense of reciprocity and fairness in his dealings with other people. The authors observed that "the boy has practically no standard of justice or fairness; his whole attitude is one of deception in order to gain his point." These observations would suggest that despite his average general intelligence, his proficiency in language, visual perceptual and general motor activities, and even "Chesterfieldian" manners, JP was not able to manage the important developmental milestones of effective collaboration in any group, agreeing on rules and participating in a regulated competition, which Piaget described for 7–12-year-old children. Role-taking and theory of mind capacities were practically nonexistent. In Kohlberg's model, JP's level of moral reasoning was in stage 2–3, at the border of pre-conventional to conventional.

Despite these marked limitations, JP did show pride in certain aspects of work. His most productive work was under direct supervision as a gas station attendant and as an orderly in a local hospital. JP "liked to help people who could not help themselves-it makes me feel important." Beyond these well-structured instrumental actions to help others, JP did not otherwise show anticipation of other's needs, accommodation to their desires or cooperation in achieving common goals.

Interestingly, Ackerly and Benton remarked that JP "also had an excellent sense of right and wrong when talking about it in an abstract manner, but showed no such sense in his actions." These observations would suggest that JP could understand and engage in some level of moral decision-making and choice, reflecting considerations of effects on others and even in some sense of fairness. However, this was quite erratic, usually manifested only when talking about it or under direct constant supervision by others and generally at an early adolescent level.

The "primary social defect" of JP appears to have its roots in a combination of fundamental cognitive, affective, and self-regulatory impairments that began in early childhood and were modified minimally by experience and consequences. Ackerly and Benton described that "the frontal lobes are essential to man for the amplification and elaboration of experience; that man can not elaborate his social sense so that it can become part of his total self without the 'great nerve net' of his frontal lobe." The limited extent of JP's social and moral development, as well as the erratic self-regulation of his behavior, may have its basis in the simple, unelaborated mental models that he employed in guiding his responses in a complex and inviting world. His primary social defect may be understood as a primitive (i.e., immature) level of differentiation and elaboration of the cognitive and affective processes that underlie role-taking, theory of mind, cooperation, and self-evaluation that generally emerge by 7 years of age.

1.3. GK and MH: The cases of Price et al. (1990)

Price et al. (1990) described two adult patients who suffered early bilateral prefrontal lobe damage. The first, GK, was a 31-year-old, right handed man who likely suffered cerebral vascular damage congenitally (Fig. 2). He was of average general intelligence and showed some similarities to JP. Early developmental history is minimal, but did indicate immaturity, little response to parental discipline, poor social and moral development, impulsivity and a tendency to wander. As an adult, he was involved in many forms of criminal behavior, and was hospitalized 27 times in psychiatric institutions and imprisoned eight times. During medical evaluation, he was noted to be cooperative, but "showed little insight or empathy and felt victimized by others."

The second case was MH, a 26-year-old ambidextrous woman who was described as having normal developmental milestones until 4 years of age when she suffered head trauma with loss of consciousness and bilateral skull fractures with right frontal hematoma. MRI scans as an adult showed extensive bifrontal damage (Fig. 3). This woman showed more diffuse effects of head trauma, including a borderline level of verbal IQ and low average range of performance IQ. Her developmental history was remarkable for frustration intolerance, aggressive and violent behavior, poor social development, substance abuse, and negligent care of her $2\frac{1}{2}$-month-old infant.

In addition to these descriptions, the investigators tested certain aspects of cognitive and moral development in these two cases. While both could perform a Piagetian concrete operational task within normal limits, neither patient could perform a task at the formal thinking level. In a role-taking task (one requiring the subject to consider the situation of another person) GK scored at a minimally normal level while MH was impaired. Finally, the "Heinz dilemma" of the Kohlberg

Fig. 3. Brain MRI scan showing residual post-traumatic lesions in MH, acquired at 4 years of age. Reprinted from *Brain, 113,* Price, B.H. et al., The comportmental learning disabilities of early frontal lobe damage, 1383–1393, 1990, with permission from Oxford University Press.

(1976) variety was presented to assess moral development. The responses of GK indicated an early conventional level (Kohlberg stage 3, interpersonal accord and conformity), with more primitive preconventional reasoning on other dilemmas. MH was concerned primarily with punishment and responded at the preconventional level. Thus, these observations are highly consistent with the real life histories of these patients and support the fundamental cognitive and affective processing impairments which emanated from early stages of development. In addition, Price and colleagues emphasized their patients' lack of premeditation for their aggressive and criminal behaviors, similar to the emphasis by Ackerly and Benton (1948) in analyzing JP's pattern of social behavior impairment. Similar to JP, both cases did not reach the formal thinking stage of Piaget, and hence the mental structures revolving around conceptions of themselves and of the world were likely primitive and poorly elaborated beyond the concrete operational stage.

1.4. DT: The case of Eslinger et al. (1992)

DT has been studied with both clinical and psychometric methods to gauge her social and moral development since a left frontal hemorrhagic lesion with surgical evacuation at 7 years of age (Figs. 4 and 5). She was not formally studied until she was 33 years of age; thus, much of her development was reconstructed from interviews and records.

DT did not have the overt truant tendencies of JP (Ackerly & Benton, 1948), nor the aggressive tendencies of GK and MH (Price et al., 1990). However, she did clearly develop progressive social impairment in the 3–5 years after her lesion, with prominent social alienation and uncooperative behaviors by middle school years. This was in marked contrast to her well-adjusted,
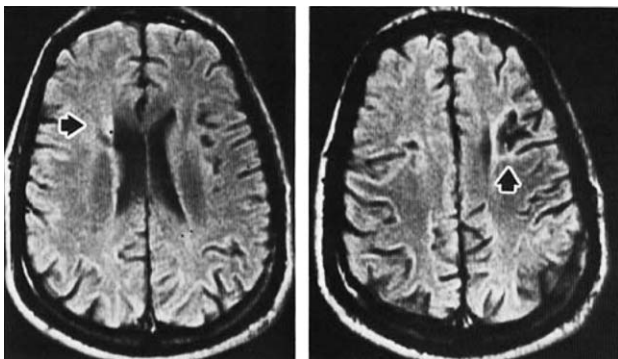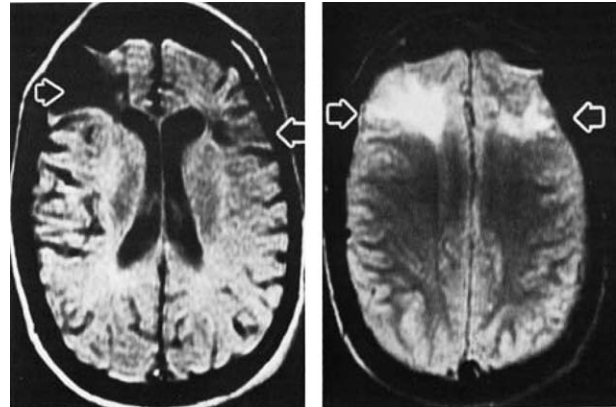

