Original article

Spatial memory alterations in children with epilepsy of genetic origin or unknown cause

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ABSTRACT – Genetic generalised epilepsy or epilepsy of unknown cause can remit before adolescence. In many children, the disease does not interfere with their academic achievement. Although there are neuropsychological studies characterising the cognitive profile, there are no studies in this population focused on spatial orientation abilities. In this study, we compared children with genetic generalised epilepsy or epilepsy of unknown cause with a control group using a virtual spatial learning task. Children with epilepsy showed worse performance on the spatial orientation task, although their visuo-spatial memory, attention, and working memory were normal. These results confirm that genetic generalised epilepsy or epilepsy of unknown cause is associated with more cognitive deficits. Virtual reality technologies can complement clinical assessment.

Key words: hippocampus, navigation, academic achievement, neuropsychology

Childhood epilepsy is associated with a good prognosis especially in genetic generalised epilepsy or epilepsy of unknown cause. Most of these children have normal intelligence and become free of seizures within the first two years after diagnosis, either spontaneously or with medical treatments (Berg *et al.*, 1995). Nevertheless, in recent years, several studies have shown that many of these children experience neuropsychological problems even in those syndromes which were previously considered benign (Vallée, 2012; Jackson *et al.*, 2013). Although the neuropsychological features of these children were addressed in other studies, to our knowledge, virtual reality-based tasks have never been applied to this population to assess spatial memory.

Virtual reality tasks were introduced in the last decade to assess human cognitive abilities (Astur *et al.*, 2002). These tests were demonstrated to be very sensitive to hippocampal disturbance (Cánovas *et al.*, 2011). In this study, we applied a virtual reality-based task to assess spatial memory in children with genetic generalised epilepsy or epilepsy of unknown cause.

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Case series

Methods

Ten children with genetic generalised epilepsy or epilepsy of unknown cause participated in this study; five 8-year-old boys and five 9-year-old boys. They were patients of the Torrecárdenas Hospital Pediatric Neurology Service (Almería). Inclusion criteria were: 8 or 9-year-old boys with two epileptic seizures, 24 hours apart, without intellectual disability or motor deficits, and normal MRI. Subjects were matched by age and sex with a control group (*n*=10). All subjects declared to have video-game experience. Five of the children were taking oxcarbazepine, three of them sodium valproate, and the last 2 boys had had their medication suspended (*table 1*). The study was conducted in accordance with the European Communities Council Directive 2001/20/EC and Helsinki Declaration for biomedical research involving humans. All subjects' parents signed informed consent before participating in this study.

The virtual task, called the "Boxes-Room", was administered on a Hewlett Packard 2600-MHz notebook. The task was described previously by Cánovas and colleagues (2008). In brief, the Boxes-Room task consisted of a virtual, decorated square room in which 16 brown boxes were symmetrically distributed on the floor. Several stimuli disambiguated spatial locations. Participants were instructed to find the position

Table 1. Clinical features of the sample.

	Age	Age at onset	Duration in months	Time since the last episode*	EEG	Epileptic syndrome	Medication	MRI
Subject 1	9y 10m	9y 4m	6m	1 week	3-Hz generalised spike-wave	CAE	Sodium Valproate 30 mg/kg/day	Normal
Subject 2	9y 7m	8y 6m	13m	13m	Generalised spike and polyspike-wave	ETCSO	Sodium Valproate 40 mg/kg/day	Normal
Subject 3	8y	7y 8m	4m	4m	3-Hz generalised spike-wave	CAE	Suspended	Normal
Subject 4	8y 11m	8y 5m	6m	6m	Normal	BECTS	Oxcarbazepine 27 mg/kg/day	Normal
Subject 5	8y 11m	8y	11m	6m	Left centrotemporal spike-wave	BECTS	Oxcarbazepine 30 mg/kg/day	Normal
Subject 6	8y	6y 11m	13m	3m	Normal	BECTS	Oxcarbazepine 22 mg/kg/day	Normal
Subject 7	8y 1m	5y 7m	30m	15m	Normal	FEUC	Sodium Valproate 22 mg/kg/day	Normal
Subject 8	9y 6m	7y	30m	18m	3-Hz generalised spike-wave	CAE	Suspended	Normal
Subject 9	9y 9m	6y 6m	39m	10m	Independent left and right centro-temporal spikes	BECTS	Oxcarbazepine 34 mg/kg/day	Normal
Subject 10	9y 11m	7y 2m	33m	33m	3-Hz generalised spike-wave	CAE	Sodium Valproate 25 mg/kg/day	Normal

