

Impairment of social and moral behavior related to early damage in human prefrontal cortex

Steven W. Anderson, Antoine Bechara, Hanna Damasio, Daniel Tranel and Antonio R. Damasio

*Department of Neurology, Division of Behavioral Neurology and Cognitive Neuroscience, The University of Iowa College of Medicine, Iowa City, Iowa 52242, USA
Correspondence should be addressed to A.R.D. (antonio-damasio@uiowa.edu)*

The long-term consequences of early prefrontal cortex lesions occurring before 16 months were investigated in two adults. As is the case when such damage occurs in adulthood, the two early-onset patients had severely impaired social behavior despite normal basic cognitive abilities, and showed insensitivity to future consequences of decisions, defective autonomic responses to punishment contingencies and failure to respond to behavioral interventions. Unlike adult-onset patients, however, the two patients had defective social and moral reasoning, suggesting that the acquisition of complex social conventions and moral rules had been impaired. Thus early-onset prefrontal damage resulted in a syndrome resembling psychopathy.

It is well established that in adults who have had normal development of social behavior, damage to certain sectors of prefrontal cortex produces a severe impairment of decision-making and disrupts social behavior, although the patients so affected preserve intellectual abilities and maintain factual knowledge of social conventions and moral rules¹⁻⁶. Little is known for certain, however, about the consequences of comparable damage occurring before the maturation of the relevant neural and cognitive systems, namely in infancy, because such cases are exceedingly rare. Information about the early onset condition is vital to the elucidation of how social and moral competencies develop from a neurobiological standpoint. A number of questions have arisen in this regard. First, would early-onset lesions lead to the appearance of persistent defects comparable to those seen in adult-onset lesions, or would further development and brain plasticity reduce or cancel the effects of the lesions and prevent the appearance of the defects? Second, assuming early-onset lesions cause a comparable defect, would there be a dissociation between disrupted social behavior and preserved factual social knowledge, as seen in the adult-onset condition, or would the acquisition of social knowledge at factual level be compromised as well? We addressed these questions by investigating two young adults who received focal nonprogressive prefrontal damage before 16 months of age.

RESULTS

The evidence presented here is based on detailed histories obtained from medical and school records, as well as legal documents, extensive interviews with the patients' parents, clinical and experimental cognitive tasks and neuroimaging studies.

Clinical evidence

The first patient (subject A) was 20 years old at the time of these studies and was ambidextrous. She had been run over by a vehicle at age 15 months. At the time of the accident, she appeared to recover fully within days. No behavioral abnormalities were observed until the age of three years, when she was first noted to

be largely unresponsive to verbal or physical punishment. Her behavior became progressively disruptive, so much so that, by age 14, she required placement in the first of several treatment facilities. Her teachers considered her to be intelligent and academically capable, but she routinely failed to complete assigned tasks. Her adolescence was marked by disruptive behavior in school and at home (for example, failure to comply with rules, frequent loud confrontations with peers and adults). She stole from her family and from other children and shoplifted frequently, leading to multiple arrests. She was verbally and physically abusive to others. She lied chronically. Her lack of friends was conspicuous. She ran away from home and from treatment facilities. She exhibited early and risky sexual behavior leading to a pregnancy at age 18. Contingency management in residential treatment facilities and the use of psychotropic medication were of no help. After repeatedly putting herself at physical and financial risk, she became entirely dependent on her parents and on social agencies for financial support and oversight of her personal affairs. She did not formulate any plans for her future and she sought no employment. Whenever employment was arranged, she was unable to hold the job due to lack of dependability and gross infractions of rules. Affect was labile and often poorly matched to the situation, but superficial social behavior was unremarkable. She never expressed guilt or remorse for her misbehavior. There was little or no evidence that she experienced empathy, and her maternal behavior was marked by dangerous insensitivity to the infant's needs. She blamed her misdeeds and social difficulties on other people, and she denied any difficulties with cognition or behavior.