Fig. 2. Brain scan showing early frontal lobe lesions in GK, presumably from congenital cerebrovascular disease. Reprinted from *Brain, 113,* Price, B.H. et al., The comportmental learning disabilities of early frontal lobe damage, 1383–1393, 1990, with permission from Oxford University Press.
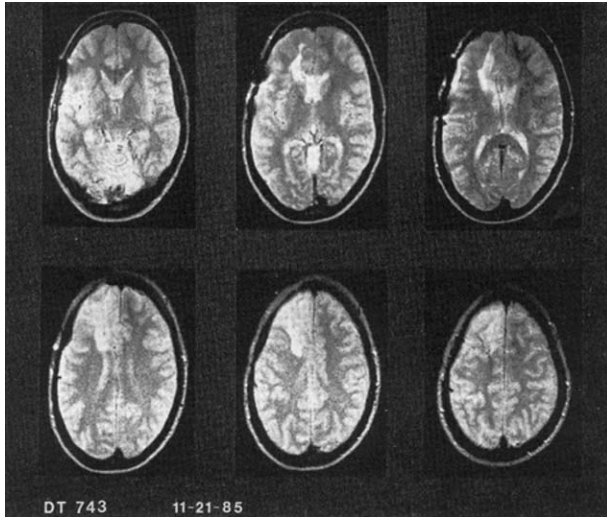
Fig. 4. MRI scan of DT as an adult (26 years after lesion) showing left mesial and polar prefrontal damage.
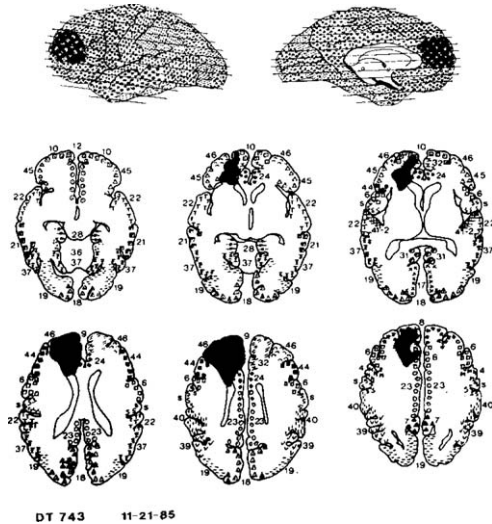

Fig. 5. Localization of DT's lesion on standardized brain templates.

pre-illness social development. Most of her social interactions were now characterized by argumentativeness, lack of sharing and little concern for others. Her achievement in school was minimal, with indications of poor attentional control, disorganization, and slower learning. This pattern of impaired learning, social ineptness, and altered adaptation to her environment carried over into early adulthood. Impulsive, erratic, and immature behaviors seriously compromised her abilities to participate in a marriage and care for her infant. These were expressed primarily by poor regulation of her emotions, disorganization in daily activities, and minimal anticipation of the needs of others. Her adaptation continued to deteriorate despite continuing support of her family and psychotherapy over a 7-year period. She gravitated toward flamboyant and unsavory

characters and became increasingly promiscuous, yet also immersed herself in religious groups rather intensely. Her vocational attempts were marred by poor job performance due to disorganization, uncooperative behaviors, and inappropriate remarks. Vocational planning and preparation was estimated to be similar to early adolescents, with emphasis on what she would like to do but little participation in and commitment to the necessary planning and training. Neuropsychological testing showed low average range of general intelligence and multiple deficits in executive function, working memory, problem solving and memory.

On standardized inventories taken as an adult, DT's self-report measure of empathy levels was quite low (Hogan Empathy Scale score = 27; 2 SDs below the mean), indicating little understanding and perception of other person's experiences, dilemmas and feelings. This would suggest that perspective-taking and role-taking abilities have been minimal. MMPI responses suggested a pattern of chronic social maladjustment, with hostile and demanding, yet dependent personality tendencies in social interaction. The Measures of Psychosocial Development (Hawley, 1988), which is a self-report inventory of adolescent and adult personality development based on Eriksonian constructs, suggested that DT has achieved only a pre-adolescent developmental stage. She appeared comfortable with early issues of self-initiating activities, but was markedly impaired in issues related to competency and productivity, identity development, and regulating needs and concerns around intimacy and isolation. Thus, both personal developmental and social developmental challenges have been met with quite limited success and adaptation.

With regard to moral development, DT has given many indications of how rigid yet erratic she can be with moral issues. On semi-structured interview with moral dilemmas (Kohlberg & Kramer, 1969), DT strives to implement stereotyped images of good and bad, and to apply fixed rules usually with skewed references to Biblical text. When questioned about the dilemma of a poor young man stealing an expensive drug from a greedy pharmacist in order to save his spouse's life, she responded "It's against the law... It's against the Ten Commandments... That's against the Bible... That's against morals." DT just as easily conceded, though, that a person should consider changing such guidelines when such rules do not allow them to do what they want. This contradictory thinking was evident, unfortunately, in many aspects of DT's adult life, where her choices surrounding her needs, relationships, and consequences were driven primarily by instrumental hedonism and personal concordance rather than a consistent set of personal guidelines. The Kohlberg model of moral development would place DT's responses and behavior patterns at an early adolescent level (approximately 10–13 years of age), concrete in her moral reasoning and

limited in cognitive flexibility and perspective-taking abilities to negotiate cooperative, reciprocal relationships, vocational pursuits, and social interactions.

DT's prefrontal lesion occurred at an age when she was likely transitioning to middle childhood cognitive, emotional and social tasks including theory of mind, cooperative and reciprocal relationships, and relational reasoning. Neural damage was centered particularly in polar and mesial aspects of the left prefrontal cortex, which is thought to be a crucial site for social and moral processing (Moll et al., 2002). Interestingly, cerebral blood flow study (SPECT) as an adult indicated bilateral low flows in the frontal region for DT, even though structural brain imaging showed only left-sided lesion. Hence, part of the long-term physiological alterations caused by such a lesion at that age may include contralateral effects—an occurrence observed in certain animal model studies of early frontal lesion (Goldman & Galkin, 1978).

