

# Decoupling of Autonomic and Cognitive Emotional Reactions after Cerebellar Stroke

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**Emotional blunting can be found after cerebellar lesions. However, the mechanism of such a modification is not clear. We present a patient with emotional flattening and increased risk taking after left cerebellar infarct who had an impaired autonomic reactivity to negative as compared with positive reinforcement. This impairment was demonstrated by the patient's undifferentiated skin conductance responses to negative and positive reinforcement, whereas controls produced larger skin conductance responses after negative feedback. The cooccurrence of emotional flattening and undifferentiated autonomic reactions to positively and negatively valenced stimuli strengthens the role of the cerebellum in the modulation of the autonomic responses.**

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Although emotional disturbances are typically found after limbic, particularly amygdalar or ventral frontal, damage,<sup>1</sup> there is growing evidence for a cerebellar contribution to affective reactions.<sup>2</sup> Emotional flattening seems to correlate with the extent of cerebellar degeneration.<sup>3</sup> Blunting of affect and inappropriate behavior have been observed, together with executive, visuospatial, and memory dysfunction, after posterior and vermian cerebellar lesions.<sup>4</sup> However, the neural mechanisms underlying cerebellar modulation of emotional experience remain poorly understood.

Theories of emotional experience have distinguished different possible mechanisms.<sup>5</sup> Referring to James' classic example (seeing the bear, running, experiencing fear), visceral feedback hypothesis postulates that emotional experience results from the perception of visceral

changes in response to pertinent stimuli.<sup>6</sup> It is not yet clear if the autonomic response occurs alone<sup>6</sup> precedes,<sup>7</sup> accompanies,<sup>8</sup> or follows a cognitive appraisal.<sup>9</sup> Importantly, all theories posit a modulation of the autonomic system during an emotional experience, whether the change is primary or secondary. The ability of the cerebellum to modulate autonomic reactions<sup>10</sup> could partly explain its importance for emotional responses. Sympathetic skin conductance responses (SCRs) to emotionally pertinent stimuli, as an index of autonomic arousal, are decreased in frontal patients with emotional loss<sup>11</sup> and therefore are well suited for the study of cerebellar patients with emotional blunting.

Here, we present a patient who, after an extensive left cerebellar stroke, showed a severe emotional flattening. This impairment is hypothesized to result from an undifferentiated sympathetic response to the valence of emotion-inducing stimuli.