*Time from the last episode takes into account the date of assessment; y: years; m: months; CAE: childhood absence epilepsy; BECTS: benign epilepsy with centrotemporal spikes; FEUC: focal epilepsy of unknown cause; ETCSO: epilepsy with tonic-clonic seizures only.

occupied by the rewarded boxes as quickly as possible, by opening the smallest number of boxes necessary. No information regarding useful strategies was provided.

When a subject opened a box, it would either turn green and a pleasant melody would sound, indicating that it was a rewarded box or, on the contrary, turn red with an unpleasant tone, indicating that it was incorrect. Once a box was opened, it remained green or red until all the rewarded boxes were found or the maximum trial duration (150 seconds) had passed, thus helping participants to remember their positions. All the boxes returned to brown when a new trial began. In this study, participants were asked to find the rewarded boxes and remember their locations that remained constant during the session. However, the starting position was different from one trial to the next, avoiding egocentric solutions to the task. Participants executed two consecutive sessions of 10 trials each, with an inter-trial interval of five seconds. Subjects had to find one and three rewards in session one and two, respectively. As reported before, the task was made more difficult by increasing the number of rewards (Cánovas *et al.*, 2008).

In addition, several neuropsychological tests were administered to assess attention, memory span, working memory, and visuo-spatial memory; Digit span (forward and backward) and the 10/36 Spatial Recall Test (SRT) (Wechsler, 2003; Strober *et al.*, 2009). The raw scores were analysed in each test. In the 10/36 SRT, the mean number of correct responses out of three trials was used, as well as the number of correct responses for long-term memory retrieval (administered 20 minutes after the end of the initial learning session).

Results

Two between- and within-subjects ANOVA tests (Group x Trial) were used to analyse the data for the virtual reality task. Since subjects opened the boxes at random in the initial trial, this trial was removed from all analyses.

The first analysis of the one-reward condition revealed differences between trials ($F_{8,144}=8.11$; $p<0.0001$) and a statistically significant interaction term ($F_{8,144}=4.02$; $p<0.001$), but no differences between the groups ($F_{1,18}=0.67$; $p=0.42$). *Post hoc* analysis of the interaction (Tukey test) showed that controls displayed less errors than the epileptic group in the second trial (mean number of errors for controls and patients were respectively 1.3 *vs* 5.5; $p<0.05$). In addition, subjects reached the asymptotic level in the fourth trial, since there was not any significant decrease in the number of errors thereafter ($p<0.05$) (*figure 1*).

For the second analysis of the three-reward condition, groups differed in the number of errors committed
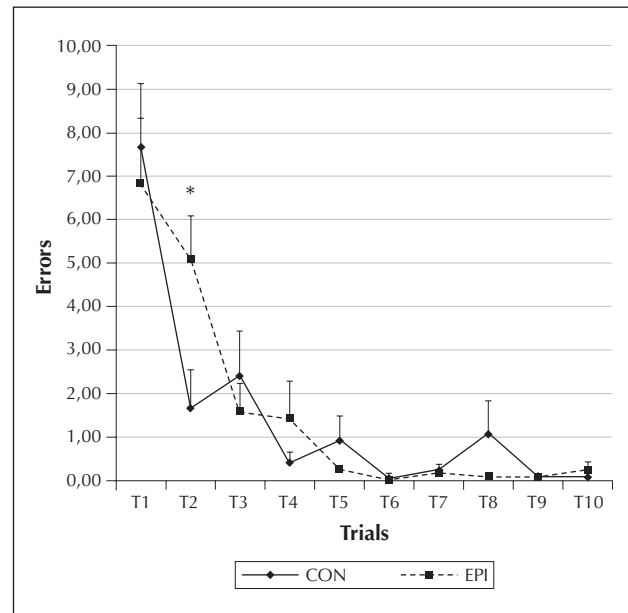

Figure 1. Number of errors in the one-reward condition. Note that controls showed a better learning curve than children with epilepsy, with a better performance in the second trial (mean + SEM).

