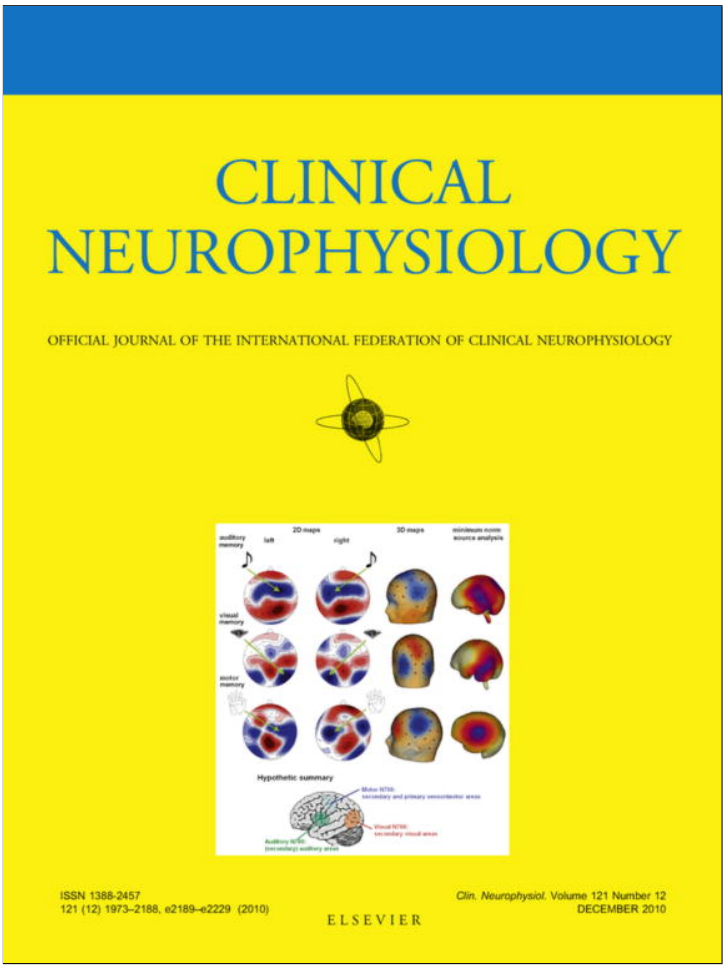

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Infant febrile seizures: Changes in declarative memory as revealed by event-related potentials

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ABSTRACT

Objective: According to a widespread opinion the vast majority of infant febrile seizures (IFS) are harmless. However, IFS are often associated with hippocampal sclerosis, which should lead to deficient episodic memory with spared context-free semantic memories. Although IFS represent the most common convulsive disorder in children, these consequences are rarely examined.
Methods: We measured the hippocampal volume of 17 IFS children (7–9 years old) and an age-matched control group on the basis of MR images. Furthermore, we examined episodic and semantic memory performance with standardized neuropsychological tests. Two processes underlying recognition memory, namely familiarity and recollection, were assessed by means of event-related potentials (ERP).
Results: The IFS children did not show a decreased hippocampus volume. Intelligence, working memory, semantic and episodic memory were intact. However, ERP indices of recognition memory subprocesses revealed deficits in recollection-based remembering that presumably relies on the integrity of the hippocampus, whereas familiarity-based remembering seemed to be intact.
Conclusions: Although hippocampus volume remains unaffected, IFS seems to induce functional changes in the MTL memory network, characterized by a compensation of recollection by familiarity-based remembering.
Significance: This study significantly adds to the debate on the consequences of IFS by differentiating the impact on memory processing.

1. Introduction

Infant febrile seizures (IFS) are commonly thought to have no negative consequences for later cognitive development (Chang et al., 2000; Knudsen, 1996; Verity et al., 1985, 1998). However, in our current study we demonstrate that even mild forms of IFS go along with subtle functional changes in MTL-dependent memory subprocesses.

Febrile seizures affect 2–8% of all children between the ages of 6 months and 5 years (for an overview, see Sadleir and Scheffer, 2008). They are classified as simple or complex. Complex febrile seizures last more than 15 min, occur within the same episode of febrile illness or are focal. These criteria are absent in simple febrile seizures, which make up 75% of all attacks.

IFS are often associated with injuries of medial temporal lobe (MTL) structures including the hippocampus (Hc). Retrospective studies have revealed that more than 50% of patients with medial temporal sclerosis have a history of IFS (Fisher et al., 1998; Scott et al., 2003). However, prospective studies have shown that IFS only rarely go along with hippocampal sclerosis (Berg and Shinnar, 1991; Shinnar, 1998). Thus, the first goal of the present study is to estimate hippocampal damage several years after mild forms of IFS. For this purpose, we analysed hippocampal volumes of 17 IFS children (7–9 years) and an age-matched control group on the basis of MR images.

If febrile seizures are associated with Hc pathology, what might be the consequences for cognitive development? The Hc plays a special role for declarative long-term memory which consists of two systems: episodic and semantic memory (Tulving, 1972). The Hc is particularly important for the formation and retrieval of contextual episodic memories (Eichenbaum and Cohen, 2001; Vargha-Khadem et al., 1997). In contrast, the perirhinal and entorhinal cortices are critically involved in context-free semantic memories (Gadian et al., 2000; Vargha-Khadem et al., 1997). So, if

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febrile seizures are associated with selective hippocampal damage IFS children should show selective deficits in episodic memory and spared semantic memories (Guillery-Girard et al., 2004; Vargha-Khadem et al., 1997).

So far, only few studies have examined episodic memory performance in school-aged IFS children. In the study by Chang et al. (2001), only children with IFS onset in the first year of life showed impairments. Kölfen et al. (1998) report stronger impairments in children with complex febrile seizures. Even though the impact of IFS on episodic memory development seems to be small, the abovementioned studies indicate that subtle impairments cannot be excluded. Regarding semantic memory, studies have consistently demonstrated that IFS children do not bear a greater risk for semantic memory impairment than controls (Al-Ajlouni and Kodah, 2000; Sadleir and Scheffer, 2008).

Since studies examining memory development in IFS children are rare and do not systematically examine different memory subsystems, our second goal is a precise diagnostics of semantic and episodic memory performance in IFS children on the basis of standardized neuropsychological tests. We expected IFS children to show subtle deficits only in episodic memory tasks.

