Original article

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Improved decision-making and psychophysiological responses in mesial temporal lobe epilepsy after anterior temporal lobectomy*

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ABSTRACT – *Aim.* The somatic marker hypothesis is an influential model of human decision-making postulating that somatic feedback to the brain enhances decision-making in ambiguous circumstances, *i.e.* when the probabilities of various outcomes are unknown. The somatic feedback can be measured as autonomic responses, which are regulated by the amygdala. The failure to evoke this somatic feedback, which occurs in patients with amygdala lesions, impairs decision-making. The purpose of this study was to investigate the decision-making behaviour of mesial temporal lobe epilepsy patients with pre- and post-epilepsy surgery to ascertain whether the decision-making abilities of groups can be explained by means of the generation of somatic feedback responses.
Methods. The preoperative group comprised 32 patients with mesial temporal lobe epilepsy due to hippocampal sclerosis, while the postoperative group comprised 23 patients who had undergone anterior temporal lobectomy. The age and gender-matched control group consisted of 30 healthy participants. Decision-making performances were assessed and skin resistance responses were measured simultaneously.
Results. The findings of this study reveal that the decision-making performance of preoperative patients with unilateral mesial temporal lobe epilepsy was impaired under conditions of ambiguity, *i.e.* they did not generate somatic feedback responses before making decisions around ambiguous outcomes, and produced significantly poor scores overall based on a decision-making task. In addition, the resection of epileptogenic limbic

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structures positively affected the generation of somatic feedback responses, as demonstrated by the significant difference between the magnitudes of autonomic responses of the pre- and post-operative groups. *Conclusion.* The findings of the study validate the contribution of mesial temporal lobe structures to decision-making behaviour, and also point to the importance of examining the connectivity patterns between the neural structures involved in the decision-making network.

Key words: temporal lobe epilepsy, decision-making, epilepsy surgery, somatic-marker hypothesis, psychophysiology

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is commonly an intractable type of epilepsy that is highly responsive to anterior temporal lobectomy (ATL), in which the uncus, entorhinal cortex, amygdala, and temporal neocortex are resected unilaterally. Hippocampal sclerosis is the major pathology, but there are electrophysiological and neuropathological data indicating a contribution from the neighbouring structures, namely the amygdala and parahippocampal gyrus (Malmgren and Thom, 2012). Patients affected by this type of epilepsy also present with various types of psychiatric, behavioural, and cognitive comorbidities (Verrotti *et al.*, 2014). While cognitive functions such as memory, language, and executive functions have been studied extensively (Zhao *et al.*, 2014), only a few studies have investigated the decision-making behaviours of MTLE patients. The findings of these studies support the role of limbic structures by showing impaired decision-making performances in these patient groups (Bonatti *et al.*, 2009). Delazer *et al.* (2010) found that in situations of ambiguity, MTLE patients showed marked decision-making deficits and did not improve their decision-making performances over the task, as compared to controls. Labudda *et al.* (2009) compared the decision-making performances of MTLE patients in risky and ambiguous situations. Patients performed normally in decision-making under risk, but showed deficits in decision-making under ambiguity.

According to the Somatic Marker Hypothesis (SMH), when an individual has to make a decision in a situation that involves complexity and ambiguity, a biasing signal known as the "somatic marker" drives the decision-making process in an advantageous direction (Damasio, 1994). The amygdala is a critical structure in terms of its contribution to stimulating this signal (Damasio, 1994). This signal is then received by the autonomic nervous system, a known function of which is the adjustment of the physiological parameters in the body, such as the increased secretion of sweat during emotional arousal (Naqvi and Bechara, 2006). This increase in the quantity of sweat can be measured either by a change in skin conductance or by a change in skin resistance (Grimnes *et al.*, 2011). In order to test SMH, Bechara *et al.* (1994) developed the Iowa Gambling Test (IGT; see Methods), which simulates real-life decision-making in terms of ambiguity, reward, and punishment, and compared the IGT performances of patients with lesions in the ventromedial prefrontal cortex (VMPFC) with those of the controls. In their first study, Bechara *et al.* (1996) found that while the controls gradually began making more advantageous decisions as the task progressed, patients with lesions in the VMPFC continued to make disadvantageous choices. Moreover, the anticipatory autonomic responses recorded from the controls before making disadvantageous decisions were higher than when making advantageous choices. This was interpreted as an absence of somatic markers to enhance the decision-making of the patients with VMPFC lesions, and positioned the VMPFC as a crucial neurobiological structure in creating somatic markers (Zahn *et al.*, 1999; Bechara *et al.*, 2001).