When first seen by us, the second patient (subject B) was 23 years old. He had undergone resection of a right frontal tumor at age three months. He had an excellent recovery and there were no signs of recurrence. Developmental milestones were normal and he was left handed. In early grade school, mild difficulties were noted with behavior control and peer interactions, but he was not especially disruptive in school or at home. By age nine, however, he showed a general lack of motivation, had limited social interac-

tions, usually exhibited a neutral affect and suffered from occasional brief and explosive outbursts of anger. His work habits were poor, and tutoring was recommended. He was able to graduate from high school, but perhaps because of the loss of structure for daily activities, his behavioral problems escalated after graduation. Left to himself, he limited his activities to viewing television and listening to music. His personal hygiene was poor and his living quarters were filthy. He consumed large quantities of foods with high fat and sugar content, and became progressively more obese. He also displayed abnormal food choices, for instance, eating uncooked frozen foods. Given his frequent absences, tardiness and general lack of dependability, he could not hold a job. He showed reckless financial behavior which resulted in large debts, and engaged in poorly planned petty thievery. He frequently threatened others and occasionally engaged in physical assault. He lied frequently, often without apparent motive. He had no lasting friendships and displayed little empathy. His sexual behavior was irresponsible. He fathered a child in a casual relationship, and did not fulfill his paternal obligations. He was dependent on his parents for financial support and legal guardianship. He showed no guilt or remorse for his behavior and could not formulate any realistic plans for his future.

Both patients were raised in stable, middle-class homes by college-educated parents who devoted considerable time and resources to their children. In neither case was there a family history of neurologic or psychiatric disease, and both patients had socially well-adapted siblings whose behavior was normal. The neurological evaluation was normal in both patients, except for their behavioral defects.

Neuropsychological evidence

Comprehensive neuropsychological evaluations (Table 1) revealed normal performances on measures of intellectual ability (for example, fund of general information, ability to repeat and reverse random sequence of digits, mental arithmetic, verbal reasoning, nonverbal problem solving, verbal and visual anterograde memory, speech and language, visuospatial perception, visuo-motor abilities and academic achievement). As in the case of patients with adult-onset lesions, the behavioral inadequacy of the two patients with early-onset lesions cannot be explained by a failure in basic mental abilities.

The patients were asked to perform several cognitive tasks designed to assess their ability to plan and execute multi-step procedures, use contingencies to guide behavior, reason through social dilemmas and generate appropriate responses to social situations. Both patients had significant impairments on these tasks. They failed to show normal learning of rules and strategies from repeated experience and feedback (Wisconsin Card Sorting Test, Subject A; Tower of Hanoi, both subjects). They also had significant impairments of social-moral reasoning and verbal generation of responses to social situations (Fig. 1). Moral reasoning was conducted at a very early ('preconventional') stage, in which moral dilemmas were approached largely from the egocentric perspective of avoiding punishment⁷. This stage of moral reasoning is characteristic of 10-year-olds, and is surpassed by most young adolescents. The patients demonstrated limited consideration of the social and emotional implications of decisions, failed to identify the primary issues involved in social dilemmas and generated few response options for interpersonal conflicts. Their performance was in stark contrast to that of patients with adult-onset prefrontal damage, who can access the 'facts' of social knowledge in the format used in the laboratory (verbally packaged, outside of real life and real time⁸).

To explore the decision-making process further, the patients participated in a computerized version of the Gambling Task^{9,10}.

Table 1. Standardized neuropsychological test data.

	Subject A	Subject B
WAIS-R		
Information	37	63
Digit span	25	37
Arithmetic	37	63
Similarities	37	25
Block design	75	75
Digit symbol	25	25
RAVLT		
Trial 5	78	11
30 min. recall	99	68
JLO	40	57
Complex figure test		
Copy	21	39
30 min. recall	32	66
WRAT-R		
Reading	86	63
Spelling	81	63
Arithmetic	32	58
COWA	43	15
WCST		
Categories	>16	>16
Persev. errors	1*	88
TOH		
Trial 1	7*	7*
Trial 2	1*	51
Trial 3	1*	1*
Trial 4	1*	1*
Trial 5	1*	1*

WAIS-R, Wechsler Adult Intelligence Scale-Revised; RAVLT, Rey Auditory Verbal Learning Test; JLO, Judgment of Line Orientation; WRAT-R, Wide Range Achievement Test-Revised; COWA, Controlled Oral Word Association; WCST, Wisconsin Card Sorting Test; TOH, Tower of Hanoi. All tests were administered according to standardized procedures^{27,28,29}. Test performances are represented as percentile scores and impairment is indicated by an asterisk.