Similar to JP (Ackerly & Benton, 1948), GK and MH (Price et al., 1990), DT's personality structure appeared simplistic, poorly integrated into an identity, and marked by superficial behavior and opportunism. That is, DT did not appear to intentionally set out to be hostile, difficult or demanding, nor was this characteristic of her family and upbringing, but her poor regulation of emotions, lack of empathy and disregard for personal boundaries inevitably led to social frictions. The accommodations she could forge with the environment and in her relationships were pre-adolescent and concrete. However, she was neither as aggressive as the Price et al. (1990) cases, nor as disinhibited in minor criminal behaviors as JP (Ackerly & Benton, 1948). This may be attributed to the later onset of injury at 7 years of age, to a more limited form of bilateral frontal dysfunction, or possibly to gender and rearing issues. While she sought rules to guide her social and moral behavior, these were concrete, rigid, and applied only to benefit herself. Within Piaget's terminology, DT achieved limited concrete, operational thought which was seriously undermined by her emotional and self-regulatory deficits.

1.5. PL: The case of Marlowe (1992)

PL was almost 4 years of age when he suffered a penetrating injury to the right prefrontal cortex from a lawn dart, requiring surgical debridement of bony fragments, hair and grass up to $1\frac{1}{2}$ cm deep in the brain parenchyma (Fig. 6). His medical recovery was excellent, but within 2 weeks after injury, behavioral changes became evident. These included mood swings, emotional lability, agitation, and destructiveness. Aggressive, impulsive and hyperactive behaviors, previously absent, were now observed. While his IQ was measured in the superior range up to 2 years after the accident, signs of
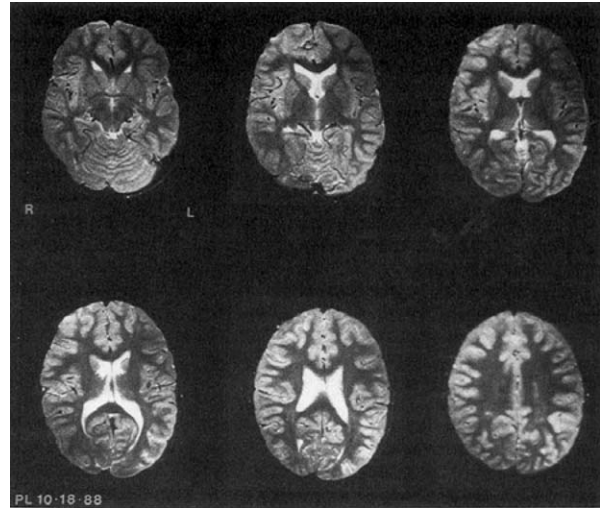

Fig. 6. MRI scan of PL showing right prefrontal cortex lesion. Reprinted from *Brain and Cognition, 20,* Marlowe, W. The impact of right prefrontal lesion on the developing brain, 205–213, 1992, with permission from Elsevier.

executive and frontal dysfunction were evident. Self-regulation and cognitive processing during social encounters required much greater effort and left him prone to frustration and angry outbursts. As Marlowe describes, many of the behavioral changes were attributed to immaturity rather than brain injury per se. He had difficulty controlling his behavioral reactions, usually becoming angry and aggressive when restrained or confronted by an unexpected situation. In pursuit of his own goals, he would act-out when thwarted and confessed no remorse for his actions. However, some improvement in social self-regulation was observed after PL received learning support services at school and restructuring during various school tasks. In less-structured settings, such as at home, he remained socially and behaviorally impaired, with increasing difficulties.

Many of the behavioral and cognitive difficulties observed 2 years after right prefrontal cortex injury in PL suggest a high-risk profile for social–moral difficulties as he matures. Marlowe emphasized that PL was taught to apply verbally mediated rules to guide his problem-solving and behavioral responses. This proved ineffective in guiding and maintaining adaptive behavior in the real world. Overtime PL's potential to develop role-taking skills, empathic responses and perspective-taking abilities, was overwhelmed by social–interpersonal expectations. In comparison to JP (Ackerly & Benton, 1948), GK and MH (Price et al., 1990), PL did not initially appear to be as socially impaired or cognitively impaired. He benefited little from training in metacognitive strategies to stop and evaluate his behavior in specific situations. Informal data on PL's developmental course indicate that he has continued to be socially impaired and struggles with self-regulatory and
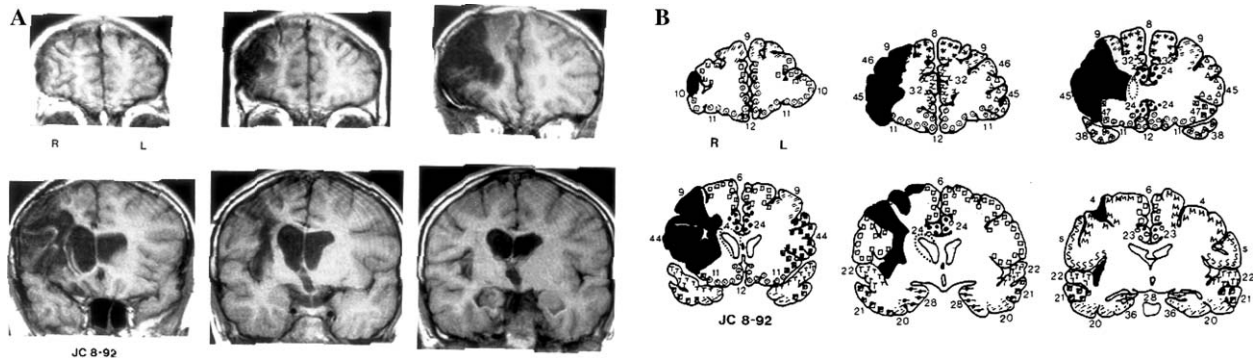
Fig. 7. (A) MRI scan showing right dorsolateral prefrontal lesion in JC. (B) Localization of JC's lesion on brain templates.

interpersonal issues to a significant degree, having experienced increasing difficulties in school and eventually legal-criminal behaviors (personal communication; Dr. W. Marlowe).