($F_{1,18}=6.4$; $p<0.02$) (mean: 0.62 *vs* 3.23 for controls and patients, respectively). The number of errors also changed across trials ($F_{8,144}=3.43$; $p<0.001$). A *post hoc* Tukey test showed that errors decreased until the third trial ($p<0.05$). The interaction term was not significant ($F_{8,144}=0.75$; $p=0.64$) (*figure 2*). The number of
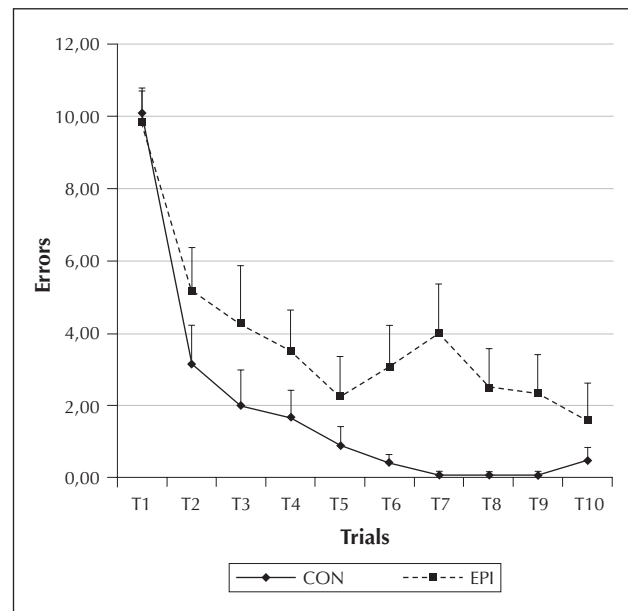

Figure 2. Number of errors in the three-reward condition. The groups clearly differed in their performance, with the controls outperforming the epilepsy group (mean + SEM).

errors on the first trial was also compared to determine if the performance of the task was influenced by motor or motivational factors. Note that in the first trial, both groups performed at random because they did not know the position of the rewards. Student t-tests for independent samples showed that there was no significant difference between the groups for the one-reward condition (t[18]=1.009, *p*>0.05) or the three-reward condition (t[18]=0.23, *p*>0.05). "Time from onset" was correlated with the "number of errors" on the virtual reality task. Pearson correlation values were -0.6 (*p*<0.05) and -0.2 (*p*>0.05) for the one-reward and the three-reward conditions, respectively. Performance did not differ for the remaining neuropsychological tests (*table 2*). In particular, groups did not differ for the forward version of the digit span task or the backward version; student t-tests for independent samples were (t[18]=0.1, *p*>0.05) and (t[18]=0.75, *p*>0.05), respectively. In addition, no differences between groups emerged in the acquisition phase of the visuo-spatial task, 10/36 SRT (t[18]=0.59, *p*>0.05). Long-term retrieval did not differ either in this task (t[18]=1.33, *p*=0.36).

Discussion

To our knowledge, this is the first study carried out on children with epilepsy using virtual reality-based tasks to assess spatial memory. As can be seen in *table 1*, the sample is heterogeneous, including children with different epileptic syndromes. We have confirmed that childhood epilepsy is associated with cognitive deficits (Cormack *et al.*, 2007; Berg *et al.*, 2013).

Other basic neuropsychological tests for assessing memory span, attention, working memory, and visuo-spatial memory did not reveal any differences between the patients and their control group. These results are consistent with Mankinen *et al.* (2014) who showed that neuropsychological performance did not differ for children with temporal lobe epilepsy with normal MRI findings and their controls. Thus, our study supports the idea that such neuropsychological processes did not form the basis of the alterations detected here.