The SMH also addresses the important role of the amygdala in this process. In a later study, Bechara *et al.* (1999) compared the IGT performance of patients with bilateral VMPFC damage to those with bilateral amygdala damage and simultaneously measured the autonomic responses of both groups. Both patient groups lacked somatic markers and performed worse than the healthy controls. Additionally, the autonomic responses recorded after punishments during the IGT were higher in both the VMPFC patients and the control group than those in the patients with amygdala lesions, leading to the supposition that the inability to evoke somatic markers might be explained by different underlying mechanisms in these patient groups.

We extend previous studies on poor decision-making in MTLE by assessing decision-making performance in addition to measurement of the accompanying autonomic responses relative to the performances of healthy controls. We hypothesize that since decision-making in ambiguous situations relies heavily on emotional and cognitive processes mediated by mesial temporal lobe structures (Bechara *et al.*, 1999), pre-operative patients would show lower autonomic responses to punishment in comparison to those of the healthy controls and to those of the postoperative patients; and their decision-making performances would be significantly poorer than those of the healthy controls and those of the postoperative patients. Additionally, as a result of the resection of the dysfunctional amygdala, the autonomic responses to punishments in the postoperative group would be higher than those of the preoperative group. Also, we hypothesize that since the postoperative patients' autonomic responses to punishment would be higher than those of the preoperative patients, their autonomic responses before making disadvantageous decisions would be significantly higher than those of the preoperative groups, which in turn, would lead them to have better decision-making performances than those of the preoperative groups.

Materials and methods

Participants

Participants in the preoperative and postoperative groups were selected among patients referred for epilepsy treatment to the Department of Neurology at the Cerrahpaşa Faculty of Medicine at Istanbul University. The inclusion criteria were diagnosis of epilepsy with typical aura and/or seizures originating from mesial temporal structures. Patients with intellectual disability and those who were illiterate were excluded. Demographic data, neuropsychological tests, routine EEGs, and MRI scans were obtained for each patient. Ictal video-EEG recordings were also obtained for all patients who were candidates for surgery or who had already undergone surgery.

Patients in the preoperative group had intractable seizures, which were defined as uncontrolled seizures despite the administration of at least two antiepileptic drugs (AEDs) at therapeutic doses. Twenty-five patients in this group had seizures 1-10 times per month. One had daily seizures. Six patients had seizures approximately 1-3 times per year. The mean frequency of seizures in this group was 4.59 ± 4.11 per month (1-20). For the postoperative group, the surgical method was the standard anterior temporal lobectomy resection of the hippocampus, uncus, entorhinal cortex, amygdala, and temporal neocortex, 4.5 to 5.5 cm, depending on the side (Binder and Schramm, 2008). For the postoperative group, the average time since ATL was 5.93 ± 4.41 (1-16) years. Nineteen patients in the postoperative group were seizure-free although six had seizure recurrences after drug withdrawal, but had achieved remission with the reintroduction of the drugs. One had rare nocturnal focal seizures with automatisms. Three patients had persistent seizures after surgery. The clinical properties of both patient groups are shown in *table 1*.

Participants without intellectual disability and without any neurological or psychiatric disorders were recruited for the control group. There were no significant differences regarding mean age or education years between the groups (p = 0.244 and p = 0.644, respectively). Chi square tests revealed no significant difference in the number of male or female participants across the groups (p = 0.757).

The study was approved by the local ethics committee (approval number: 19451483/604.01-5548) under the guidelines of the Declaration of Helsinki and supported by the Scientific Research Projects Coordination Unit of Istanbul University (project number: 44547).