1.6. JC: The case of Eslinger et al. (1997, 1999, 2002)

JC was 7 years of age when he underwent surgical treatment of a right frontal intraparenchymal hematoma and deep arteriovenous malformation (AVM). After topectomy in the right middle frontal gyrus, the hematoma was drained and the AVM, embedded in the wall of the ventricle, was successfully resected (Figs. 7A and B and 8). In the early recovery phase, JC spoke fluently and followed commands. Mild left facial, sixth nerve and left-sided weakness were the only neurological signs and they continued to improve. Emotional lability was the only behavioral change clearly noted. JC underwent rehabilitation with discharge home soon after and returned to school within 3 months, following summer break. Initial neuropsychological examination at 6 months after illness revealed left hemispatial neglect with constructional apraxia, distractibility, impulsive responding, impaired visual memory for designs, difficulties completing multi-step tasks, and emotional lability. Behaviorally, he was also noted to talk and fidget
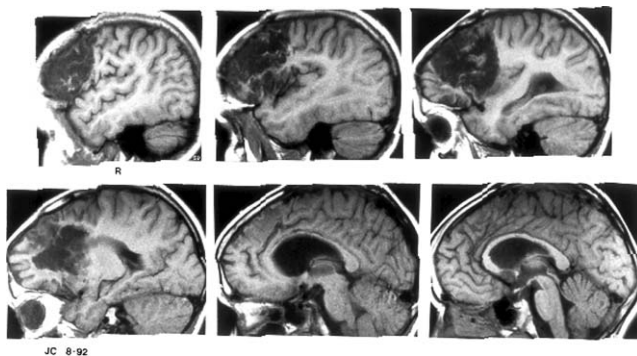
excessively, to have a short attention span when without structure and supervision, to constantly smell items (e.g., clothes, carpet, objects in addition to foods), with reduced initiation, inability to play by himself and a preference for younger playmates-none of which were evident or characteristic prior to his illness. It was difficult for him to prepare for school in the morning due to following multi-step activities on a time schedule. He was noted to call out in class and digress from the subject. However, these behaviors improved over the subsequent year and he remained well liked by his teachers and friends, and involved in family and community activities. Modifications to his school assignments helped minimize his difficulties with organization of ideas in writing, following multi-step tasks through to completion, reading clock faces and comprehending other visuospatial materials, and losing his place during multiple and division problems.

At the 4-year follow-up phase, JC was continuing in regular school classes and community activities, without medical complications or need for any other treatment services. He also remained emotionally and socially connected within family, school and community settings. Most problematic or atypical behaviors previously noted had subsided. His sense of time and ability to gauge time within the context of activities and tasks was impaired and frequent cues and reminders were needed. As he became more active in sports, subtle difficulties were noted, such as difficulty in keeping track of which ends of the basketball court were offense and defense (a manifestation of a visuospatial working memory deficit which was offset fortunately by the team learning to shout "offense" and "defense" as they went up and down the court). Academically, JC experienced the most difficulties in organizing and writing his thoughts on paper, but he fared well in grades otherwise. Neuropsychological testing was expanded at this phase and revealed a number of significant executive function impairments, particularly as visuospatial processing, attentional control, and multi-step activities were required. His general intelligence levels improved from

Fig. 8. Sagittal view of JC's lesion on brain MRI.

the post-acute period and varied from high average to superior range. Most previously impaired primary visuospatial functions such as judgment, memory, constructional praxis, had recovered to normal levels. Prominent impairments in visuospatial working memory and visuospatial scanning and processing speed were evident. Mild attentional control, verbal learning and cognitive flexibility difficulties were revealed. JC exhibited sufficient symptoms of attention deficit and hyperactivity to suggest an acquired form with prominent inattentive features. Social discourse measures revealed a more sparse and unelaborated style of responses. Socially and emotionally, he continued to show developmental progress and remained involved with friends, family and community activities. At the 8-year follow-up phase, JC maintained most of the gains that he achieved during the first 4 years after his illness. Most cognitive measures continued to improve along with social-behavioral adaptation. He attended in regular classes throughout high school and remained active in sports. He maintains a stable set of friends and activities, without evidence of any delinquency or social limitations. Some of his neuropsychological test scores declined between the 4 and 8 year follow-up phases, which we propose is secondary to a performance type of deficit related to attentional difficulties and occasional impulsive responding. A brief trial of a low dose stimulant medication led to improved class performance but reduced spontaneity of behavior and emotional expression, causing him to discontinue the trial.

JC's profile of test scores, social–emotional development and adaptation through adolescence suggests a developmental profile and outcome that is vastly different from most other reported cases of early prefrontal cortex damage. He has shown a tremendous degree of recovery and was able to participate in a full schedule of regular high school classes, playing competitive hockey, maintaining stable and nurturing family and peer relationships, and showing typical adolescent maturation

and adjustment. A key factor underlying this favorable outcome may be the location of his frontal lobe lesion— right lateral prefrontal cortex with notable sparing of orbital, polar and mesial regions in both the right and left frontal lobe. Additional factors to consider include the age of onset (7 years), at a time when many aspects of executive function, social cognition and self-regulation are already evident, the positive nurturing environment in which he continues to be raised, and JC's own efforts at continuing to compensate for and adjust to his neurological limitations.

1.7. MJ: The case of Eslinger et al. (1997)

In comparison to Marlowe's (1992) case PL, MJ suffered a similar area of damage to the right prefrontal cortex at a similar age (Figs. 9A and B). Both had involvement of the right middle frontal gyrus and Brodmann's areas 9 and 46 (PL has further extension of the lesion to areas 8 and 10), and both were 3 years of age with normal developmental milestones. MJ has been studied and treated by various psychologists at 8, 14, and 16 years of age, with neuropsychological data available from the latter two evaluations. Hence, follow-up observations are available up to 13 years after early right prefrontal cortex lesion (PL has been followed formally up to 6 years of age thus far).

MJ acquired his lesion from an abscess which was surgically evacuated without complication. His recovery and general health have been excellent, although parents noted a change in behavior very soon after the illness. The earliest psychological evaluation was sought because of concerns for social and attentional abilities. MJ had difficulty establishing friendships, showed disinhibited and acting-out behavior in school and had trouble focussing on schoolwork. Although measured intelligence has consistently been average, his mild perseverative tendencies, impulsive responses and erratic attention required a much greater degree of supervision
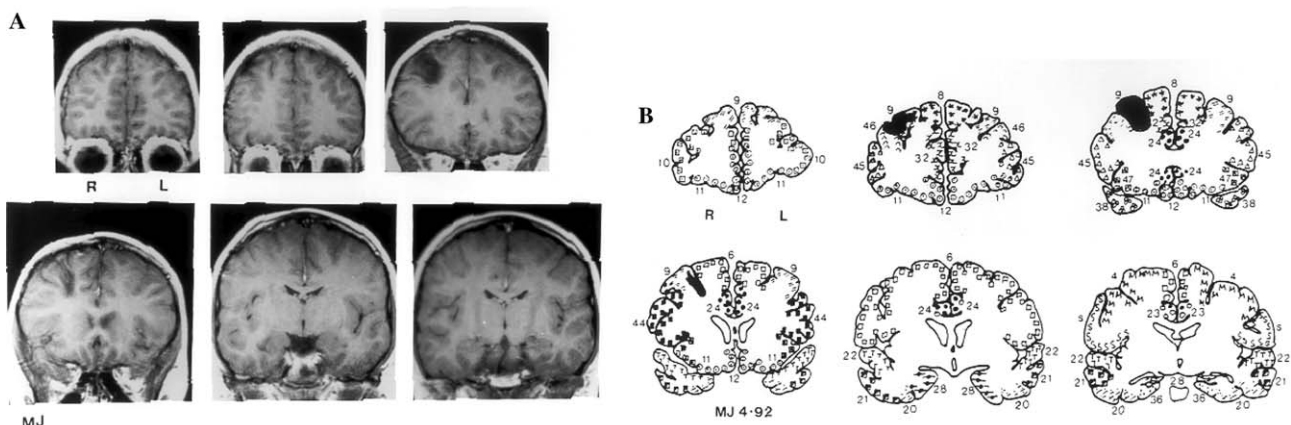

