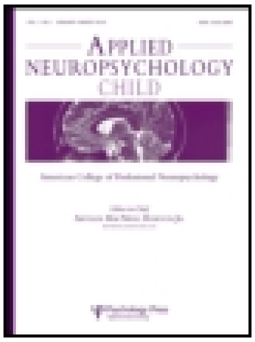

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Working memory in pediatric frontal lobe epilepsy

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ABSTRACT
Thirty-two children with frontal lobe epilepsy (FLE) were assessed using different working memory measures. In addition, parents and teachers completed the working memory scale of the Behavioral Rating Inventory of Executive Functioning (BRIEF) to assess the children's "daily life behavior." Results suggested minimal working memory deficits as assessed with performance-based measures. However, the BRIEF showed more working memory deficits suggesting that, on a daily life level, working memory problems seem to be associated with FLE. We discuss why the results of the performance-based measures are not consistent with results of the BRIEF.

HIGHLIGHTS
- Parents as well as teachers report working memory dysfunction in daily life to the same extent
- Performance based measures show minimal deficits of working memory
- Correlation between working memory tasks and proxy measures are low

KEYWORDS
Executive function; frontal lobe epilepsy; pediatric epilepsy; working memory

Introduction

In general, cognitive and learning problems are common in children with epilepsy (e.g., Fastenau, Shen, Dunn, & Austin, 2008; van Iterson, de Jong, & Zijlstra, 2015). Findings are based on populations with different types of epilepsy; over recent years frontal lobe epilepsy (FLE) has been increasingly investigated, but it is still not well represented in research publications (Berl et al., 2015; Fuentes & Smith 2015; Law, Widjaja, & Smith, 2018; Luton, Burns, & DeFilippis, 2010; Sepeta et al., 2017; Verche, San Luis, & Hernandez, 2018). This is undesirable since FLE is the second most common type of focal epilepsy, causing 20 to 30% of all focal seizures (Rugg-Gunn, Sander, & Smalls, 2011), with an average age at onset ranging from 4.6 to 7.5 years (Braakman et al., 2011).

To date, only five review articles have been published on cognition in FLE, and they suggest that cognition is compromised (Braakman et al., 2011; Helmstaedter, 2011; Patrikelis, Angelakis, & Gatzonis, 2009; Risse, 2006; Verche et al., 2018). The impact of epilepsy variables (age at onset, duration of epilepsy, lateralization, and medication), however, is still debated.

Thus far, most empirical studies have focused on adult populations with FLE; most of the few studies conducted in children with FLE lack statistical power. Consequently, there is a need for cognitive research on FLE in children.

The present study focuses on working memory, which is an important aspect of executive functioning (EF), considered a frontal lobe function. Working memory is key in both academic settings and daily life (Gathercole & Alloway, 2011) and is associated with IQ performance (see, also, van Iterson & de Jong, 2018). Many definitions of working memory are available (e.g., Baddeley, 2003, 2010, 2012); for this study we used the 2013 definition (Lezak, Howieson, Bigler, & Tranel, 2013, p. 28): "the ability to hold in mind and mentally manipulate information over short periods of time."

There are three reasons why studying working memory is important in children with FLE. First, many children with FLE and normal intelligence have learning difficulties (Braakman et al., 2013; Exner

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et al., 2002; Luton et al., 2010; Riva et al., 2005). This could be related to their compromised working memory (Hernandez et al., 2003; Modi, Vannest, Combs, Turnier, & Wade, 2018), because working memory problems are often associated with learning problems (Gathercole & Alloway, 2011; Bull & Scerif, 2001; Gathercole & Pickering, 2000; Gathercole, Pickering, Knight, & Stegmann, 2004; Geary et al., 1999; Jarvis & Gathercole, 2003). Second, working memory is linked to a network of prefrontal and parietal areas (Curtis & D'Esposito, 2003; Kane & Engle, 2002; Østby, Tamnes, Fjell, & Walhovd, 2011; Gerton et al., 2004). Neuroimaging studies suggest that FLE might lead to structural and functional disorders (Braakman et al., 2011; Dinkelacker, Dupont, & Samson, 2016) as seizures, as well as interictal epileptic discharges, are increasingly recognized as interfering with physiological brain circuitry (Braakman et al., 2011; Dinkelacker et al., 2016; Smith, 2016). An epileptic focus in the frontal network could, therefore, lead to executive function problems, including working memory problems (Riva, Saletti, Nichelli, & Bulgheroni, 2002). Third, recent studies report working memory deficits in groups with different types of epilepsies (van Iterson & de Jong, 2018, Krivitzky, Walsh, Fisher, & Berl, 2016; Modi et al., 2018, 2019) and relate this to behavioral problems (Modi et al., 2019). Furthermore, some studies suggest that auditory working memory is compromised in people with FLE (Exner et al., 2002), while research on visual working memory is lacking. The visual domain can act alone, but can also interact with the verbal domain and is thought to be located in different areas of the brain (Rudner, Fransson, Ingvar, Nyberg, & Ronnberg, 2007). Surprisingly, one study (van Iterson & de Jong, 2018) found no association of FLE with working memory problems, although other types of epilepsy did show working memory problems.