Assessing decision-making: The Iowa Gambling Test

All participants were administered a computerized version of the Turkish adaptation of the IGT (Bechara *et al.*, 1994; Icellioglu, 2015). In the IGT, participants are seated in front of a computer screen which shows four decks of cards, labelled A, B, C, and D. The screen also shows that the participant has a stake of 2,000 Turkish Liras (TL) prior to the start of the game. The task requires participants to select one card from four

Table 1. Clinical variables of patient groups.

	n	F/M	Age (years) (M±SD)	Education (years) (M±SD)	Onset age of epilepsy (years)	Duration of epilepsy (years)	Number of antiepileptic drugs	Lateralization of lesion (R/L)
Preoperative group	32	23/9	31.3± 9.73	9.2±3.46	15 (1-46)	15.5 (3-37)	2.15 (1-3)	21/11
Postoperative group	23	12/11	35.3±11.1	8.5±3.55	10.69 (1-28)	24.85 (8-52)	1.69 (0-3)	10/13
Control group	30	21/9	30.8±11.18	9.4±3.09				
p value		0.75	0.24	0.64	0.11	0.00	0.49	0.21

F/M: number of female and male participants respectively; M±SD: mean and standard deviation; R/L: right and left (for the calculation of duration of epilepsy in the postop group, three patients who were seizure and drug-free were excluded).

identical-looking decks of cards for 100 trials. Unbeknownst to the subject, each card choice leads either to a variable monetary reward or to a combination of a variable monetary reward and punishment. For each selection from decks A and B, participants win 100 TL, and for each selection from decks C and D, participants win 50 TL. Overall, the high-reward decks (A and B) lead to higher levels of punishment (*i.e.* causing a net loss of 250 TL every 10 trials), whereas the low-reward decks (C and D) lead to lower levels of punishment (*i.e.* leading to a net gain of 250 TL every 10 trials). Thus, successful task performance relies on choosing more from decks C and D (the advantageous decks) than from decks A and B (the disadvantageous decks). A visual representation of profits and losses, reflected by a green bar that increases or decreases in size on the screen, to record the total money held by the participants is displayed after each selection. Participants are instructed that the game requires them to choose cards from any one of the four decks until they are told to stop. The goal of the game is to acquire as much money as possible and to avoid losing money as far as possible. As in conventional analyses of IGT performance (Mazas *et al.*, 2000; Ernst *et al.*, 2003; Bechara *et al.*, 2005), the task was divided into five blocks of 20-card selections to examine the changes in performance over time. A total net score for 100 trials and net scores for each five consecutive blocks of 20 trials were computed by subtracting the total number of choices from decks C and D from the total number of choices from decks A and B [(C′+D′)-(A′+B′)]. This calculation provided six net scores for the IGT, including a net score for each of the five blocks and an overall net score for 100 trials.

Skin resistance response during the Iowa Gambling Test

We used electrodermal skin resistance response (SRR) as the dependent measure of autonomic nervous system activation. Electrodermal activity was recorded as skin resistance values during the IGT using the DERMAN system (TEKNOFIL Research, Inc., Istanbul, Turkey) at a rate of 10 samples per second. Electrodes were attached to the thenar and hypothenar palms of the non-dominant hands of the participants. Although the measured skin resistance was computed by measurement of impedance value, these impedance values were transformed into random real numbers. In other words, although the measurements were computed as kOhm, these values were considered real numbers.

The moment at which a participant made a choice was shown as a marker on the recording screen for the SRRs. Inter-trial intervals were fixed at a minimum of six seconds in this version of the IGT to ensure the recording of an anticipatory SRR (Guillaume *et al.*, 2009). The SRRs generated during the task were divided into two categories: (1) punishment SRRs as mean amplitudes of SRRs recorded during the five-second interval after clicking on a card which was followed by an overall loss of money; and (2) anticipatory SRRs as mean amplitudes of SRRs generated during the period between the end of the five-second interval of the SRR outcome and the following selection of a deck (Guillaume *et al.*, 2009).

Statistical analysis

The data were analysed using the Statistical Package for the Social Sciences for Windows, Version 23 (SPSS Inc., Chicago, IL) and were inspected for normality to ensure that the assumptions of parametric statistics were met before analyses were performed. Performance on the IGT was analysed by means of a repeated-measures analysis of variance (ANOVA), with block (five levels) as the within-subjects factor and groups (preoperative, postoperative, control) as between-subjects factors. Differences between the net scores of the first and last blocks of the IGT were analysed by means of pairwise t tests for each group separately. Magnitudes of anticipatory SRRs were compared by means of two-way ANOVA with decks (two levels; AB/CD) as the within-subjects factor and groups (preoperative, postoperative, control) as between-subjects factors. Magnitudes of punishment SRRs were compared by means of one-way ANOVA. For multiple comparisons, Scheffe post hoc tests were conducted. Finally, Pearson correlation analysis was conducted to investigate whether IGT performance and SRR magnitudes correlated with the duration of illness and the number of AEDs in each of the patient groups.