Fig. 9. (A) MRI scan showing right dorsolateral lesion in case MJ. (B) Localization of MJ's lesion on brain templates.

and cuing for school and daily activities. Later studies of other neuropsychologic functions revealed disproportionate problems in the visuospatial aspects of executive processes (e.g., spatial planning, spatial working memory) and poor organizational strategies, even 13 years after his illness.

MJ has grown up in a stable, well-adjusted family, with highly educated and productive parents within a community with supportive services. MJ views himself as "athletic, nice" and denied any form of disability. His parents' report via interview, the Child Behavior Checklist (Achenbach & Edelbrock, 1983) and other inventories, however, indicated concerns about social maturation dating back to nursery school. His social development was judged to be poorer than average, with rare friendships, near-constant conflict with siblings (none of whom showed similar behaviors) and awkward emotional and pragmatic communication skills. Interestingly, while he has been emotionally indifferent to family members, he has always been very kind to the family pets. His social interactions and moral behavior outside the home have always been within legal bounds (he has not shown any delinquent or violent behavior), but can be rude and indifferent to others. This often takes the form of inappropriate jokes about others' misfortunes. He is not a very good liar or manipulator of others, often being foiled in any schemes before long. Being placed in a small, private school actually exacerbated his adjustment difficulties, as he stood out as different from others much more easily than in a large public school. However, he has thrived academically within the larger school setting and has been academically successful even through a college setting.

As with DT (Eslinger et al., 1992), MJ completed the Measures of Psychosocial Development (Hawley, 1988) and also showed relative strengths in his initiation of independent activity (autonomy). He was more comfortable with decision-making and personal competency than DT, and did not feel as distressed or alienated. The social world was more confusing than distressing to him. He viewed the social world with much greater indifference than DT and has not shown her tendencies toward excessive emotional needs and disregard for personal boundaries.

From the data and observations available thus far, MJ appears to have shown several difficulties that have altered his social development after early right prefrontal cortex lesion. One of the most prominent is his emotional indifference which provides a more limited basis on which to interact with others, develop relationships and share experiences. Hence, levels of empathy, perspective-taking and elaborated models of affective experiences and theory of mind are immature. His view of the social world suggests more confusion than alienation, possibly related to the lack of integration between cognitive and emotional processing.

However, within structured settings (college, business office) he has fared well, achieving very good grades and graduating from college, and maintaining a productive position in a business office that requires much telephone and computer communication activities. He has developed a steady relationship with an age-appropriate girl who considers him funny and creative. He is now evaluating the possibly of attending graduate professional school.

1.8. SC: The case of Daigneault et al. (1997)

After an early bout of suspected meningitis at one year of age and recurrence of symptoms at two and one-half years age, SC2 was diagnosed at three years of age with a large, deep cavernous hemangioma in the left frontal lobe. The lesion involved primarily the deep white matter rostral to the head of the caudate (Fig. 10). She was surgically treated at three years and 5 months with no complications, though gait apraxia continued. Pathology confirmed congenital arteriovenous malformation. Because of mother's concerns about SC2's persistent lack of initiative, communicativeness and school achievement over the ensuing three years, she was examined neuropsychologically at 7 and 8 years of age.

As investigators described, neuropsychological examination was most remarkable for "...sluggishness of working memory in the tasks requiring original solutions or requiring goal-oriented reflections ... she was mentally inert ... it was necessary to prod her on affectionately and provide consistent encouragement for her to complete even as much as individual items of several
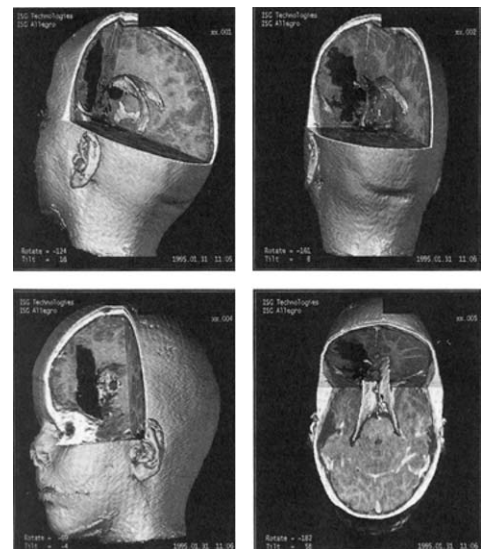

Fig. 10. 3-D reconstruction of SC2's lesion from brain MRI. Reprinted from *Developmental Neuropsychology, 19,* Daigneault, S. et al., Pseudodepressive personality and mental inertia in a child with a focal left-frontal lesion, 1–22, 1997, with permission from Lawrence Erlbaum Associates, Inc.

of the various tests administered" (p. 9). As an example, they reported that spontaneous copy and recall of the Rey complex figure was quite poor. When presented with the same visuospatial material in multiple steps that highlighted new features to be added in each step, she then performed at normal levels, even in delayed recall. Throughout cognitive testing, a range of problematic behaviors were observed, e.g., aloofness, slowness, concreteness, and perseveration. In contrast, SC2 was also described as friendly, affectionate and compliant during testing. Mother and teacher commented on her generous, compliant, and kind behaviors, though at the same time noting her lack of initiative and communication, and emotional dependence on adults. Based on observations and behavior rating scales, the investigators further argued that SC2 gave no evidence of being sad, depressed, irritable or lonely, and hence her persistent symptoms could not be attributed to depression.