In addition, we assume that deficits in episodic memory after IFS may affect specific MTL-dependent subprocesses only. Thus, the third goal of the present study is to examine these (episodic memory) subprocesses in IFS children. Therefore, we conducted a recognition memory experiment that included the remember/know procedure (Tulving, 1985) and the measurement of event-related potentials (ERP). Both techniques are suitable to dissociate two subprocesses of recognition memory: (1) *familiarity*, a fast acting, global matching process that does not rely on the integrity of the Hc and (2) *recollection*, a Hc-depended slow and recall-like process by which detailed memories about prior episodes are retrieved (Brown and Aggleton, 2001; Norman and O'Reilly, 2003).

In the remember/know procedure (Tulving, 1985), subjects are required to introspect about the basis of their memory judgments and report whether they recognize items on the basis of remembering (i.e., recollection of episodic information about the study event) or knowing (i.e., the item is familiar in the absence of recollection). This procedure was already used to estimate familiarity and recollection in children (Billingsley et al., 2002; Piolino et al., 2007).

We also used ERP measures of recollection and familiarity. Studies consistently report ERP old/new effects, that is, differences in the ERPs to correctly classified old and new items. An early (300–500 ms) old/new effect at frontal recording sites can be considered an ERP correlate of familiarity, whereas a later old/new effect at parietal recordings can be taken as the putative correlate of recollection (Friedman and Johnson, 2000; Jäger et al., 2006; Mecklinger, 2006; Rugg et al., 1998). Similar to adults, children at early school age show a parietal old/new effect indicating that memory in this age already relies on recollection (Cycowicz et al., 2003; Czernochowski et al., 2005; Friedman et al., 2009; van Strien et al., 2009). However, children mostly do not display an early frontal old/new effect, the correlate of familiarity (Friedman et al., 2009; van Strien et al., 2009). This could result from a conservative response bias (Czernochowski et al., 2005), or from a component overlap with a negativity that reflects the allocation of attention to novel and unexpected events (see Czernochowski et al., 2009).

Furthermore, in a recent ERP study by Düzel et al. (2001) a patient with bilateral hippocampal volume reduction showed an attenuated late parietal old/new effect and a preserved early frontal effect, indicating that ERP old/new effects are sensitive to specific memory deficits caused by hippocampal damage. With respect to the third goal, the assessment of familiarity and recollection by means of the remember/know procedure and ERP indices, we expected IFS children to show episodic memory deficits in recollection-based remembering, as this form of memory relies on the integrity of hippocampal structures. These deficits should become apparent in a reduction of remember responses and in a modulation of the parietal old/new effect. Conversely, familiarity-based remembering should be spared in IFS children. To control for general modifications of ERP waveforms in IFS children, an additional three-stimulus oddball task was conducted.

2. Methods

2.1. Subjects

Details about IFS and control group are given in Table 1. All children were right-handed (assessed by the Edinburgh Inventory by Oldfield, 1971). German was their native language. None of the children suffered from neurodevelopmental abnormalities. All children were paid for participation. Informed consent was obtained from the parents. The current study was approved by the Ethics Committee of the Saarland Medical Association (ID No. 151/07).

2.1.1. IFS group

The patient sample consisted of 20 children who had received medical treatment at the Saarland University Hospital after suffering the first febrile convulsion. Due to strong movement artifacts in the EEG session, three children had to be excluded. The mean age of the 17 children (seven with simple, 10 with complex IFS) that entered statistical analyses was 7;11 years. The socio-economic status (SES) was determined according to Ganzeboom et al. (1992) and had a mean value of 50.12. None of the children was on regular medication, had developed epilepsy, or showed noticeable abnormalities in the EEG. The MR images of four children could not be analysed because of movement artifacts or technical failures. Hence, the brain volumetric analyses are based on the data of 13 IFS children.

2.1.2. Control group

Eighteen children participated in the study. The children were recruited from local elementary schools. One child had to be excluded from analysis due to strong movement artifacts in the EEG session. The average age of the 17 children was 8;04 years and did not differ from that of the IFS group ($t(32) = 1.33$, $p = .19$). The SES was 67.88 and thus higher than in the IFS group ($t(32) = 3.70$, $p < .001$). To rule out that memory differences between both child groups are confounded with this factor we carried out additional covariance analyses with SES as a covariate, in case of group differences. No child had experienced prenatal or postnatal health problems. The MR images of three children could not be analysed due to movement artifacts and technical failures. Therefore, the brain volumetric analyses are based on the data of 14 control children.

Table 1
Demographic data of control and IFS groups.

	Control group	IFS group
N	17	17
Male/female	11/6	10/7
Age	8;04 (6;11–9;10)	7;11 (7;01–9;11)
Socio-economic status[a]	67.88 (42–88)	50.12 (23–82)
Age when first IFS occurred	–	1;10 (0;07–3;00)
Seizure type	–	7 simple/10 complex – 4 focal – 8 > 15 min – 3 recurrent
Number of episodes	–	– 2.65 (1–8)

[a] Determined according to Ganzeboom et al. (1992).

2.2. Procedure

The children performed three sessions: (1) structural MR imaging (duration 1 h), (2) neuropsychological tests to assess intellectual functioning, working memory, semantic, and episodic memory (1 h), and (3) an item recognition experiment and an auditory oddball task, both with EEG recording (2½ h).

2.2.1. Magnetic resonance protocol and volumetric analyses

Structural MR imaging was performed on a 1.5-T Siemens Sonata scanner. A 3D MP-RAGE sequence was obtained with a repetition time of 1900 ms; echo time, 3.93 ms; inversion time, 1100 ms; flip angle, 15°; matrix size, 256 × 256; field of view, 256 mm; partition thickness, 1 mm; 176 sagittal partitions.

Cerebral volumes (CV) and hippocampal (Hc) volumes were measured manually using MRIcron software. CV was estimated from coronal sections, using every tenth slice and calculating the final volume by summing up the cross-sectional areas and then multiplying this with the slice distance (i.e., 10 mm).