## Case Report

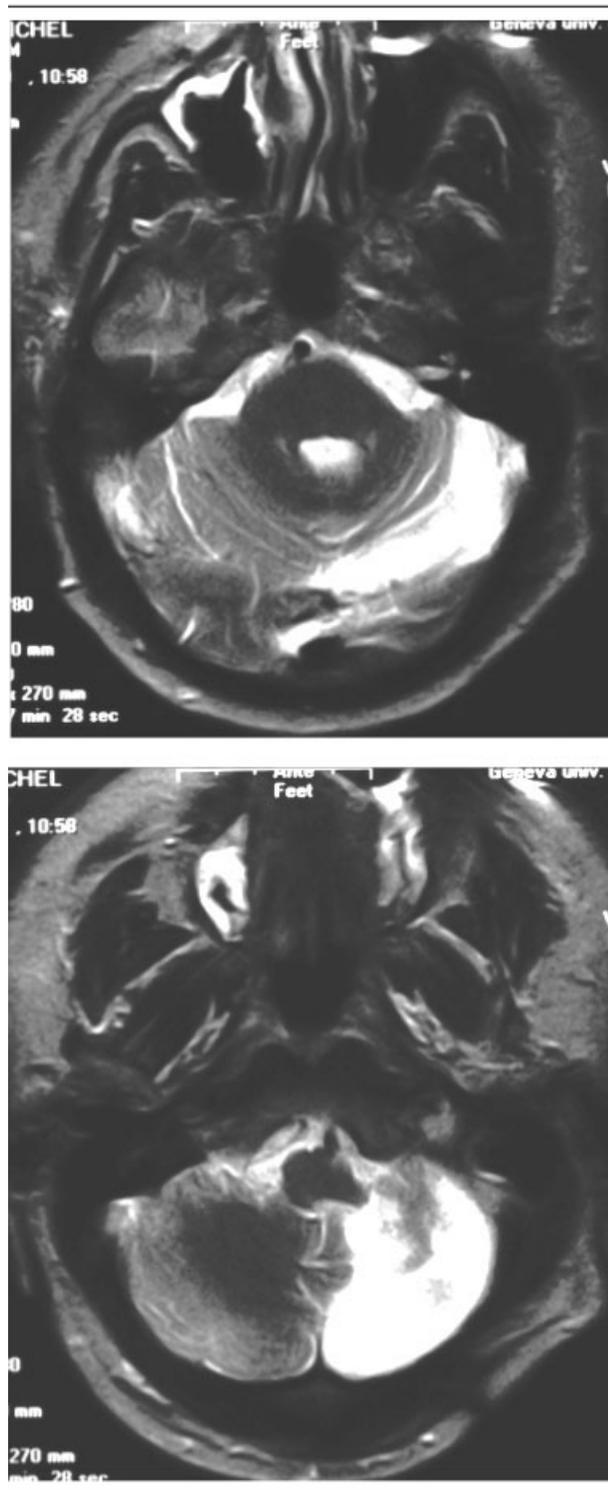
M.F., an overweight and hypertensive 53-year-old right-handed patient was admitted because of unusual headaches, vomiting, instability, and progressive stupor (for approximately 48 hours). On admission, he was bradycardiac, scored 14 at the Glasgow coma scale, and showed Parinaud's syndrome and left hemiataxia at the finger-to-nose and heel-to-shin tests. Pupillary, corneal, and oculomotor reflexes were normal. Computed tomography scan showed a large left cerebellar stroke including the left fastigial nucleus, with mass effect on the fourth ventricle and obstructive supratentorial hydrocephalus. After lateral cerebellar aspiration (at 24 hours), Parinaud's syndrome and hemiataxia disappeared after 2 days. After a subsequent reintervention (10 days later) for an abscess in the epidural layer under the craniotomy scar, neurological recovery was flawless. It was then that M.F.'s wife noticed that her husband appeared more apathetic and "detached from life" than before the stroke. Postoperative magnetic resonance imaging (Fig 1) indicated left posterior inferior and anterior inferior cerebellar infarcts.

Three months after surgery, the patient reported lack of recent memory, difficulties following complex conversations, and difficulties making decisions in daily life. However, his most persistent complaint concerned the loss of emotions. He could neither feel sadness, nor anger or joy. The sensation of pain and hunger was diminished. He also declared that other persons' emotional states had lost importance for him ("Before my stroke, when a person of the family was suffering, it was as if a part of myself was ill. Now, it is a simple fact, like something written in a newspaper.") Self-evaluation of his life situation was marked by affective indifference. At 10 months, reports remained unchanged, particularly concerning loss of emotions and decreased decision-making ability. Neurological status and autonomic evaluations (Table 1) were normal. Neuropsychological evaluation showed slowed reaction times and a relatively low performance in tests of cognitive flexibility and interference control (Table 2). M.F.'s facial expressions (recorded during verbal recall of his own previously experienced emotional re-

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*Fig 1. Transverse magnetic resonance imaging (MRI) sections (at 21mm interval) of the cerebellar lesion 3 months after the stroke (Transverse 7mm thick fast spin echo T2). MRI images demonstrate that M.F.'s stroke included the territories of both anterior inferior and posterior inferior left cerebellar arteries. The dentate nucleus seems partly preserved. No other lesion has been found across the brain.*

actions of joy, anger, and sadness) were analyzed using the Facial Action Coding System.<sup>12</sup> They were undifferentiated, joyful most of the time, and unaffected by the emotional content of the discourse. To assess M.F.'s vocal expression of emotions, his voice was acoustically analyzed.<sup>13</sup> Although talking about joyful experiences produced a higher level of vocal arousal, sad and angry experiences produced undifferentiated responses. M.F. scored 13 of 21 at the Hospital Anxiety and Depression scale,<sup>14</sup> suggestive of moderate depression. Blood tests, including measures of ACTH and TSH levels, were normal, suggesting normal hypothalamic function. Antidepressive medication (citalopram 20mg) was stopped after 6 months, because it changed neither apathy nor depression. A subsequent cognitive therapy focusing on emotional reactions and prosody improved his affective prosody and social integration, but not depression (11/21) nor perception of emotional experiences.