This task simulates real-life decision-making in the way it factors uncertainty of rewards and punishments associated with various response options. Unlike normal controls, but precisely as patients with adult-onset prefrontal lesions, both patients failed to develop a preference for the advantageous response options. They failed to choose options with low immediate reward but positive long-term gains; rather, they persisted in choosing response options which provided high immediate reward but higher long-term loss (Fig. 2).

The electrodermal skin conductance response (SCR) was used as a dependent measure of somatic-state activation, according to methods described elsewhere¹¹. After repeated trials, normal controls begin to generate anticipatory SCRs when pondering the selection of a risky response (a response which may lead to

<p>Level 3: Postconventional</p> <p>Stage 6: Personal commitment to universal moral principles.</p> <p>Stage 5: Recognition that moral perspective may conflict with law. Consider rights and welfare of all.</p>	<p>Achieved by a minority of adults.</p> <p>One of 6 adult-onset patients at this level.</p>
<p>Level 2: Conventional</p> <p>Stage 4: Recognition of obligations to society. The individual is viewed within the system.</p> <p>Stage 3: Reliance on the Golden Rule. Be a good person in your own eyes and those of others.</p>	<p>Characteristic of most adults and adolescents.</p> <p>Five of 6 adult-onset patients at this level.</p>
<p>Level 1: Preconventional</p> <p>Stage 2: Concrete reasoning that, to serve one's own needs, you must recognize other's rights.</p> <p>Stage 1: Egocentric perspective with decisions based on avoidance of punishment.</p>	<p>Characteristic of most children under age 9.</p> <p>Both early-onset patients at this level.</p>

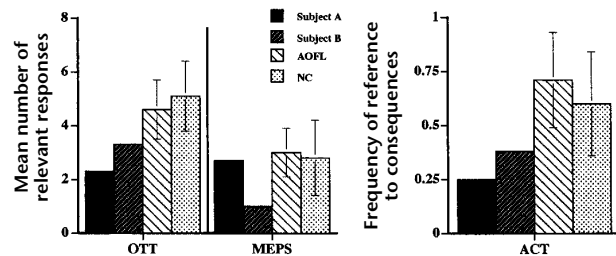


Fig. 1. Social and moral reasoning. (a) Kohlberg Moral Judgment Task. (b) Social fluency; OTT, optional thinking test; MEPS, means-ends problem solving; ACT, awareness of consequences.

long-term punishment). However, both patients failed to acquire these anticipatory SCRs, although they did show normal SCRs to a variety of unconditioned stimuli. Again, these findings were similar to those from patients with adult-onset prefrontal damage¹¹.

Neuroimaging evidence

The patients were studied with research-protocol magnetic resonance imaging, which permitted reconstruction of their brains in

three dimensions using the Brainvox technique and subsequent analysis of their anatomical defects. Both patients had focal damage to prefrontal regions, and had no evidence of damage in other brain areas (Fig. 3). The lesion in subject A was bilateral and involved the polar and ventromedial prefrontal sectors. The lesion in subject B was unilateral, located in the right prefrontal region, and involved the polar sector, both medially and dorsally. The lesions of both patients were located in sites whose damage in adults is known to produce the emotional and decision-making defects discussed above^{2,3,12}. Most frequently, these defects are caused by ventromedial and bilateral lesions, but the condition also has been noted with exclusively right, medial or lateral prefrontal lesions. The critical issue seems to be dysfunction in the medial prefrontal cortices (which can be caused either by direct cortical damage or white matter undercutting) and the sparing of at least one dorsolateral prefrontal sector.