An illustration of the manual segmentation procedure regarding the Hc is shown in Fig. 1. To determine the posterior limit of the Hc, we looked for the slice with the maximal visible length of the fornix and started Hc measurement two contiguous slices before. Anteriorly, the disarticulation of the Hc from the amygdala was performed using the alvear covering of the Hc, which was included in the measurements. The medial and inferior limits were drawn using the contrast between gray and white matter. Uncus and subiculum were included in the measurements (Cook et al., 1992). Fimbria and choroid plexus were excluded. Hc volume was normalized by dividing absolute Hc volume by total cerebral volume, and also by the covariance method as described by Jack et al. (1989). As both methods revealed the same results, only the data from the former method will be reported.

As suggested by Free et al. (1995), the volumes of all subjects were measured by a single observer, blind to the group membership of the children. Variation in the volume measurement was assessed by measuring six hippocampi a second time. Intra-observer consistency was high, with a correlation value of 0.96.

2.2.2. Neuropsychological assessment

2.2.2.1. Intelligence. Intellectual functioning was assessed using the Raven's Coloured Progressive Matrices Test, a multiple choice test on abstract reasoning (Raven et al., 2002).

2.2.2.2. Working memory. The forward and backward digit span test, a subtest of HAWIK-R (German version of the WISC; Tewes, 1997), was administered.

2.2.2.3. Semantic memory. Three additional subtests of the HAWIK-R were used: general knowledge, general comprehension, and vocabulary.

2.2.2.4. Episodic memory. The German version of the Auditory Verbal Learning Test (AVLT) – the Verbaler Lern- und Merkfähigkeitstest (VLMT; Helmstaedter et al., 2001; Schweisthal, 1997) – was used. It measures immediate and delayed recall, recognition, learning gradient, and interference sensitivity. It can be considered as a reliable measure of the integrity of the Hc and surrounding MTL structures (Elger et al., 1997; Helmstaedter et al., 2001). To measure visual memory, we used the Rey–Osterrieth Complex Figure (Osterrieth, 1944).

Between-group differences in these tests were assessed by means of two-tailed *t*-tests.

2.2.3. EEG assessment

2.2.3.1. Auditory oddball task. A low-frequency sinus tone (600 Hz) was used as the standard tone, which occurred in 400 trials (80%). A second tone (1000 Hz) was used as the target tone and was presented in 50 trials (10%). In another 50 trials (10%), environmental sounds (novels) were presented (Mecklinger et al., 1997). The tones and sounds were presented in randomized order with a duration of 200 ms and an inter stimulus interval of 800 ms. They were delivered via external speakers at 70 dB/SPL. The trials were split into two blocks. The subject's task was to silently count the target tones; the novel sounds were not mentioned in the instruction.

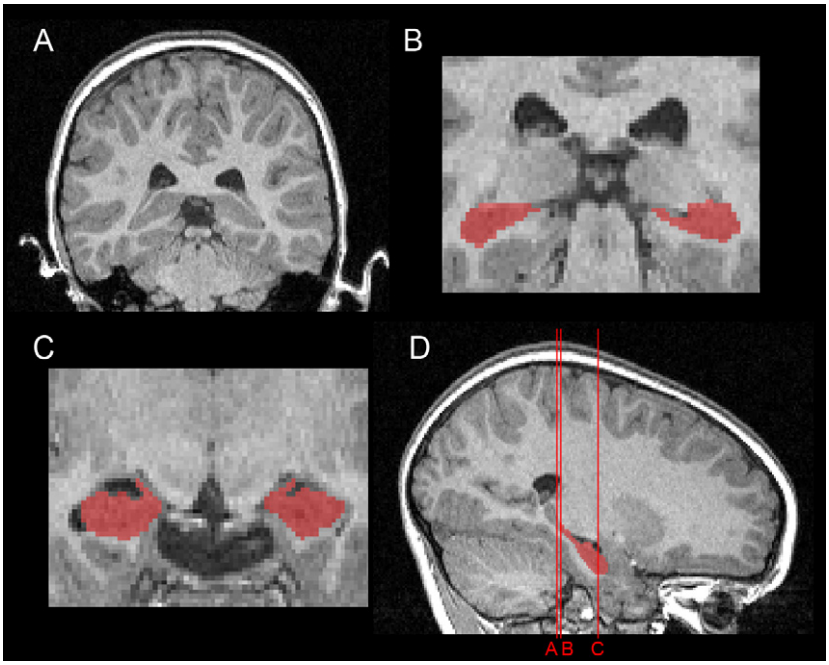

Fig. 1. Illustration of the manual segmentation procedure: (A) sample slice where the greatest length of the fornix becomes visible, (B) two contiguous 1-mm slices more anteriorly: first slice taken for Hc segmentation, (C) Hc head including the uncal cleft, and (D) Hc in sagittal sections to control the anterior boundary of the Hc (red lines correspond to the slices in A–C).

2.2.3.2. Recognition memory task. The stimuli were 252 colour drawings of common objects taken from the Snodgrass and Vanderwart data base (Snodgrass and Vanderwart, 1980). Each picture was framed within an area of 280 × 280 pixels.

There were two study-test blocks. Each study phase comprised 60 pictures and each test phase comprised 120 pictures – 60 studied (i.e., "old") and 60 new pictures. A preceding practice block comprised six study pictures and 12 test pictures (six old plus six new). Old and new images were pseudo-randomized in the test phase, such that no more than five old or five new stimuli succeeded each other. The assignment of pictures to old/new status and experimental block was balanced across subjects. All pictures were consecutively presented on a computer monitor, located 1 m from the participants' chair.

In the *study phase*, each trial started with the presentation of a central fixation cross (400 ms), followed by a blank screen (400 ms), the stimulus (1000 ms), and another blank screen (1000 ms). The participants' task was to memorize the pictures and to make an indoor–outdoor decision for each picture by pressing the corresponding key on an external key pad as quickly as possible. The assignment of response key to indoor/outdoor status ("indoor" left index finger/"outdoor" right index finger or visa versa) was balanced across the subjects. During the retention interval, participants completed a simple arithmetic task for 1 min.

In the *test phase*, after presentation of the fixation cross (400 ms) and a blank screen (400 ms), an old or a new item was presented (1000 ms), followed by a blank screen (1800 ms) after which – in case of a missing response – a prompt appeared on the screen demanding a response. Participants had to make an old–new decision and press the corresponding key as quickly as possible (again each index finger was assigned to either the "old" or the "new" key on the external key pad and the assignment of keys to old/new status was balanced across the subjects). In case of an *old decision*, the words 'remember/know' appeared on the screen and according to the instruction by Gardiner and Parkin (1990) the participants had to specify whether they had judged the item as old because they explicitly remembered it (remember) or because it felt familiar (know). Just as after an old decision, the participants had to press a second key after *a new decision*. For this crosses appeared on the screen and the participants had to press any of two keys. After an interval of 1000 ms the next test trial started.