Her cerebral lesion extended from the ventral tier of mid and mesial left frontal white matter, sparing the head of the caudate, to dorsal white matter undercutting a fair extent of left dorsolateral prefrontal cortex, possibly mesial premotor cortex as well. Hence, it would be fair to postulate that SC2 suffered extensive white matter disconnection within the left prefrontal region as well as left prefrontal cortical disconnection from thalamic, basal ganglia, limbic and posterior cortical regions. The term "pseudo-depressive" may not be the most accurate or informative label for SC2's neurobehavioral syndrome, as it potentially confuses a clinical emotional syndrome with an acquired one that is multidimensional and has primary cognitive, behavioral, and emotional deficits associated with disruption to prefrontal cortex and its extended neural networks. SC2 presented with an array of developmental deficits not typically associated with early prefrontal cortical damage, as most cases are described as disinhibited and socially callous. Her lesion location may be the key difference, as mesial hemispheric lesions are frequently associated with loss of initiative and motivation in adults and children, the latter suggested by the acute deficits of tumor resection cases described by Stelling, McKay, Carr, Walsh, and Eauman (1986). Most importantly, SC2's deficits were persistent. Cues and urgings from those around her have helped improve her behavior, but on her own she remains significantly impaired in self-regulation. Whether dopamine agonist agents would be of pharmacological benefit, as has been suggested in adults (e.g., Eslinger & Geder, 2000), remains unclear.

1.9. FD and ML: The cases of Anderson et al. (2000)

Studied as a young adult, FD suffered unfortunate traumatic brain injury at 15 months of age when she was run over by a vehicle. She was thought to have fully recovered but by three years of age, mother noted that

FD did not respond to any form of punishment or negative feedback and would take whatever items were about her, often breaking or abusing them. Her behavior was not well-regulated in elementary grades with concerns about an attention deficit disorder and failure to complete assignments. Nevertheless, she was considered intelligent and achieved average grades. Behavior problems became severe by the fourth grade and have persisted since, precluding regular schooling, vocational pursuits and independent living. She required continual placement in psychiatric treatment facilities for poorly regulated behavior, e.g., running away, stealing, poor personal habits, collections of useless objects and continual rule violations. Interventions have ranged from contingency behavioral management to multiple medications, and have not produced any sustainable beneficial effects on her deficits. Socially, she was rejected by peers though could be friendly and even charming toward adults in authority positions. Her emotions were superficial, labile and often exaggerated. Neuropsychological testing revealed broadly average range of general intelligence, academic achievement, short-term memory, speech, language and visual perception. Impairments were evident on some aspects of executive function tasks but not others. Assessment of social–moral reasoning indicated a pre-adolescent stage that centered around avoidance of punishment and egocentric concerns. Brain MRI scan revealed cystic formation in the frontal polar region and structural lesions in the right mesial orbital and left polar cortices (Fig. 11). As reconstructed from her history, FD's adaptive deficits have persisted from childhood and disable her from functioning within real world settings and even structured treatment settings with any degree of independence and productivity. Given the early age of her lesion, key developmental transitions for cognitive and social maturation have been severely disrupted in FD, affecting theory of mind, emotional, empathic, cooperative, self-monitoring, and other executive processes.

Studied as an adult, ML was diagnosed with brain tumor at three months of age and underwent resection of the right frontal lobe. As reconstructed from history, his developmental milestones were on track until kindergarten when behavior problems were identified. These included difficulties staying on task, interacting with peers and adjusting to new situations. Academic achievement levels continued to be grade-appropriate through eighth grade despite persistent problems in attention, inhibition and completion of assignments. Throughout this developmental period, his personal habits were noted to be poor (overeating, erratic hygiene) as were his judgment and awareness of his behavior. After high school his attempts at working and living independently were failures due to motivational, self-regulatory and higher cognitive deficits. He accumulated large debts, ate profusely and was unable
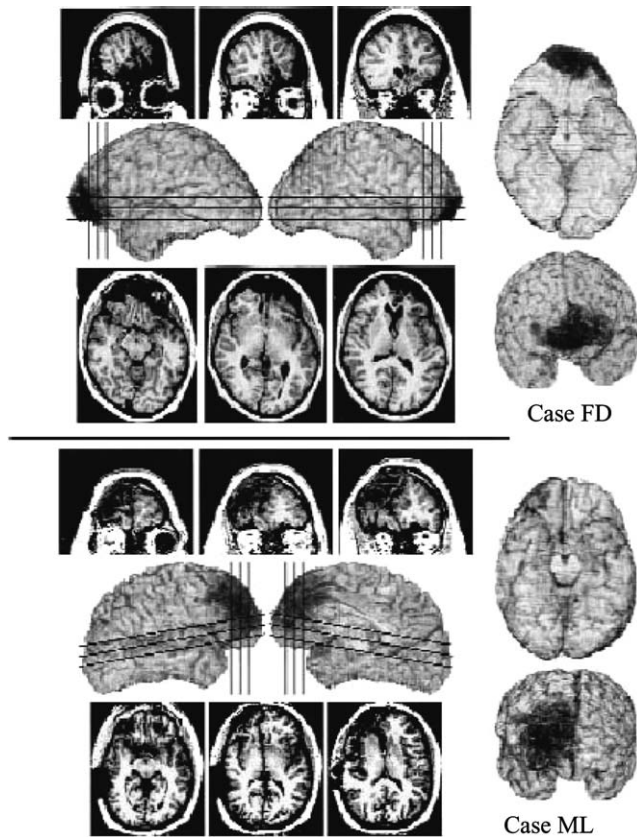
Fig. 11. Lesion reconstructions for FD and ML. Reprinted from *Nature Neuroscience, 2,* Anderson, S. et al., Impairment of social and moral behavior related to early damage in human prefrontal cortex, 1032–1037, 1999, with permission from Nature America Inc.

to anticipate consequences of his actions. Socially and emotionally he developed no sustained or reciprocal relationships, and displayed little to no anxiety, empathy or remorse. As a young adult, he has required the continuing supervisory care of his parents and has maintained at best a part-time restaurant job. Neuropsychological testing revealed an average range of general intelligence, academic achievement and visual perception but erratic levels of short-term memory and executive function performance. Interestingly, his Wisconsin Card Sorting Test scores were entirely normal. Social-moral reasoning abilities were at a pre-adolescent stage with egocentric concerns and avoidance of punishment. Brain MRI scan indicated that ML suffered extensive damage to the right frontal lobe including mesial, polar and lateral sectors. In addition, the lateral half of the right orbital frontal and anterior cingulate regions were damaged along with white matter subjacent to the inferior frontal gyrus.