### Results

M.F. consented to participate to this investigation addressing the following questions: (1) Does he have an intact semantic knowledge of emotional stimuli? (2) Does he have normal autonomic reactions to emotionally pertinent stimuli?

M.F.'s semantic knowledge was first assessed using a picture categorization task (240 pictures selected from the International Affective Picture System, rated for arousal and affective valence<sup>15</sup>). Pictures, depicting emotionally positive and negative situations (eg, beautiful scenes, disaster, death) were either low arousal (mean,  $4.3 \pm 0.8$ ;  $n = 120$ ) or high arousal (mean,  $6.3 \pm 0.6$ ;  $n = 120$ ). Images were pseudorandomly presented on the computer screen, and M.F. decided whether they represented positive or negative situations. His performance (19/240 errors) was comparable to that of a control group (mean,  $32 \pm 11.5$  errors;  $n = 11$ , 7 women, age,  $29 \pm 6$ ). Categorization of facial expressions into happy, sad, or neutral<sup>16</sup> was perfect. Auditory categorization of recorded voices expressing sadness, joy, or anger was also correct,<sup>17</sup> indicating that M.F.'s semantic knowledge of emotional stimuli was intact.

To evaluate M.F.'s autonomic responses, SCRs were measured in response to an orientation stimulus (a sudden noise) and to his first name appearing unexpectedly among neutral words (Fig 2A). In both tasks, his SCRs were within the range of control subjects ( $n = 10$ ; 5 women; age,  $45 \pm 9$  years), suggesting that his autonomic system responded normally to stimuli with high salience ( $Z$ -score =  $-0.51$  for sudden noise and  $-0.31$  for his first name).

SCRs also were collected during two other experiments. The first was a conditional learning task requiring M.F. to learn four form-figure pairs across 32 trials; feedback was given after each correct and wrong choice. M.F. showed normal learning ( $Z$ -score =  $0.59$ ), and SCRs were comparable to those of controls

Table 1. Bedside Testing of M.F.'s Autonomic Functions

Evaluation of Autonomic Responses	Score	Norms
Pupillary reactivity to light <sup>a</sup>	4mm/2mm	Clinical judgement
BP (supine position) (mm Hg) <sup>b</sup>	140/90	Systolic: 100 to 150
BP response to standing up (from supine) <sup>c</sup>	120/80	≤30/15 than when supine
Cardiac frequency (baseline)	55/min	<sup>d</sup>
Expiration-inspiration (beats/min) <sup>c</sup>	7	≥9(60 y)
Vaslsalva index (pulse)	1.53	≥1.16

<sup>a</sup>Diameter of each pupil in shadow/diameter after exposure to the light of a pocket electric torch.

<sup>b</sup>Blood pressure after 10 minutes of lying down; BP = blood pressure.

<sup>c</sup>Measured after 1 minute of standing upright (patient moves from supine to standing in about 3 seconds).

<sup>d</sup>Concerning the pulse rate, the low cardiac frequency is probably related to propranolol intake for blood pressure control.

<sup>e</sup>Average difference between maximal and minimal heart during a forced breathing with a frequency of 6 breath/min) is moderately low. However the Valsalva index (defined by Wieling<sup>24</sup> as the longest R-R interval in phase 4 reflex bradycardia/shortest R-R interval in phase 2 compensatory increase in heart rate, when the patient exhales against a resistance of 40 mm Hg for 20 seconds) was normal, suggestive of intact cardiovascular parasympathetic reactive ability (for age-matched controls, see Wieling<sup>24</sup>).

Table 2. Neuropsychological Profile of Patient M.F. 10 months after stroke.

Cognitive evaluation	Score	Percentile
Language		
Boston Naming (34 items)	32	62
Verbal memory		
RAVLT (total trials 1–5)	59	89
RAVLT (trial 5)	15	93
RAVLT (delayed recall)	15	84
Visuospatial memory		
RVDLT (total trials 1–5)	63	90
RVDLT (trial 5)	14	90
RVDLT (delayed recall)	15	99
Attention		
Selective attention (d2): items correct	322	46
Simple reaction times (msec)	414	1
Executive functions		
Phonological fluency (letter)	22	59
Categorical fluency (animals)	33	51
Design fluency (5-point test)	38	91
Stroop interference (time/errors)	121/1	34/—
TMT (time A/time B in sec)	35/104	50/14
WCST, categories	6/48	>50
WCST, perseverations (index)	2/48 (29%)	>50

The Boston Naming 34 items is a shortened French version of original test.