2.2.3.3. Behavioral analyses. Trials were excluded whenever a response time was below 200 ms or above 5000 ms. Memory accuracy was analysed by means of a discrimination measure (Pr; Snodgrass and Corwin, 1988), subtracting the proportion of false alarms to new items (FA) from the proportion of hits. Hits were further classified into remember and know judgments. The proportion of know answers was corrected according to the assumption that recollection and familiarity operate independently (Yonelinas and Jacoby, 1995). Following Snodgrass and Corwin (1988), response bias (Br) was defined as FA/(1-Pr), i.e., the probability of saying "old" when in an uncertain state. Between-group differences in response times, Pr, and Br were assessed by means of two-tailed *t*-tests.

2.2.3.4. EEG recording and analyses. EEG was recorded with 28 Ag/AgCl-electrodes attached in an elastic cap according to the extended 10–20 system (Sharbrough et al., 1994). The sampling rate was 250 Hz. AFz was the ground electrode. Electrooculogram (EOG) was recorded with additional electrodes located above and below the right eye (vertical EOG) and at the outer canthi of both eyes (horizontal EOG). EEG was referenced to the left mastoid and re-referenced off-line to linked mastoids. All channels were amplified with a band pass from DC to 70 Hz and a 50 Hz notch filter. Electrode impedance was kept below 5 kΩ.

For the auditory oddball task, the EEG was segmented into epochs of 1000 ms including a 200 ms prestimulus baseline. Epochs including artifacts were rejected prior to averaging and eye blink and eye movement artifacts were rejected or corrected using a linear regression estimate (Gratton et al., 1983). The number of rejected trials did not differ between both child groups, neither for standards (control group: 178.4; IFS group: 200.8; $t(32) = 0.79$, $p = .43$), nor for targets (control group: 21.4; IFS group: 24.6; $t(32) = 0.94$, $p = .35$) or for novels (control group: 23.5; IFS group: 26.2; $t(32) = 0.72$, $p = .49$) allowing the computation of reliable ERP averages in both groups. Since target- and novelty-P3s are components that are most pronounced at midline electrodes (e.g., Ceponiene et al., 2004; Czernochowski et al., 2005), the effects can be covered reliably by analysing the midline electrodes Fz, Cz, and Pz. Mean amplitudes at these electrodes were measured in the following time windows: for the target-P3 500–600 ms, for the novelty-P3 300–400 ms. The time windows were selected on the basis of previous studies with similar age groups (e.g., Ceponiene et al., 2004; Czernochowski et al., 2005) and on visual inspection of the waveforms. For the target-P3, we analysed mean amplitudes in the 500–600 ms time window by means of an ANOVA with the factors Group (control vs. IFS children), Anterior–Posterior (Fz, Cz, Pz) and Condition (target vs. standard). For the novelty-P3, we conducted an equivalent ANOVA for the 300–400 ms time window; the two levels of the Condition factor were novels and standards.

For the recognition memory task, the EEG was segmented into epochs of 1200 ms including a 200 ms prestimulus baseline. The number of rejected trials due to artifacts did not differ between both child groups, neither for hits (control group: 36.9; IFS group: 41.7; $t(32) = 1.07$, $p = .29$) nor for correct rejections (control group: 44.0; IFS group: 44.6; $t(32) = 0.10$, $p = .92$). ERP averages were calculated for hits and correct rejections at nine electrodes, three frontal (F3, FZ, F4), three central (C3, Cz, C4), and three parietal (P3, PZ, P4), allowing the analysis of the scalp distribution of old/new effects. Consistent with prior ERP studies with children (Czernochowski et al., 2005; Cycowicz, 2000), mean amplitude measures in an early (400–500 ms) and late time window (700–800 ms) were used for the quantification of the early frontal and late parietal old/new effect. Initial ANOVAs were calculated with the factors Item Status (old, new), Anterior–Posterior (frontal, central, parietal), and Laterality (left, middle, right). For the sake of clarity, only effects that include the factor Item Status are reported here. Due to low trial numbers, ERP analyses taking into account the remembered/known status could not be performed.

Whenever appropriate, Greenhouse–Geisser corrections for non-sphericity were used, and corrected *p*-values are reported together with uncorrected degrees of freedom. Scalp potential maps were generated by using a two-dimensional spherical spline interpolation (Perrin et al., 1989) and a radial projection from Cz, which respects the length of the median arcs.

3. Results

3.1. Hippocampus volumetry

The control and IFS groups did not differ with respect to absolute and normalized Hc volume. This is confirmed by Mann–Whitney *U*-tests that did not reveal differences between both groups in the absolute volume of the left Hc (control group: 2.48 cm^2; IFS group: 2.34 cm^2; $U = 75.0$, $p = 0.44$) or the right Hc (control group: 2.62 cm^2; IFS group: 2.44 cm^2; $U = 67.0$, $p = 0.24$). Also, there were no differences in the normalized volume of the left Hc (control group: 0.195; IFS group: 0.188; $U = 85.0$, $p = 0.77$) or the right Hc (control group: 0.207; IFS group: 0.195; $U = 73.0$, $p = 0.38$).

Table 2
Neuropsychological assessment: results for the control and IFS groups (standard errors in parentheses). An ANCOVA with socio-economic status (SES, Ganzeboom et al., 1992) as a covariate was only carried out in case of group differences in the initial *t*-test.