These two clinical cases have been studied as adults with detailed reconstruction of their respective developmental histories. Both have fared poorly in maturation of social, emotional and executive functioning despite broadly average range of general intelligence,

language, perceptual and sensorimotor abilities. Their pattern of poor developmental outcome after early prefrontal cortex damage confirm that previously reported by Ackerly and Benton (1948) for JP, Price et al. (1990) for GK and MH, Eslinger et al. (1992) for DT and Marlowe (1992) for PL, emphasizing the crucial role of frontal polar, orbital and inferior medial prefrontal structures.

2. Discussion

These prospective and retrospective studies of children and adults who suffered early injuries to prefrontal cortex provide an informative array of observations and data about their psychological development and adaptation as well as clues to the neural systems that mediate these processes. The findings in these cases support an indispensable role of the prefrontal cortex in early and later aspects of psychological development, spanning early childhood through adulthood. Most but not all cases have shown chronic, profound impairments that severely limited their abilities to participate in school, form cooperative relationships within their families and communities, live independently, maintain jobs, and benefit from their positive and negative experiences. These effects have been reflected in a wide range of cognitive, social, emotional and behavioral domains, and would be consistent with the convergent, multi-modal types of anatomy and physiology that characterizes the prefrontal cortices. Damage to this integrative neural region, particularly in its formative stages, may be one of the main reasons for such pervasive adaptive deficits in most of these individuals and the very limited treatment success, psychologically and medically. Neurobiologically, correlates of such outcome may entail not only the prefrontal damage itself but also the profound changes that can be found in interconnected cerebral regions (Goldman & Galkin, 1978; Kolb, Petrie, & Cioe, 1996, 2000) that affect cellular connectivity, brain weight, dendritic arborization, and spine density.

The available cases of early prefrontal cortex damage provide some of the experimental evidence supporting a crucial role for this neural region in psychological development. All exhibited some degree of cognitive alteration, ranging from mild to severe. Most showed ample evidence of marked emotional, social, and moral deficits (the exceptions being MJ, JC, and SC2 whose social comportment have been only minimally affected, not sufficiently disabling to interfere with school and early vocational success where known). Those less affected suffered unilateral damage to dorsolateral prefrontal cortex or deep white matter regions. Those cases most severely affected involved either unilateral or bilateral damage to the frontal poles and/or the orbital

and inferior mesial prefrontal regions, virtually regardless of age of onset. Among these latter cases (JP, GK, ML, FD, PL, MH, and DT), the following deficits were prominent:

- *Social cognition*: Difficulties in cooperative and reciprocal behaviors, limiting ability to abide by, negotiate and agree with others on basic rules and guidelines, to formulate friendships and virtually any other kind of productive or stable relationship. An important underlying deficit may be their limited role-taking and perspective-taking skills that contribute to little understanding of others (i.e., their intentions, beliefs, experiences—their minds) and themselves in relation to others. However, formal testing of social cognition, theory of mind and emotional processing capabilities is very limited in these cases. In addition, they have only indirectly been studied for their expression and comprehension of social signals, for linguistic/pragmatic aspects of social discourse, for other aspects of social cognition including theory of mind, and for risk-taking decision-making (Brothers, 1997; Damasio, Tranel, & Damasio, 1991; Voeller, 1994)—fundamental and longlasting impairments that were suggested by the emotional, social, and moral difficulties they manifested in their everyday lives. Examining the role and influence of social context (e.g., peer interactions, family, and authority figures) in development has also not yet been possible with these cases. Sinclair (1994), for example, suggested that Piaget's theoretical and observational notions supported a "close relationship between logical and moral rules, and the elaboration of both with the gradual development of reciprocity and mutual respect in social interaction." One investigative approach that may be fruitful would entail determining the types of exchanges that occur between the frontally injured children and their peers, in structured and unstructured dyadic and group formats, as well as within family units and other social settings. Though their developmental outcomes underscore consistent impairments, underlying mechanisms of such remain unclear. Investigations could inform models of what common frames of reference are possible in such children, what types of agreements, reciprocity and collaboration can occur, and what interventions (e.g., behavioral, environmental, hormonal, trophic, and other pharmacological) might be tested at various stages to advance both underlying neural compensation and emotional, social and moral development. Deficits in social interactions may be related to social signaling impairments including language (attentional–perceptual level), self-awareness/self-monitoring (metacognition level), emotional indifference (affective level), disinhibition (self-regulation level), or social cognition (theory of mind and social knowledge) that do not permit the development of mental models and emotional processes pertinent to social and moral behavior (Grafman, 1995).

- *Learning*: There was evidence of minimal contingency-based learning and learning from experience in real world contexts. In some cases, such adaptive learning extended little beyond avoidance of punishment, while in others there was not even concern for punishment and hence even less learning. Achievement in school was generally poor though at least one case (FD) attained average grades. Thus, social, adaptive, and systematic academic learning were prominent areas of deficit that significantly limited the cognitive development and behavioral repertoire of cases. However, none would be considered amnesic. Performance on neuropsychological tests of learning and memory was by contrast comparatively better and usually commensurate with general intellectual levels.

- *Cognition*: Cases showed preserved intellectual capacities (as measured by standard IQ tests) but cognitive impairments particularly relating to attention, self-regulatory, and executive functions such as inhibition, planning, organization, working memory, self-awareness/self-monitoring, anticipation of consequences, and goal-directed behavior. While many aspects of 'crystallized intelligence' and semantic processing appeared relatively preserved in these cases, at least until adolescence, 'fluid' or more adaptive aspects of intellectual functions were impaired throughout most developmental phases. Questions about "intellectual" capabilities after early frontal lobe damage are important to refine and investigate. Our impression has been that their intellectual capabilities are indeed dampened by early frontal damage. Duncan et al. (2000) recently argued that measures of general intelligence or Spearman's g factor actually correlated best with functional activation of lateral prefrontal regions in normal volunteers. In these cases, mental models of many human actions, options, possibilities, and behaviors (as reflected through social, emotional and vocational domains) appear to be poorly elaborated and at more primitive levels of development. Waltz et al. (1999) recently argued that the prefrontal cortex mediates important aspects of relational reasoning, allowing individual to inter-relate objects, events, outcomes, and probabilities into more elaborated schemas or models of events and behavior. These cases appeared to show very limited relational reasoning, which is an important component of fluid intelligence.