RAVLT = Rey Auditory Verbal Learning Test; RVDLT = Rey Visual Design Learning Test; d2 = d2 attention test (1982 Version); TMT = Trail Making Test; WCST = Wisconsin Card Sorting Test (Nelson's short version).

(n = 10; 5 women; age, 45 ± 9 years), indicating a preserved overall reactivity. However, whereas healthy participants showed higher SCRs to feedback for wrong (0.94μS) than for correct (0.29μS) choices (Wilcoxon Z = 2.4; p < 0.05), M.F. did not respond differently to these two conditions (0.42 and 0.39μS, respectively, see Fig 2B).

The second assessment involved the “gambling” task,<sup>11</sup> which requires subjects to select a card from one of four stacks representing advantageous (ie, associated with small money gain but an even smaller loss) or disadvantageous (associated with a large gain but an even larger loss). Patients with ventromedial damage consistently preferred the disadvantageous cards and showed diminished SCRs preceding their choice.<sup>11</sup> Like these patients, M.F. chose more frequently disadvantageous (62/100) than advantageous decks (38/100) and thus gradually lost his money. Afterward, he reported that some decks seemed worse than others, without being able to specify why. His disadvantageous choices did not appear to be caused by a lack of anticipation, since, as previously reported in controls,<sup>11</sup> his SCRs preceding disadvantageous choices were significantly higher (0.24μS) than SCRs preceding advantageous choices (0.17μS; p < 0.05). In contrast, M.F. did not show differential responses to low (0.42μS) and high (0.38μS) money loss, supporting the results found in the conditional learning task.

## Discussion

The cerebellar cognitive-affective syndrome<sup>4</sup> presented by this patient appears particularly interesting in view of his self-reported inability to experience emotion and of his moderate depression. Our investigation indicates that M.F.'s emotional flattening was caused neither by an inability to cognitively evaluate emotional situations nor by a general autonomic dysfunction. Actually, both his Valsalva index and his SCRs to sudden noise, to his name, and before disadvantageous choices (gambling task) were normal. These findings indicate that arousal responses to salient stimuli were unaffected. The major difference between M.F. and healthy subjects concerned the failure of his autonomic system to generate different arousal responses to positive and negative situations. In the conditional learning task, based on cognitive deduction, absence of differential autonomic re-