Cognitive ability	Control group	IFS group	*p*-Values (*t*-tests)	*p*-Values of the ANCOVA: SES as a covariate
Intelligence functioning				
Coloured Progressive Matrices	10.47 (0.30)	10.12 (0.24)	0.26	–
Working memory				
Digit span (HAWIK-R)[a]	11.53 (0.40)	12.65 (0.76)	0.21	–
Semantic memory (HAWIK-R) [a]				
General knowledge	13.47 (0.60)	11.47 (0.84)	0.06	0.50
General comprehension	13.59 (0.79)	12.53 (0.57)	0.29	–
Vocabulary	14.71 (0.61)	14.41 (0.73)	0.76	–
Episodic memory				
Verbal memory (VLMT) [b]				
– immediate recall	7.18 (0.43)	6.35 (0.45)	0.20	–
– learning gains	49.44 (2.46)	44.53 (2.89)	0.21	–
– recall after interference	9.71 (0.83)	9.29 (0.62)	0.69	–
– delayed recall	10.47 (0.74)	9.52 (0.85)	0.41	–
– recognition	12.82 (0.96)	13.67 (0.37)	0.54	–
Visual memory (Rey–Osterrieth Complex Figure)				
– copy	28.77 (1.32)	26.94 (1.74)	0.41	–
– immediate recall	16.82 (1.53)	13.74 (1.74)	0.19	–
– delayed recall	17.12 (1.49)	12.53 (1.59)	**0.04**[a]	0.36

All scores except for HAWIK-R scores are raw scores.
[a] HAWIK-R (Tewes, 1997) is the German version of the WISC. Scores are standardized scores based on chronological age norms (Mean = 10, SD = 3).
[b] VLMT (Helmstaedter et al., 2001) is the German version of the Auditory Verbal Learning Test (AVLT).

3.2. Neuropsychological assessment

The results of both child groups in the neuropsychological tests are illustrated in Table 2.

The control and IFS group did not differ with respect to intellectual functioning (Coloured Progressive Matrices) or working memory (digit span). Regarding semantic memory, the child groups did not differ in general comprehension or vocabulary. In general knowledge IFS children performed slightly worse than the control children ($t(32) = 1.94$, $p = .06$) but this difference disappeared when taking SES as a covariate into account ($F(1,31) = 3.36$, $p = .50$). Regarding episodic memory, no group differences were obtained for verbal memory (immediate recall, learning gains, recall after interference, delayed recall, recognition) or immediate visual memory (immediate recall). The only significant between-group difference was found for delayed visual memory (Rey–Osterrieth Complex Figure) but again this difference disappeared when SES was used as a covariate ($F(1,31) = 0.87$, $p = .36$).

3.3. ERP measurement

3.3.1. Auditory oddball task

The ERP waveforms elicited by standards, targets, and novels in the oddball task are illustrated in Fig. 2a. In both child groups targets elicited a large P300 with a maximum at the Pz electrode and novel sounds elicited an earlier rising P3a with a frontocentral maximum.

These observations were confirmed by statistical analyses (see Table 3 for details): For the target-P3, an ANOVA with the factors Group (control vs. IFS), Anterior–Posterior (Fz, Cz, Pz) and Condition (targets vs. standards) revealed neither an effect of Group nor any interactions involving the Group factor. There was a main effect of Condition and an Anterior–Posterior × Condition interaction. The interaction was due to the targets, eliciting larger P3s than standards at Cz and Pz and a converse effect at Fz. Effect size analyses revealed a clear parietal maximum of the target-P3.

A similar ANOVA for the novelty-P3 revealed neither a group effect nor any interaction with the factor Group. The factor Condition and the Anterior–Posterior × Condition interaction yielded significance. This interaction was reflected in the effect size analyses demonstrating a frontal maximum of the novelty-P3. Thus, the ERP components in the oddball task did not differ between the two groups.

3.3.2. Recognition memory task

3.3.2.1. Behavioral results. No differences between both child groups were found, neither in accuracy nor in reaction times. Two-tailed *t*-tests demonstrate the same discrimination accuracy (Pr) in both groups (control group: Pr = 0.57; IFS group: Pr = 0.51; $t(32) = 0.62$, $p = .54$). In addition the response bias did not differ between both groups (control group: Br = 0.34; IFS group: Br = 0.36; $t(32) = 0.32$, $p = .93$). Thus, both groups used a similar response criterion. The analysis of remember and know responses did not reveal any group differences. There were also no response time differences, neither for hits (control group: RT = 1171 ms; IFS group: RT = 1223 ms; $t(32) = 0.36$, $p = .72$) nor for correct rejections (control group: RT = 1179 ms; IFS group: RT = 1314 ms; $t(32) = 0.98$, $p = .33$). Hence, regarding behavioral results, the control and the IFS group did not differ in any respect.

On the basis of recent structural brain imaging findings (Isaacs et al., 2000; Raz et al., 2005), we assume that regional brain volumes are related to behavioral measures. Accordingly, the Hc volume should correlate with measures of memory performance. Indeed, in our study the absolute left and right Hc volumes collapsed across both child groups correlated positively with the proportion of hits in the item recognition experiment (Spearman's rank correlation, left Hc: $R = 0.38$, $p < 0.05$; right Hc: $R = 0.43$, $p < .05$).[1]

3.3.2.2. ERP results. Fig. 2b shows the grand-average ERPs for correct old and new responses and the topographic maps of the old/new effects in the early familiarity-related and late recollection-related time windows. In the control group, there was no difference between the ERPs elicited by hits and correct rejections in the early, familiarity-related time window at frontal electrodes. At parietal electrodes, hits elicited more positive-going ERPs than

[1] This correlation was not significant for the Hc volume normalized following the covariance method (Jack et al., 1989; left Hc: $R = 0.26$, $p = 0.20$; right Hc: $R = 0.22$, $p < .28$).