DISCUSSION

We begin by acknowledging that our sample was small, but our findings accord with the only two other recorded instances of patients with early onset frontal lobe damage^{13,14}, both with lifelong behavior dysfunction, although in neither case is there precise neuroanatomical information. (One case, from 1947, predates modern neuropsychological and neuroimaging techniques, and lesions of the other are not described satisfactorily and may not be confined to the prefrontal region.) The sample is valuable, nonetheless, because of its rarity, and the evidence is offered in the hope that it calls attention to other existing cases and facilitates their study and the extension of the preliminary investigation noted here.

In answer to the first question we posed, the evidence presented above suggests that patients with early-onset prefrontal lesions in bilateral ventromedial or right sectors resembled patients with comparable adult-onset lesions in a number of ways. In early-onset patients, emotional responses to social situations and behavior in situations that require knowledge of complex social conventions and moral rules were inadequate. But whereas the early-onset patients were comparable, at first glance, to patients with adult-onset prefrontal lesions, a comprehensive analysis reveals several distinctive features. First, the inadequate social behaviors were present throughout development and into adulthood; second, those behavioral defects were more severe in early-onset patients; third, the patients could not retrieve complex, socially relevant knowledge at the factual level.

The greater severity of impairment in these two subjects was especially notable. The adult-onset prefrontal-lesion patients we studied ($n > 25$) generally do not show the sort of antisocial behavior noted in the early-onset patients, for example, stealing, violence against persons or property. Beyond the acute period, the disruptive behavior of adult-onset patients tends to be more constrained, although impulsiveness and susceptibility to immediately present environmental cues leave them at risk of violating the rights of others. More often than not, the victims are the adult-onset patients themselves, not others, and their social and moral ineptitude can hardly be described as antisocial.

Patients with impairments of social behavior caused by adult-onset lesions of the prefrontal cortex acquire varied aspects of socially

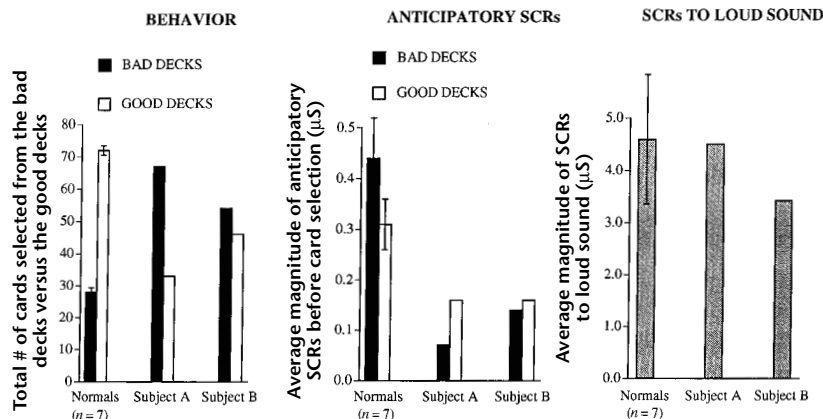


Fig. 2. Experimental decision-making and psychophysiology. (a) Responses on the gambling task. (b) Anticipatory skin conductance responses (SCRs). (c) SCRs to an unconditioned stimulus (sudden onset of 110-dB noise).