Results

Decision-making task performances of patient and control groups

Because the assumption of sphericity was not met (Mauchly's $W = 0.63$; $p < 0.01$), the degrees of freedom for tests of within-subjects effects were adjusted using the Greenhouse-Geisser F test. Between-subjects tests revealed a significant main group effect (F [2.45, 448.8] = 4.64, $p = 0.01$; $\eta 2=0.102$). Scheffe post hoc tests indicated that, overall, the preoperative group made significantly more disadvantageous choices than the control group ($p = 0.01$); the postoperative group did not differ from the other groups. Within-subjects tests showed a significant main effect of block (F [3, 255] = 7.29, p = 0.00, $\eta 2=0.08$), but there was no

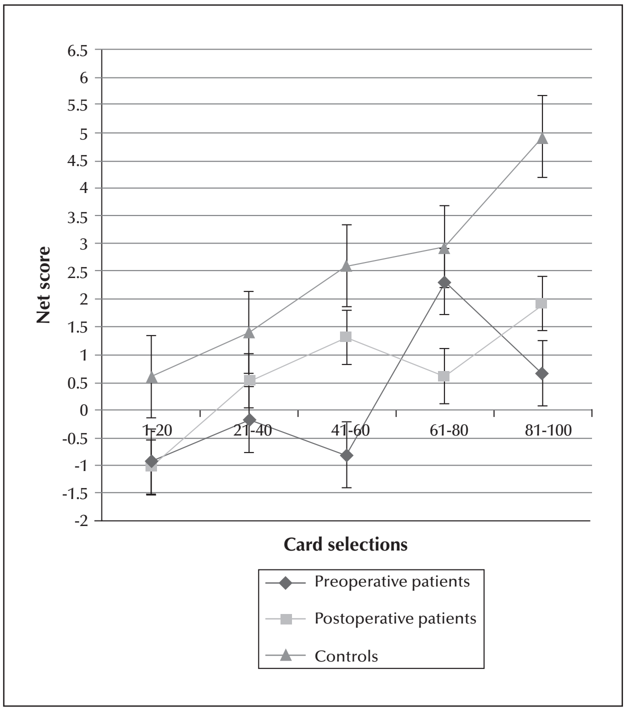

Figure 1. Mean ± SEM number of selections from advantageous/disadvantageous decks by control (*n*=30), preoperative (*n*=32), and postoperative (*n*=23) patients across blocks of 20 card selections in the Iowa Gambling Test (Preop: preoperative, postop: postoperative).

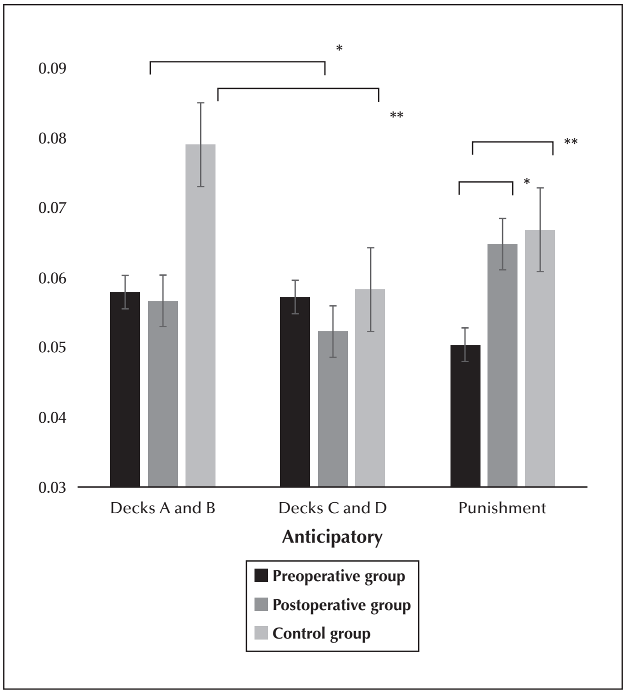

Figure 2. Mean ± SEM amplitudes of anticipatory and punishment SRRs generated by control (*n*=30), preoperative (*n*=32), and postoperative (*n*=23) patients averaged across all cards selected from advantageous (C and D) and disadvantageous (A and B) decks. **p*<0.05, ***p*<0.01.

significant block x group interaction (F [6, 255] = 1.61, p = 0.14, η2=0.04) (*figure 1*).