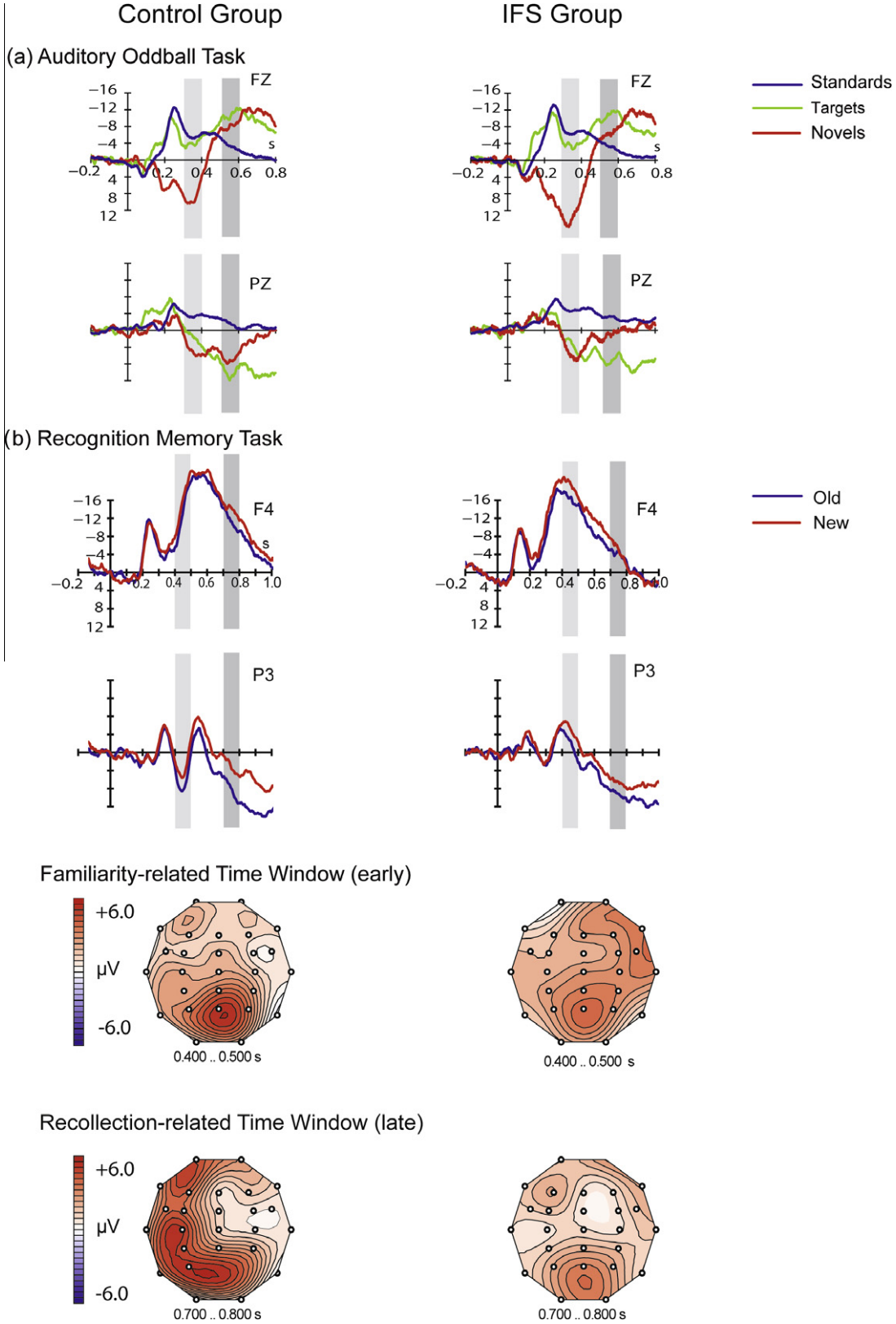

Fig. 2. (a) Auditory oddball task: ERPs elicited by standards, targets, and novels for the control and IFS groups at one frontal (Fz) and one parietal electrode (Pz). (b) Recognition memory task: ERP old/new effects for the control and IFS groups at the frontal (F4) and parietal (P3) electrodes where the effects were largest, and topographical maps for ERP difference waves (old minus new) in the early familiarity-related and late recollection-related time windows.

correct rejections, beginning 300 ms after stimulus onset and lasting until the end of the epoch. In contrast to the control group, for the IFS group there was a widespread old/new effect in the early, familiarity-related time window that covered also the frontal recording sites and the old/new effect in the recollection-related time window was diminished.

Table 3
Statistical analyses of the target-P3 and Novelty-P3: results of ANOVA with the factors Group (control vs. IFS), Anterior–Posterior (Fz, Cz, Pz) and Condition (targets vs. standards and novels vs. standards, respectively).

	Target-P3			Novelty-P3		
	F	*df*	*p*	*F*	*df*	*P*
Group			n.s.			n.s.
Condition	6.32	1, 32	<.05	117.39	1, 32	<.001
Condition x Anterior–Posterior	66.52	2, 64	<.001°	16.97	2, 64	<.001°
Effect sizes at single electrodes	$\acute{\omega}^2$			$\acute{\omega}^2$		
Fz	Converse effect			.85		
Cz	.31			.72		
Pz	.50			.43		

°Adjusted *p*-value according to the Greenhouse–Geisser correction.

These results were confirmed by statistical analyses. An overall ANOVA comparing the ERPs of both child groups revealed marginally significant Group × Item Status × Laterality ($F(2,64) = 2.36$, $p = .10$) and Group × Time Window × Item Status × Anterior–Posterior × Laterality ($F(4128) = 1.97$, $p = .10$) interactions. When carrying out an analysis of covariance (ANCOVA) with SES as a covariate the Group × Item Status × Laterality interaction diminished ($F(2,62) = 1.53$, $p = .23$) but the Group × Time Window × Item Status × Anterior–Posterior × Laterality interaction yielded significance ($F(4124) = 2.83$, $p < .05$). Thus, the ERP old/new effects tend to differ between groups and these differences are not modulated by differences in SES. To test our hypotheses regarding different contributions of familiarity- and recollection-based retrieval mechanisms in the two child groups, we conducted group-specific analyses in both time windows (see Table 4 for details).

3.3.2.3. Control group. In the early, familiarity-related time window, there was a significant main effect of Item Status, a significant Item Status × Anterior–Posterior, and an Item Status × Anterior–Posterior × Laterality interaction, indicating that old/new effects varied across the Anterior–Posterior axis. Next, separate ANOVAs for the three levels of the Anterior–Posterior factor were performed. At frontal locations there was no Item Status effect. It was marginally significant ($F(1,16) = 4.32$, $p = .05$) at central locations and significant at posterior locations ($F(1,16) = 16.19$, $p < .001$).

In the late recollection-related time window, there was a main effect of Item Status, a significant Item Status × Anterior–Posterior, and Item Status × Laterality interaction. At frontal locations a significant Item Status × Laterality interaction emerged ($F(2,32) = 7.40$, $p < .01$), which could be traced back to a significant Item Status effect only at the left frontal electrode (F3; $p < .05$). At central locations the main effect of Item Status ($F(1,16) = 7.21$, $p < .05$) as well as the Item Status × Laterality interaction ($F(2,32) = 8.59$, $p < .01$) were significant. The latter interaction was again induced by an Item Status effect only at the left central electrode C3 ($p < .01$). At parietal locations Item Status was highly significant ($F(1,16) = 22.25$, $p < .001$) which was due to significant effects at all three electrodes (all $p < .01$). In sum, for control children there was a significant left parietal old/new effect that comprised the early and the late time window (Fig. 2b).