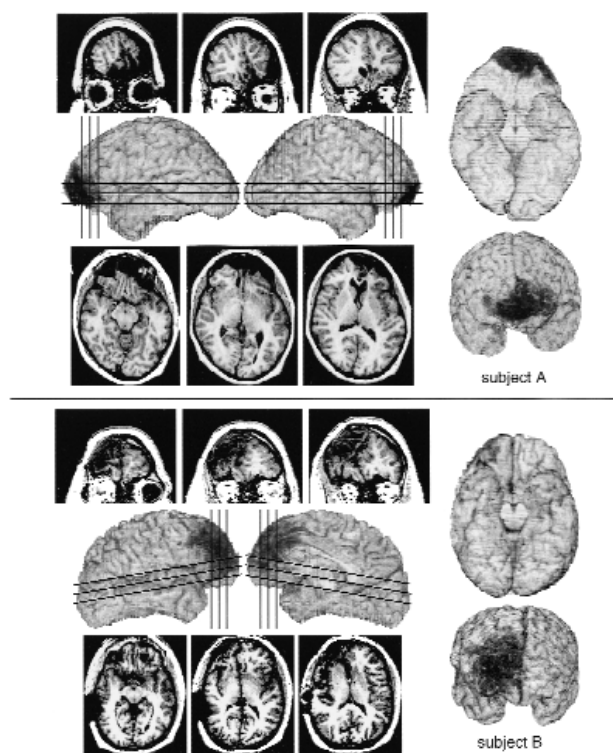


Fig. 3. Neuroanatomical analysis. **(a)** 3-D reconstructed brain of patient 1 (subject A). There was a cystic formation occupying the polar region of both frontal lobes. This cyst displaced and compressed prefrontal regions, especially in the anterior orbital sector, more so on the left than on the right. Brodmann areas 11, 10 and 9 bilaterally, and 46 and 47 on the left, were involved. Additionally, there was structural damage in the right mesial orbital sector and the left polar cortices (Brodmann areas 11, 47 and 10). **(b)** 3-D reconstructed brain of patient 2 (subject B). There was extensive damage to the right frontal lobe, encompassing prefrontal cortices in mesial, polar and lateral sectors (Brodmann areas 10, 9, 46 and 8.) Both the lateral half of the orbital gyri and the anterior sector of the cingulate gyrus were damaged. (Brodmann areas 12, 24 and 32.) The cortex of the inferior frontal gyrus was intact (Brodmann areas 44, 45 and 47), but the underlying white matter was damaged, especially in the anterior sector.

relevant knowledge during normal development, and usually have had decades of appropriate application of such knowledge to social situations before incurring brain damage. As shown here and previously, following lesion onset in adulthood, they can continue to access socially relevant knowledge at the level of declarative facts⁵, and they can even solve social problems when presented in a laboratory setting, that is, in a verbal format, outside of real time. This distinction might explain why the two patients described here seemed to show less of a sense of guilt and remorse relative to their conduct than do adult-onset patients. Admittedly, however, this is a clinical impression, and we have no controlled measurement yet to substantiate it.

The mechanisms whereby adult-onset patients fail in social behaviors are still under investigation, but we have suggested that an important mechanism of the defect is the disruption of the systems that hold covert, emotionally related knowledge of social situations^{2,9}. Emotionally related knowledge is presumed to bias the reasoning process covertly, namely, by enhancing attention and working memory related to options for action and future consequences of choices, as well as to bias the process overtly, by qualifying options for action or outcomes of actions in emotional terms. When emotionally related knowledge, covert or overt, is no longer available or cannot be retrieved, as shown in experiments involving failure of anticipatory psychophysiological responses^{10,11}, the declarative recall of socially relevant facts either does not occur or is insufficient to ensure adequate social behavior in real-life and real-time circumstances. Given that early-onset patients failed in both emotionally-related and factual modes of retrieval, it is possible that they never acquired socially relevant knowledge, either in emotional or factual modes, and that their profound behavioral inadequacy is explained by an absence of the diverse knowledge base necessary for social and moral behavior.

The cognitive and behavioral defects present in these patients arose in the context of stable social environments that led to nor-