According to paired-sample comparisons, significant differences were found between the first and last block net scores in both the postoperative (t [22] = -2.63, *p* = 0.01) and the control groups (t [29] = -3.74, *p* = 0.001), showing that the performance of these participants improved over time, consistent with learning. In the preoperative group, no significant difference was found.

Anticipatory and punishment SRRs across groups

A two-way ANOVA on the means of anticipatory SRRs generated by the preoperative, postoperative, and control groups in association with the disadvantageous decks (A and B) and advantageous decks (C and D) revealed a significant main effect of deck (F [1, 77] = 18.178; η2 = 0.19; *p* = 0.00), *i.e.* the magnitudes of anticipatory responses before choosing from disadvantageous decks were larger than the magnitudes of anticipatory responses before choosing from advantageous decks. A significant interaction of group with deck (F [2, 77] = 10.151; η2 =0.21; *p* = 0.00) was also found. Further investigations of the significant interaction were analysed by means of pairwise t tests. For the preoperative group, the difference between the magnitudes of anticipatory SRRs before choosing from advantageous and disadvantageous decks were not significant. For the postoperative and control groups, the magnitudes of SRRs to the disadvantageous decks were significantly higher than SRRs to the advantageous decks, indicating that the groups generated larger anticipatory responses prior to choices from the disadvantageous decks than to choices from the advantageous decks (*p* = 0.01 and *p* < 0.01, respectively).

One-way ANOVAs of punishment SRRs revealed a significant difference between the magnitudes of groups' responses (F [2, 80] = 5.96; η2 = 0.13; *p* = 0.04). Scheffe post hoc tests revealed that the punishment SRRs of the postoperative patients and those of the control group were significantly higher than those of the preoperative group (*p* = 0.01, *p* = 0.001, respectively) (*figure 2*).

Correlations of decision-making performances and SRRs with clinical variables

Since significant differences were found in the number of AEDs and the duration of illness between the preoperative and postoperative patient groups, as shown in *table 1*, we examined the relationship of these variables with decision-making performances and the magnitudes of autonomic responses for each of the groups separately. No significant relationships were found between these variables in patient groups (*table 2*).

Discussion

In the present study, we assessed the decision-making performance of preoperative and postoperative patients with unilateral MTLE with hippocampal sclerosis under ambiguity and compared the scores of patient groups with those of a control group.

The first major finding of this study was that the decision-making performances of the preoperative group were poorer than those of the control group. Patients in the preoperative group made more disadvantageous choices and showed no learning over time. This finding is consistent with previous studies that examined the decision-making performances of MTLE patients (Bonatti *et al.*, 2009; Labudda *et al.*, 2009; Delazer *et al.*, 2010). On the other hand, the decision-making performance of the postoperative group did not differ significantly from those of the control group. Second, the autonomic responses to punishments in the preoperative group were significantly lower than those in both the postoperative and control group. The third major finding of this study is that in both the postoperative and control groups, the autonomic responses generated before making disadvantageous decisions were significantly higher than those generated before making advantageous decisions. However, this difference did not reach a significant level in the preoperative group. It can be inferred from this finding that both the postoperative and control groups acquired somatic markers which acted as warning signals during the time the participants were deciding which deck they would choose, as suggested in SMH.

Decision-making behaviour is a function of a neural network that involves various neural structures including the hippocampus, dorsolateral prefrontal cortex, amygdala, VMPFC, insula, and somatosensory cortex (Damasio, 1994; Cohen *et al.*, 2008). In this neural network, the amygdala is responsible for the acquisition and/or association of information regarding the emotional value of an event or a stimulus (*e.g.* monetary reward or punishment). The VMPFC receives this information and uses it to induce somatic signals that are thought to be involved in ensuing decision-making behaviour in an advantageous way. This suggests that the VMPFC can induce these somatic signals only in the presence of a healthy, functioning amygdala. In our study, the autonomic responses recorded after choosing from the disadvantageous decks were measurements of these somatic feedback responses elicited by the amygdala and were found to be smaller in the preoperative group. Furthermore, they did not produce a distinct anticipatory response to a disadvantageous versus advantageous situation, suggesting that the seizures originating from limbic structures such as the amygdala undermine the functioning of the decision-making network, including its connections to the VMPFC (Bechara *et al.*, 1999; Gupta *et al.*, 2011). The correlation analysis between the number of seizures or the number of AEDs used and the decision-making performance and the magnitudes of autonomic responses revealed no significant relationship in the preoperative group. Thus, in our study, the poor decision-making performance of the preoperative group cannot be accounted for by either their ongoing seizures or the number of drugs they took.