3.3.2.4. IFS group. In the early, familiarity-related time window, a main effect of Item Status emerged indicating that an old/new effect was present at frontal electrodes (Fig. 2b). Examination of the recollection-related (late) time window revealed neither an effect of Item Status nor any interaction involving this factor. Thus, the IFS group, in contrast to the control group, did not show an old/new effect in the late time window (Fig. 2b).

The differences in the familiarity- and recollection-related time windows between the two child groups are exemplified in Fig. 3 at the frontal (F4) and parietal (P3) electrode sites where effects were largest.

To further explore these group differences we took the size of the old/new effect in the early time window at the frontal electrode F4 as an indicator for familiarity and the old/new effect in the late time window at the parietal electrode P3 as an indicator for recollection. An ANOVA with factors Group (IFS vs. control) and old/new effect (early frontal vs. late parietal) revealed a significant Group by old/new effect interaction ($F(1,32) = 4.24$; $p < .05$). As indicated by contrast analyses, the early frontal old/new effect was significant for the IFS children ($F(1,16) = 5.66$, $p < .05$) but not for the control children ($F(1,16) = .89$; $p = .36$). Conversely, the late parietal old/new effect yielded significance for the control children ($F(1,16) = 11.90$, $p < .01$) but not for the IFS children ($F(1,16) = 3.08$, $p = .10$).

4. Discussion

The main goals of the present study were to estimate structural changes in the Hc of 7–9 years old children who had suffered from

Table 4
Statistical analyses of the old/new effects: results of ANOVA with the factors Item Status (old, new), Anterior–Posterior (frontal, central, parietal), and Laterality (left, middle, right) over two time windows. The data presents effects involving the factor Item Status.

	400–500 ms			700–800 ms		
	F	*df*	*p*	*F*	*df*	*p*
Control group						
Item Status	8.14	1, 16	<.05	13.34	1, 16	<.001
Item Status × Anterior–Posterior	5.88	2, 32	<.05°	4.10	2, 32	<.05°
Item Status × Laterality			n.s.	5.04	2, 32	<.05
Item Status × Anterior–Posterior × Laterality	2.62	4, 64	<.05			n.s.
IFS group						
Item Status	9.14	1, 16	<.01			n.s.
Item Status × Anterior–Posterior			n.s.			n.s.
Item Status × Anterior–Posterior × Laterality			n.s.			n.s.

°Adjusted *p*-value according to the Greenhouse–Geisser correction.

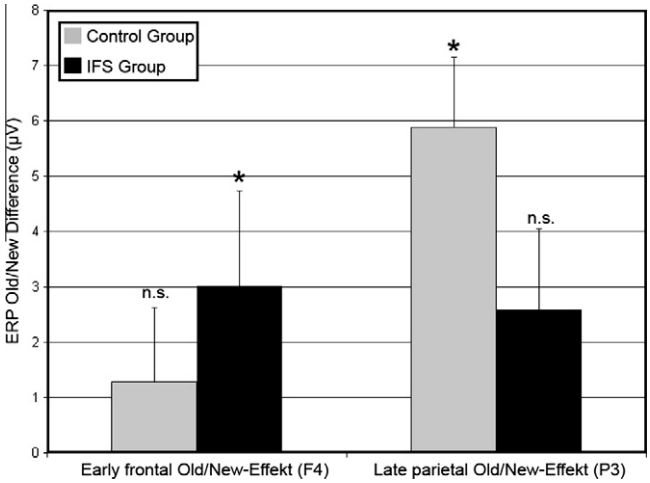

Fig. 3. ERP old/new amplitude differences (in µV) and error bars in the two child groups at the frontal (F4) and parietal (P3) electrodes where the effects were largest. (The 95% confidence intervals were: control group −1.60 to 4.15 for the early and 2.27–9.49 for the late old/new effect, IFS group 0.33–5.71 for the early and −0.54–5.70 for the late old/new effect).

relatively benign IFS, to assess their semantic and episodic memory abilities, and to assess the relative contribution of familiarity and recollection to their recognition memory performance. Hc volumes of the IFS children were not reduced relative to an age-matched control group. Contrary to our expectation, using standardized neuropsychological tests we did not find any differences between the two child groups, particularly no selective impairment in episodic memory when SES was controlled for. However, a more thorough examination of episodic memory by means of ERP indices revealed deficits in recollection-based remembering, a form of memory that relies on the integrity of hippocampal structures (Düzel et al., 2001). Since there were no corresponding group differences in the target-P3 and novelty-P3 in the oddball task the aforementioned ERP pattern can be taken to reflect between-group differences in memory processes.

4.1. Hippocampus volumetry

Volumetric measurements showed that neither absolute nor normalized Hc volumes were smaller in our IFS than in our control group as revealed by structural MR images, suggesting that IFS are not related to fundamental injuries of the Hc in children aged between 7 and 9. However, due to the small sample size this conclusion, derived from a null effect, is preliminary and must await reassessment in a follow-up study with a larger sample size. To further explore the question of power, we conducted post hoc analyses to estimate the critical sample size for the absolute left and right Hc volumes, the two volumetric measures for which the between-group differences were largest. This analysis revealed that, given the between-group differences in Hc volumes obtained in this study, sample sizes of 55 and 70 participants per group would have been required to reject the null hypothesis of no group differences in right and left Hc volumes respectively.[2] However, the relevance of the Hc for episodic memory performance was confirmed by the observed correlations between the absolute Hc volume and memory performance in the recognition memory task.

[2] For this analysis the program GPower (Erdfelder et al., 1996) was used. The effect size (d) was calculated on the basis of the group mean values and standard deviations of the absolute left and right Hc volumes. Alpha and 1-β were set to .05 and .80, respectively.