mal and well-adapted social behavior in their siblings. In spite of extensive exposure to appropriate social behavior in their home and school environments, and in spite of the relevant instruction, the patients failed to acquire complex social knowledge during the regular development period. Moreover, they failed to respond to programs aimed at correcting their inappropriate behavior during adolescence and young adulthood. This is an intriguing finding. Although comparison of different complex functions should be cautious, it is noteworthy that patients with early damage to language cortices, including those who undergo ablations of the entire left cerebral cortex at ages comparable to those at which our patients acquired their lesions, emerge into adolescence and adulthood with language defects whose magnitude seems smaller than the defects we encounter in the prefrontal patients described here. That the magnitude of compensation seemed smaller in our patients suggests that neural systems impaired by their lesions were critical for the acquisition of social knowledge, at least in the manner in which that acquisition traditionally occurs. It is possible, for instance, that by destroying a critical cortical control for the punishment and reward system, the acquisition of knowledge that depends on the coordinated contributions of punishment and reward situations becomes severely compromised. Should this be the case, it is possible that other neural systems might be recruited for the learning and processing of social knowledge, provided appropriate behavioral or pharmacological interventions could be developed. For example, cognitive-behavioral strategies that rely on a different balance of punishment and reward contributions might prove successful, and administration of neuromodulators such as serotonin and dopamine might conceivably help those interventions.

The cognitive and behavioral profiles resulting from early prefrontal damage resembled, in several respects, the profiles resulting from adult-onset damage. Unlike adult-onset patients, however, early-onset patients could not retrieve complex social knowledge at the factual level, and may never have acquired such knowledge. Overall, the profiles of early-onset patients bore considerable similarity to those of patients with psychopathy or sociopathy ('Conduct Disorder' or 'Antisocial Personality Disorder', according to DSM-IV nosology¹⁵), another early onset disorder characterized by a pervasive disregard for social and moral standards, consistent irresponsibility and a lack of remorse. Psychopathy may be associated with dysfunction in prefrontal regions¹⁶⁻¹⁸, especially in persons without predisposing psychosocial risk factors¹⁸. Also of note, children with antisocial tendencies have deficiencies of moral reasoning relative to age-matched controls^{19,20}, and abnormal psychophysiological arousal and reactivity are found in adults with antisocial behav-

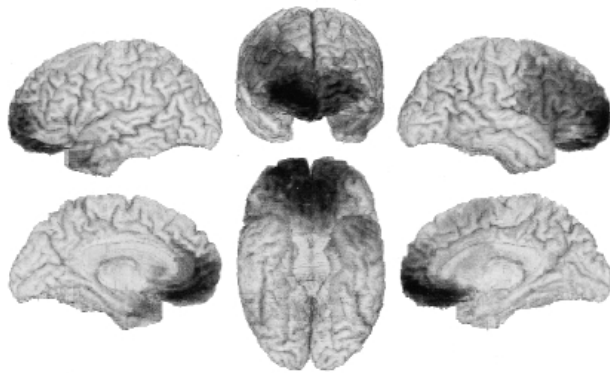


Fig. 4. Control subjects with adult-onset prefrontal damage. The overlap of lesions in the 6 patients with adult-onset lesions is depicted on a normal reference brain. Lesions of individual subjects were transferred onto the reference brain using MAP-3 (ref. 24). Darker shade indicates a higher number of overlapping subjects. The areas involved include all sectors damaged in the target subjects.

ior²¹. The behavior of our patients differed from the typical profile of psychopathy in that our patients' patterns of aggression seemed impulsive rather than goal-directed, and also in the highly transparent, almost child-like nature of their transgressions and their attempts to cover them.

In conclusion, early dysfunction in certain sectors of prefrontal cortex seems to cause abnormal development of social and moral behavior, independently of social and psychological factors, which do not seem to have played a role in the condition of our subjects. This suggests that antisocial behavior may depend, at least in part, on the abnormal operation of a multi-component neural system which includes, but is not limited to, sectors of the prefrontal cortex. The causes of that abnormal operation would range from primarily biological (for instance, genetic, acting at the molecular and cellular levels) to environmental. Further clarification of these questions requires not only additional studies in humans, relying on both lesions and functional neuroimaging, but also experimental studies in developing animals, such as those demonstrating defects in social interactions of neonate monkeys with lesions of the amygdala and inferotemporal cortex²².

METHODS

The behavioral histories were based on evidence obtained from medical and school records and legal documents, as well as extensive interviews with the patients' parents. Participants in this research provided informed consent in accord with the policies of the Institutional Review Board of the University of Iowa College of Medicine. Neuroimaging analysis was conducted by an investigator blind to neuropsychological information, on the basis of thin-cut T1 weighted magnetic resonance (MR) images using Brainvox^{23,24}.