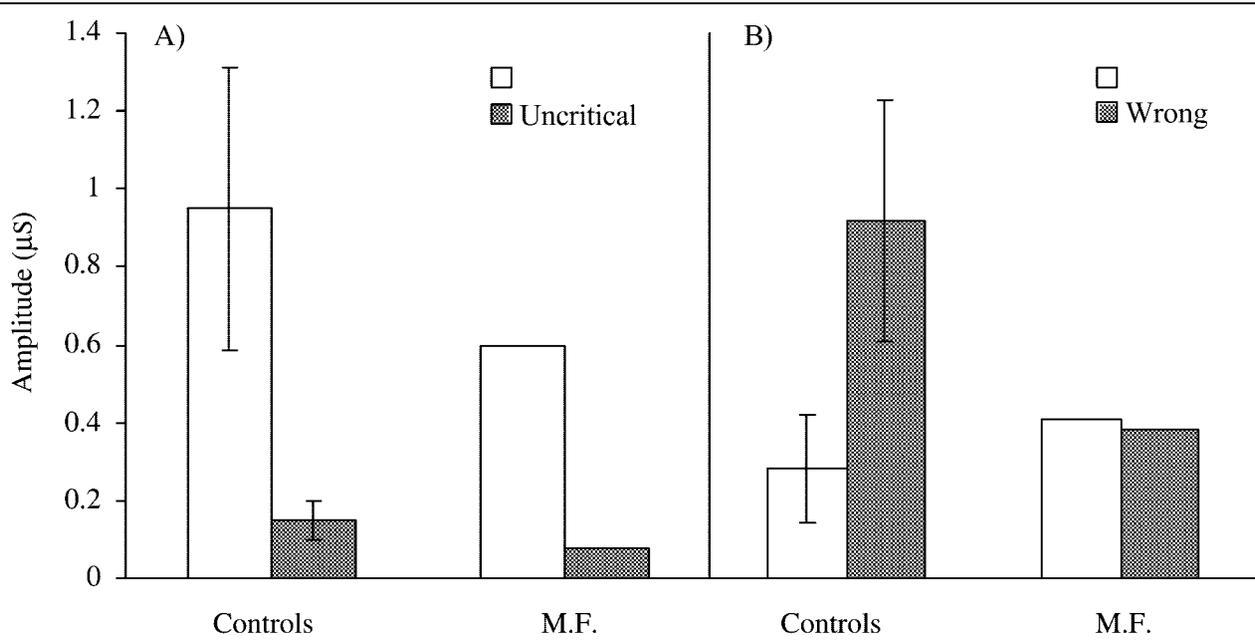


Fig 2. Mean ( $\pm$  SEM) skin conductance responses (SCRs) of control subjects and patient M.F. in two tasks. (A) The pattern of M.F.'s SCR to the critical (first name, white histograms) and uncritical stimuli (neutral words, dark histograms) is comparable to that of control subjects. (B) SCRs in the conditional learning task after positive feedback for correct responses (unshaded bars) or negative feedback for wrong responses (shaded bars). Unlike control subjects, M.F. did not show differential responses in these two conditions.  $\mu S$  = microsiemens.

actions to positive and negative outcomes did not interfere with M.F.'s performance. In contrast, in the gambling task, where decisions are hypothesized to rely on experienced somatic arousal,<sup>11</sup> SCR undifferentiated responses to positive and negative outcomes were associated with behavioral failure. Interestingly, despite his failure in the gambling task, M.F. generated normal anticipatory SCRs. This pattern, being the inverse of that observed after ventromedial damage,<sup>11</sup> suggests a possible independence between self-generated anticipatory autonomic activity and reactions to external stimuli (externally provided feedback). We hypothesize that M.F.'s autonomic inability to react differentially to positively and negatively valenced external stimuli constitutes a possible explanation for his reported loss of to experience emotions.

Although alterations of SCRs in cerebellar patients are not well documented, several studies suggested the involvement of the cerebellum in autonomic function. Autonomic dysfunction was shown to increase in cerebellar atrophy.<sup>18</sup> Electrical cerebellar stimulation was shown to induce autonomic arousal and predatory behavior<sup>19</sup> and to modulate ventrolateral medullary adrenergic vasomotor neurons.<sup>20</sup> Cerebellar damage was shown to alter autonomic cardiovascular responses.<sup>10</sup> Finally, in accordance with anatomical findings demonstrating dense connections between the fastigial nucleus and the hypothalamus (strongly implicated in sympathetic and parasympathetic modulation),<sup>21</sup> func-

tional imaging studies proposed the involvement of the left cerebellum in autonomic arousal and in SCR generation.<sup>22</sup> In line with the above evidence, but also with works suggesting a role for the cerebellum in depression,<sup>23</sup> this single case investigation points to a role for the cerebellum in the generation of emotionally congruent autonomic reactions. Additional group studies are needed to confirm this interpretation.

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## Polymicrogyria and Absence of Pineal Gland Due to *PAX6* Mutation

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**Identification of genes involved in human cerebral development is important for our understanding of disorders with potential neurodevelopmental causes such as epilepsy and learning disability. Murine models suggest that *PAX6* plays a key role in human brain development. With magnetic resonance imaging in 24 humans heterozygous for defined *PAX6* mutations, we demonstrated widespread structural abnormalities including absence of the pineal gland and unilateral polymicrogyria.**

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*PAX6* is a highly conserved developmentally regulated gene, encoding a transcription factor containing two DNA-binding domains, a paired domain, and a homeodomain. *PAX6* is known to influence cellular proliferation, neuronal migration, and axonal guidance in the brain.<sup>1–5</sup> Mice homozygous for mutations in the perfectly conserved *Pax6* gene die neonatally, with a wide variety of neurodevelopmental abnormalities, including polymicrogyria, subcortical heterotopia, and absence of the corpus callosum, olfactory bulb, cerebellar vermis and pineal gland,<sup>6,7</sup> and anophthalmia and absence of nasal structures and the pancreas. Murine heterozygotes have microphthalmia, iris hypoplasia, cataracts and corneal anomalies, and olfactory bulb and cerebral abnormalities, which are much less severe than

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