4.2. Neuropsychological assessment

Examination of intelligence, working memory, episodic and semantic memory with standardized neuropsychological tests only revealed group differences in the visual delayed recall of the Rey–Osterrieth Complex Figure and a marginally significant difference in general knowledge. However, as revealed by covariate analyses, these effects were rather due to differences in SES and not related to the history of IFS. The fact that general knowledge is influenced by SES is supported by previous studies (Lynn and Irwing, 2002). It is less clear why the performance in the visual delayed recall in our study is also influenced by SES as SES is unlikely to account for any portion of the variance in the visual, visuospatial, or memory composites (Noble et al., 2005). However, a previous study showed that the performance in the Rey–Osterrieth Complex Figure Test correlates with scores of several tests of cognitive control functions in children (Watanabe et al., 2005). Since SES has an impact on these latter functions (Kishiyama et al., 2009; Noble et al., 2005) it is reasonable to assume that it also has influenced performance in the visual delayed recall in the IFS group.

On the one hand the missing IFS-related impairments of episodic memory in the neuropsychological tests contradict our hypotheses, as episodic memory relies on the Hc, which has been reported to be highly vulnerable to IFS. However, our results resemble those of earlier studies that only found memory deficits after complex IFS (Kölfen et al., 1998) or when the onset of the first IFS was within the first year of life (Chang et al., 2001). In our IFS group only 10 children (less than 60%) suffered from complex IFS and two children had experienced their first IFS within the first year of life. By this, our IFS group mainly comprises relatively benign IFS characteristics and so IFS-related injury of the Hc and related memory deficits could be too subtle and specific to be detectable by neuropsychological tests.

4.3. ERP data

The assessment of the ERP components in the oddball task enabled us to test for possible memory-unspecific ERP differences between the two groups. As both groups showed highly similar target-P3s associated with the updating of working memory contents (Donchin and Coles, 1988) and similar novelty-P3s associated with bottom-up aspects of attention (Polich, 2007) any between-group differences in the recognition memory task cannot be accounted for by general between-group differences in the ERP components.

In the item recognition experiment we found that the ERP correlates of familiarity and recollection differed between the two child groups even though, there were no group differences in behavioral memory performance. In fact the IFS group showed the same proportion of remember and know responses as the control group. According to our assumption that the hippocampal network is impoverished in IFS children, we had expected these children to give less remember responses. One reason for the missing effect might be that behavioral measurements are not sensitive enough to detect subtle changes in Hc-based memory processing. Another reason can be derived from the introspective nature of the remember/know procedure (Tulving, 1985). The ability to follow the remember/know instruction may change with age and by this it remains unclear whether it can reliably assess recollection and familiarity in child groups (Ghetti and Angelini, 2008).

Conversely, ERPs can dissociate recollection and familiarity without relying on introspective reports of recognition awareness. The control children did not show an early frontal old/new effect, but there was a parietal old/new effect in both, the early and the late time window. These results are consistent with recent ERP studies with children (Cycowicz et al., 2003; Czernochowski

et al., 2005, in press; Friedman et al., 2009; van Strien et al., 2009) and support the view that the ERP correlate of recollection can reliably be recorded at early school age.

Notably, the IFS group showed a qualitatively different ERP pattern. Firstly, there was a widespread old/new effect in the early, familiarity-related time window that, in contrast to the control group also covered frontal recording sites. Since this effect is very similar to the mid-frontal old/new effect in adults with regard to its morphology, timing and scalp topography it can be taken to be functionally equivalent in children and adults and, by this, to represent the ERP correlate of familiarity irrespective of age group. Secondly, and also in contrast to the control group the IFS children did not show a late parietal recollection-related old/new effect. Albeit just like the control group, they showed a parietal old/new effect in the early time window. As this latter effect diminished quickly and was not present in the late time window anymore, it cannot reflect an early onset of recollective processing. Also it did not show a left parietal maximum that is usually reported for the ERP correlate of recollection. Notably, early parietal differences between old and new items have been interpreted as indices of implicit memory (Groh-Bordin et al., 2005; Rugg et al., 1998). Thus, the early parietal difference between old and new items in the IFS group could reflect some form of implicit memory, such as repetition priming.

On the basis of the view that the observed ERP differences in the item recognition experiment reflect differential memory processing we take the absence of the late parietal old/new effect in IFS children to reflect a breakdown in recollection. This conclusion is in line with the assumption that IFS come along with functional changes in the MTL memory network, in particular the Hc. Even though we could not detect structural differences in Hc volumes in our IFS group given the present sample size, an acute Hc injury in the months after the febrile seizures, namely hippocampal edema (Scott et al., 2003; Sokol et al., 2003), could have modified brain maturation at a key stage of brain development. This could have changed memory functions without leading to reductions of Hc volumes detectable in MR measures. Since the Hc is essential for recollection, this highly specific retrieval process, in turn, could have been impaired.

Regarding familiarity-based remembering, under the assumption that the early frontal old/new effect indexes familiarity in children in a similar way as in adults, the present data suggest that familiarity is preserved after IFS. As the IFS group achieved equal discrimination accuracy as the control group but recollection was deficient (as suggested by the absent parietal old/new effect), it is conceivable that the early frontal old/new effect reflects a compensation mechanism by which familiarity compensates for degraded recollection. This interpretation, though intriguing, has to be taken with some caution. We could not find direct evidence for a compensation mechanism, as for example, that high-functioning IFS children showed a larger frontal old/new effect than low-functioning IFS children. Nevertheless, the observation that the IFS group performed as well as the control group in the recognition memory task without showing a parietal old/new effect suggests that the IFS group used a neural network that differs from the one used by the age-matched control group in that familiarity compensates for impaired recollection.

Another objection against this interpretation could be that the two child groups used different strategies in the recognition memory task which caused different familiarity-/recollection-specific ERPs. However, the children made an indoor–outdoor decision in the encoding phase that minimized the use of encoding strategies. Also, the groups did not differ with respect to response bias (Br), a measure which reflects response strategies in making recognition judgments (Payne et al., 2004). Therefore, it is unlikely that the ERP differences in the present study merely reflect strategic differences in task performance.

To conclude, the current study challenges the widely accepted opinion that IFS do not have any consequences for memory development during childhood. Although the relative benign forms of IFS under investigation here are not associated with a higher risk for structural changes in the Hc or general memory difficulties, they seem to induce functional changes in the MTL memory network. This is characterized by impaired recollective processing, a Hc-dependent retrieval process, and its putative compensation by familiarity.

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