Earlier studies showed that performance-based measures were associated with isolated cognitive deficits in children with epilepsy (e.g., Fastenau et al., 2008; van Iterson et al., 2015). Behavior in daily life, however, is reflected more by subjective measures such as the Behavioral Rating Inventory of Executive Functioning (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000; Smidts & Huizinga, 2009). Only a few studies have addressed the relationship between tested and reported information about EF in children with epilepsy (Hessen, Alfstad, Torgersen, & Lossius, 2018; MacAllister et al., 2012; Parrish et al., 2007).

As suggested by others (MacAllister et al., 2012; Modi et al., 2018), we studied working memory using clinical tests and combined these with a questionnaire about daily life behavior: the working memory scale of the BRIEF for parents as well as teachers. The BRIEF was recently studied in this population for the first time (van den Berg, de Weerd, Reuvekamp, Hagebeuk, & van der Meere, 2018). The aim of the current study was to increase the knowledge about working memory in children with FLE, because this may be relevant for the development of intervention strategies (Isquith, Roth, Kenworthy, & Gioia, 2014). We hypothesized that children with frontal epilepsy would score lower on working memory tasks overall compared with the normative reference group. Second, we hypothesized that parents and teachers would report working memory problems in daily life behavior. Third, we hypothesized that teachers would report more problems in the BRIEF than parents, because of the differences in executive function demands in various settings.

Materials and methods

Participants

Children with FLE were referred by neurologists for a broad neuropsychological assessment. The definition of the type of epilepsy was based on the International League Against Epilepsy criteria and confirmed by an EEG registration. The assessment of executive functioning with validated and normative tests is possible from the age of eight. Further executive function demands differ in primary and secondary school; in the Netherlands children go to secondary school at approximately twelve years old. Previous work (Hernandez et al., 2003) has shown significantly poorer performance in children with FLE aged 8–12 years compared to other children with other epilepsies. Inclusion criteria were therefore children aged between 8 and 12 with a diagnosis of frontal lobe epilepsy and IQ $>$ 70 or school achievement scores above C level (Dutch CITO) in math and language. Exclusion criteria were health and/or psychiatric problems, which could influence the neuropsychological assessment, apart from attention deficit and hyperactivity disorder (ADHD), which is commonly diagnosed in children with epilepsy (Williams, Giust, Kronenberger, & Dunn, 2016). Because of the small group, we also enrolled 7-year old children who would soon be 8, one 6 year old, and one 12 year old. A total of 32 children (18 boys, 14 girls) met these criteria. Five had a confirmed ADHD diagnosis. For several reasons, the full protocol was not applied to all individuals (see Table 1). A few children refused to

Table 1. Test protocol.

Test	*N*[a]	Description
Visual WM[b]		
FePsy:		
Corsi-block	29	Stimuli (starting with three blocks, up to nine) are presented with a presentation time of 1 second per item in a sequence digitally. After a delay the sequence has to be mimicked.
Recognition figures serially	25	Stimuli (four figures) are presented digitally serially during a learning phase with a presentation time of 1 second per item. After a delay of 2 seconds the screen shows one of these figures and the testee has to indicate the order of presentation. The number of correct items is scored, with a maximum of 24.
Recognition figures simultaneously	27	Reaction time is measured in milliseconds (ms). Stimuli (four figures) are presented digitally simultaneously during a learning phase with a presentation time of 4 seconds. After a delay of 2 seconds the screen shows one of these figures between distracters. The target items have to be recognized. The number of correct items is scored, with a maximum of 24. Reaction time is measured in ms.
Auditory WM[b]		
Fepsy:		
Recognition words serially	29	Stimuli (four words) are presented digitally serially during a learning phase with a presentation time of 1 second per item. After a delay of 2 seconds the screen shows one of these figures and the testee has to indicate the order of presentation. The target items have to be recognized. The number of correct items is scored, with a maximum of 24. Reaction time is measured in ms.
Recognition words simultaneously	29	Stimuli (four words) are presented digitally simultaneous during a learning phase with a presentation time of 4 seconds. After a delay of 2 seconds the screen shows one of these words between distracters. The target items have to be recognized. The number of correct items is scored, with a maximum of 24. Reaction time is measured in ms.
Wechsler Intelligence Scale for Children: Digit span	28	Orally given sequences of numbers are asked to be repeated, either as heard of in reverse order.
Questionnaires		
Working Memory Scale of the Behavior Rating Inventory of Executive Functions (BRIEF) parent (p) and teacher (t) form	32 (p) /30 (t)	This is a subscale of the Metacognition index. It consists of 10 items and measures a child's ability to hold information in mind with the objective of completing a task. Items include "Forgets what he/she was doing" and "Has trouble remembering things, even for a few minutes."