It is interesting to note that the groups did not differ in their visuo-spatial abilities, since their performance in the visuo-spatial test (10/36 SRT) was similar, yet controls outperformed children with epilepsy in the virtual-reality spatial memory task. This taps spatial orientation demands that require more cognitive resources, relative to traditional visuo-spatial tests. Specifically, the 10/36 SRT requires subjects to stare at a 6×6-two-dimensional grid and remember 10 occupied positions. This task could be solved by retrieving a fixed image of the occupied positions on the grid. On the other hand, the virtual reality task demands exploring a 3D environment, with the view changing as the subject moves. Only by understanding the changing spatial relationships between the cues available, could subjects successfully retrieve rewarded positions.

Since controls committed more errors in the first trial than children with epilepsy (mean: 7.67 and 6.83, respectively; *see figure 1*), motivational or motor factors, or video-game experience could not account for the results reported. It is also noteworthy that differences were more pronounced when the level of difficulty increased. As reported previously, by modifying levels of difficulty of the task, it is possible to reveal differences between groups that were masked at very low levels (Cánovas *et al.*, 2008).

The time period since onset of epilepsy did not correlate highly with the number of errors and this variable was associated with impaired cognitive development (Vendrame *et al.*, 2009). However, we did not find a strong correlation with the number of errors in the three-reward condition. Nevertheless, sample and age at onset differed in both studies, which could explain the different correlations reported.

It is well known that the hippocampal system is one of the most epileptogenic regions in the brain and is involved in memory and spatial learning functions (Squire, 1992). Previous work addressed spatial navigation abilities in epileptic patients, showing that epilepsy altered spatial memory in different tasks (Weniger *et al.*, 2012). In addition, the hippocampal system demonstrates late maturation. The dentate gyrus and other hippocampal areas, such as CA1 and CA3, provide new cells and undergo molecular changes during the first postnatal years (Lavenex and Lavenex,

Table 2. Results for each of the neuropsychological tests employed.

	Digits (Forward)	Digits (Backward)	10/36 SRT Short-term	10/36 SRT Long-term	Virtual Task 1R	Virtual Task 3R
Epilepsy	5 + 0.94	3.5 + 0.97	5.6 + 1.9	5.7 + 2.4	1.08+0.8	3.23+2.1
Controls	5 + 1.24	3.2 + 0.78	6.3 + 0.96	6.9 + 1.5	0.75+0.8	0.62+1.2

Virtual Task 1R : Virtual Task 1 Reward; Virtual Task 3R : Virtual Task 3 Rewards.

2013). Presumably, anomalous brain activity during this critical period could modify hippocampal physiology, leading to altered cognitive functions. Hence, children with genetic generalised epilepsy may experience a reduction of hippocampal volume (Eroglu *et al*., 2007). It is necessary to stress that children in our study showed normal MRI. However, this did not exclude the possibility of subtle hippocampal changes undetected by MRI. Another possibility is the presence of dysfunctional cognitive networks involving the hippocampal system. Note that during development, maturation is characterised by growth and reshaping of connectivity to promote efficiency of cognitive processing (Hagmann *et al*., 2010). Moreover, Widjaja *et al*. (2013) demonstrated a correlation between abnormal white matter and neuropsychological functions in children. These network abnormalities were also observed in the temporal lobe of patients with epilepsy, extending beyond the seizure onset region (Maccota *et al*., 2013). Finally, the use of virtual reality-based tasks allows the use of a reduced sample size to detect significant effects. Virtual reality-based experiments do not require more than 10 to 15 subjects to achieve reliable results (Astur *et al*., 2002; Cánovas *et al*., 2008; Weniger *et al*., 2012).

In conclusion, genetic generalised epilepsy or epilepsy of unknown cause may manifest with neuropsychological alterations, of which virtual reality tasks are highly sensitive to. □

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