Comprehensive clinical neuropsychological evaluations were conducted according to standardized procedures (Table 1). Assessment of social knowledge and moral reasoning was based on four measures, Standard Issue Moral Judgement (SIMJ)⁷, the Optional Thinking Test (OTT)²⁵, the Awareness of Consequences Test (ACT)²⁵ and the Means-Ends Problem Solving Procedure (MEPS)²⁶. All of these procedures involve standardized verbal presentation to the subject of moral dilemmas or social situations, and require verbal responses.

In the SIMJ task, a subject is presented with a conflict between two moral imperatives (a man must steal a drug in order to save his wife's life). The subject is asked to describe the protagonist's proper actions and their rationale through a series of standard questions (for example, "Should he steal the drug?", "Is it right or wrong for him to steal it?" or

"Why do you think that?"). Responses were scored according to explicit criteria to allow staging of specific levels of moral development. The OTT is designed to measure the ability to generate alternative solutions to hypothetical social dilemmas (for instance, two people disagree on what TV channel to watch). A series of probes are used to elicit as many potential solutions as the subject could produce. The number of discrete relevant alternative solutions is scored. The ACT is intended to sample a subject's spontaneous consideration of the consequences of actions. Hypothetical predicaments involving temptation to transgress ordinary rules of social conduct are presented (for instance, receiving too much money in a business transaction through a mistake), and the subject must describe how the scenario evolves, including the protagonist's thoughts prior to the action and the subsequent events. Scoring reflects the frequency with which the likely consequences of response options are considered. The MEPS is intended to measure a subject's ability to conceptualize effective means of achieving social goals. Scoring is based on the number of effective instrumental acts described as methods of achieving goals in hypothetical scenarios (for example, how to meet people in a new neighborhood).

In the Gambling Task, subjects are presented with four decks of cards (named A, B, C and D) and instructed to select cards from the decks in a manner to win as much play money as possible. After each card selection, they are awarded some money, but certain selections are also followed by a loss of money. The magnitude of the yield of each deck and the magnitude and frequency of punishment associated with each deck are controlled such that choosing from the decks with low initial reward turns out to be the most advantageous strategy over a long series of selections⁹. Subjects are required to make a series of 100 card selections, but they are not told in advance how many card selections they will be allowed to make. Cards can be selected one at a time from any deck, and subjects are free to switch from any deck to another at any time and as often as they wish. The decision to select from one deck or another is largely influenced by schedules of rewards and punishment. These schedules are pre-programmed and known to the examiner, but not to the subject. They are arranged in such a way that every time a card is selected from deck A or B, the subject gets \$100, and every time a card deck is selected from C or D, the subject gets \$50. However, in each of the four decks, subjects encounter unpredictable money loss (punishment). The punishment is set to be higher in the high-paying decks, A and B, and lower in the low-paying decks, C and D. In decks A and B, the subject encounters a total loss of \$1,250 in every 10 cards. In decks C and D, the subject encounters a total loss of \$250 in every 10 cards. In the longer term, decks A and B are disadvantageous because they cost more (a loss of \$250 in every 10 cards). Decks C and D are advantageous because they result in an overall gain in the end (a gain of \$250 in every 10 cards⁶).

The methods for the psychophysiological recordings (Fig. 2) are described¹¹. Response selection in the gambling task was temporally linked by computer to ongoing SCR recordings, and SCRs generated in the four seconds before behavioral response selection were considered to be anticipatory responses. The normal control subjects (three male, four female) were matched to the target subjects for age and education. The control subjects with adult onset prefrontal damage (three male, three female) were selected from our database on the basis of lesion location, in order to provide representation of adult-onset damage to prefrontal areas including, and more extensive than, the areas of damage in the early-onset cases (Fig. 4). Lesions were due to a vascular event ($n = 3$) or resection of a meningioma ($n = 3$). Age of lesion onset ranged from 26 to 51 years, and subjects were studied at least one year following onset.

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