- *Personality and emotion*: Poor outcome cases showed acquired personality disorder, with by poor judgment, minimal insight and little anticipation of consequence, and personality development that strives for self-initiation and autonomy, but also suggests dissat-

isfaction and confusion with their own sense of competency, identity and relationship to the social world. Irritability, impatience with others, and overriding egocentric concerns were prominent features as well. Emotions in these individual were generally shallow, labile and strongly influenced by immediate situations. They appeared unable to integrate emotions into adaptive processing domains such as learning from experience, development and maintenance of relationships, and motivated, goal-directed behaviors in almost any sphere. Most cases seemed to experience neither anxiety nor very much depth of any emotions, and hence could not utilize emotional experiences and consequences to evaluate events and to guide or monitor their subsequent behavior.

- *Moral behavior and empathy*: Their empathic processes, moral decision-making and behavior were concrete, erratically rule-based and formulated primarily around their own needs. Moral comprehension and behavior depend upon cognitive and emotional empathic processes, and are necessary foundations for many human social and cultural institutions such as family structures, legal and political government systems that affect the lives of virtually every person (Eslinger, Moll, & Oliveira-Souza, 2002; Greene, Sommerville, Nystrom, Darley, & Cohen, 2001). Recent fMRI studies of moral processing suggest that there are at least two distinctive facets to consider: (1) an automatic or implicit level mediated through orbital and inferior mesial prefrontal regions that is highly responsive to moral violations and may be more emotionally based, and (2) a slower acting, cognitive level that becomes alerted secondarily and is mediated through frontal polar and dorsolateral regions that contributes to moral reasoning and perspective-taking (Grattan & Eslinger, 1991; Moll et al., 2002, 2003). The inability to acquire implicit levels of moral sensibility may be related to the frontal polar, orbital and lower mesial prefrontal damage in these cases, and suggest deficits in the processing that typically develops to moral and social norms and transgressions, characterized in recent literature as 'social emotions' (Haidt, 2000: Rozin, Loewry, & Imada, 1999).

The role of particular brain structures and brain maturation in general in psychological development is rapidly becoming a more feasible area of investigation, following in the footsteps of such studies on cognitive development in learning disabilities (e.g., Lyon, 1994; Segalowitz & Rose-Krasnor, 1992), and now being mobilized through the advent of new functional brain imaging (e.g., Bunge, Dudukovic, Thomason, Vaida, & Gabriel, 2002; Bunge, Ochsner, Desmond, Glover, & Gabriel, 2001; Casey et al., 2000). Some initial brain-behavior distinctions can be drawn from early onset cases with primarily dorsolateral, orbital-mesial and

polar prefrontal lesions as well as right vs. left frontal damage. Case JC (Eslinger et al., 2000) provides a clear example of developmental right dorsolateral prefrontal cortex damage. His profile is characterized as one entailing primarily visuospatial and attentional impairments without significant emotional, personality and behavioral problems. A comparable left dorsolateral prefrontal case is not yet reported. SC2 (Daigneault et al., 1997) provides a striking example of developmental mesial frontal impairment with deep white matter disconnection leading to profound loss of initiative and motivation as well as inattention and emotional dependency. Early orbital and polar prefrontal cases (JP, Ackerly & Benton, 1948; DT, Eslinger et al., 1992; PL, Marlowe, 1992; ML and FD, Anderson et al., 2000) provide perhaps the largest subset of the most problematic cases whose intractable deficits in self-regulation, emotion and executive functions have been severely disabling and most challenging to treatment approaches and to legal complications. These varying presentations after damage to dorsolateral, mesial and orbital-polar prefrontal regions are similar in many respects to those reported in adults (Eslinger & Geder, 2000).

Other cases suggest that the effects of early prefrontal cortex damage must be viewed within a dynamic, developmental framework. That is, during development there are very strong interactions among diverse frontal lobe regions, including dorsolateral, ventral, and mesial sectors along with their diverse interactions with thalamic, basal ganglia, limbic, and posterior cortical systems, Thus, an early lesion within the frontal lobe can be viewed as both a localized event and as a reverberating event that affects the maturation of interacting areas mediating the acquisition of representational knowledge, actions and response control through contingency learning. Such multi-system disruption may have underlied the poor developmental outcomes of GK and MH (Price et al., 1990). Viewed in this way, the roles of environmental and experiential factors are heightened and parallel to neurobiological events in brain maturation. This approach may help account for the varying effects of early prefrontal cortical damage that seem to range from being more severe and intractable than comparable adult-onset lesions to showing a better recovery of function pattern than expected.

A comment is warranted regarding the so-called "Kennard effect" that refers to the relatively milder deficits and greater recovery of function that occurs after brain damage early in life (see Finger, 1991 for a review of these issues). Kennard's experiments, completed in animal models during the 1930s and 1940s, did indeed support such a conclusion particularly for the motor system. However, she did not always observe this pattern and other experimental results suggested that more problematic behavioral outcomes occurred after

early damage to association cortices that included the prefrontal region. She also observed the phenomenon of *progressive onset of deficits* as subjects grew. Hence, the Kennard effect is not a consistent finding or feature of early cerebral damage, as the cases reviewed in this paper demonstrated, and may be mitigated and/or modified by differences in the timing of early damage in brain structures with varying rates of maturation.

Returning to the developmental psychology and Piagetian models, observations from these clinical cases would suggest that an early and prominent developmental role for prefrontal cortex would be in organizing and integrating rather disparate and seemingly elusive information about ourselves, others and the world into more consistent rules, guidelines and mental conceptions that allow increasing flexibility to elaborate knowledge and experiences. Early prefrontal cortical damage significantly altered these children as active engineers of their mental and emotional structures as well as beneficiaries of their experiences. Thatcher (1991) and Case (1992) have emphasized, for example, that periodic electrophysiological re-organization occurs throughout development, roughly following a Piagetian model, that brings more structural and functional domains under the influence of prefrontal cortex for the purpose of meeting increasing goals and challenges. Early prefrontal cortex damage likely significantly disrupts such integration and continued re-organization, setting up varying degrees of life-long adaptation difficulties. Rather than a single underlying deficit associated with early prefrontal cortex damage, we interpret the findings from these cases to suggest that it is the impaired integration and interplay of cognitive, emotional, self-regulatory and executive/metacognitive processes that contribute to diverse developmental frontal lobe syndromes. Within these syndromes, core deficits in working memory, inhibition, learning, emotion, elaboration of knowledge, planning and theory of mind can provide some explanation of lifelong adaptive impairments. The findings support the fundamental importance of prefrontal cortex maturation in protracted cognitive, social–emotional and moral development. Further studies are needed to confirm and elaborate on these basic observations and extend the systematic study of cognitive, social, and moral development to many different children with neurodevelopmental conditions.

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