Table 2. Correlations between clinical variables, IGT performances, and autonomic responses in patient groups.

		Preoperative group		**Postoperative group**	
		Duration of illness	**Number of AEDs**	**Duration of illness**	**Number of AEDs**
aSRR (AB)	*r*	0.39	-0.09	-0.34	0.08
	p	0.14	0.72	0.41	0.84
aSRR (CD)	*r*	0.38	-0.09	-0.42	-0.02
	p	0.14	0.74	0.31	0.97
pSRR	*r*	0.01	-0.18	-0.32	0.10
	p	0.99	0.53	0.44	0.79
IGT Total net score	*r*	0.29	0.56	0.49	-0.13
	p	0.28	0.05	0.22	0.73

aSRR (AB): magnitudes of anticipatory skin resistance responses to decks A and B; aSRR (CD): magnitudes of anticipatory skin resistance responses to decks C and D; pSRR: magnitudes of skin resistance responses to a card which was followed by an overall loss of money.

On the other hand, the autonomic responses generated by the postoperative group both before and after making disadvantageous decisions were found to be similar to those of the control group and their decision-making performances were no different from those of the control group. These results may be interpreted as a demonstration of the positive effects of surgery on cognitive domains, including decision-making behaviour. Frequently, cognitive impairments affect the contralateral temporal and frontal functions (Simons and Spiers, 2003; McAndrews and Cohn, 2012; Malikova *et al*., 2015). Epileptic activity spreading from mesial temporal lobe structures including the amygdala may worsen the related functions of the contralateral hemisphere. After successful ATL surgery, the removal of the chronically discharging epileptic foci and a contralateral amygdala released from this spreading may activate reorganization processes, including the recruitment of a widespread decision-making network comprising the VMPFC. Consistently, studies that have examined neuroplasticity after surgery have found compensatory functional MRI activation contralateral to the resection site (McClelland *et al*., 2006; Wong *et al*., 2009; Benuzzi et al., 2014).

We also compared the number of advantageous choices in the first and last blocks of the decision-making test to see if the groups significantly improved their performances throughout the test. Despite significant differences found in control and postoperative groups, in the preoperative group, no difference was found in the number of advantageous choices between the first and last block. These results confirm the presence of an improvement in performance in the decision-making behaviour of the postoperative group following surgery.

This study provides new data to the existing literature by showing that a dysfunctional amygdala results in poor generation of different patterns of autonomic responses, for the purposes of enhancing decision-making in ambiguous situations.

To achieve a more precise understanding of the changes in behaviour after ATL, it would be more reliable to compare the same patients before and after surgery, thereby overcoming the major limitation of the current study. In the future, we plan to examine those patients who will undergo surgery after participation in this study. In addition, the absence of direct correlations between magnitudes of autonomic responses and decision-making performances could be considered a limitation of this study. A few studies have investigated the relationship between these variables, however, these studies involved healthy participants and differ from our study in terms of their aim and methodology (Carter and Smith-Pasqualini, 2004; Jenkinson *et al*., 2008).

In conclusion, the findings of this study validate the contribution of mesial temporal lobe structures to decision-making behaviour. The findings also highlight the importance of examining the connectivity patterns between the neural structures involved in the decision-making network. In addition, our study clearly shows that some quantitative benefits in various cognitive domains, including decision-making, are observed following surgery in patients with intractable epilepsy. However, these results should be validated with further studies. From a clinical point of view, it may be suggested that assessment of decision-making performance be included in the standardized neuropsychological examination of MTLE patients both before and after surgery, to provide a broader examination of cognitive functions. The results of the decision-making tests may be relevant to treatment, as therapy designed to strengthen decision-making abilities of MTLE patients may facilitate and help them deal with complex situations they face in daily life. ☐

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) Does the amygdala contribute to decision-making behaviour?

(2) Do MTLE patients show deficits in decision-making?

(3) Did anterior temporal lobectomy have an impact on the Iowa Gambling Test scores in mesial temporal lobe epilepsy in the present study?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".