Note. [a]N = Number of participants assessed. [b]WM = working memory.

finish some tasks; one child did not complete all tasks, but the child's parents completed the questionnaires.

Procedure

As part of a broad neuropsychological assessment routine undertaken by a psychology assistant, working memory was assessed using visual and verbal recognition tasks, with serial as well as simultaneous presentations of the FePsy, a computerized test battery (Alpherts & Aldenkamp, 1995). The Digit Span of the Wechsler Intelligence Scale for Children-Third edition-Nederlandstalige (WISC-III-NL) was used to assess auditory working memory (Wechsler, 2005). Executive function behavior in daily life was assessed with the working memory scale of the BRIEF, parent and teacher form (Gioia et al., 2000; Smidts & Huizinga, 2009). Table 1 shows the details of the tests. The study was approved by the Ethical Committee of MST Enschede, and parents gave their informed consent.

Statistical analysis

The data, corrected for age, were compared with normative data from the Dutch population. A score 2SD below average on the digit-span of the WISC-III-NL and the FePsy tasks was considered statistically significant and suggests a deficit in this domain. In the FePsy, the normative reference group is divided into two groups: older and younger than 10 years, and in the WISC-III-NL, the Digit Span is divided into four age groups. For the BRIEF a score of 1.5 *SD* ($>=$ percentile 93) above average was considered statistically significant and suggests EF problems. Differences in normally distributed neuropsychological test results and scores on the questionnaire between the FLE cohort and the reference values were tested using one sample *t*-tests at a 5% significance level. To explore group differences based on epilepsy variables, children were categorized into left versus right versus bifrontal lateralization (based on EEG), age at seizure onset (young $<$ 5 years vs. old $\geq$ 5 years), duration of FLE (short $<$ 5 years vs. long $\geq$ 5 years), and drug load (monotherapy, polytherapy, none). Severity of the epilepsy was not taken into account due to the unknown frequency of seizures, with most occurring at night. However, children were enrolled from a tertiary epilepsy center, suggesting that their epilepsy is more difficult to treat. Imaging, where conducted, did not show lesions (apart from one participant whose scores were in the average range) or specific localizations; therefore no participant was a surgical candidate at the time. Correlation analyses were used to assess the relationship between all measures. Independent *t*-tests and ANOVA, and nonparametric tests in case of small numbers in subgroups, at the 5% significance level were used to compare the groups for continuous variables. Sample sizes were small; therefore, effect sizes are shown when appropriate using Cohen's *d*. Data were analyzed using the Statistical Package for Social Sciences (IBM SPSS Statistics 20.0).

Results

The children's demographic characteristics and epilepsy variables are shown in Table 2.

Table 2. Demographic and epilepsy variables.

Characteristics	Value
N	32
Participants	
• Gender (male:female)	18:14
• Mean age (±*SD*) in years at assessment	9.2 ± 1.6
Age at seizure onset	
• Mean age (±*SD*)	4.6 ± 2.8 years
• Younger age (< 5 years)	16 (50%)
Duration of epilepsy	
• Mean duration (±*SD*)	4.6 ± 2.7 years
• Short duration (< 5 years)	17 (53%)
Seizure lateralization based on EEG	
• Left frontal	11 (34%)
• Right frontal	6 (19%)
• Bifrontal	11 (34%)
• Unknown lateralization	4 (13%)
AED treatment	
• Monotherapy	12 (38%)
• Polytherapy	16 (50%)
• No AED	4 (12%)

Note. EEG = electroencephalogram; AED = automated external defibrillator.

Test results

Mean scores for each age group were given in Figure 1.

For the word recognition only 10–16% of the participants (3–5 participants) showed impaired function. For the figure recognition 26–55% of the participants (8–17 participants) showed impaired function. For the digit span, this could not be calculated due to missing standard deviation for the normative data.

Correlation between all performance based measures was low. Recognition Figures Serially correlated with Recognition Words Serially ($r = .61$, $p = .006$) and with Digit Span backward ($r = .49$, $p = .035$). Recognition Words Simultaneously correlated with Recognition Words Serially ($r = .46$, $p = .049$).

Results from the participant group did not differ significantly from those of the reference group, apart from Simultaneously Presented Figures ($p < .001$ ($t(6) = -5.767$, CI [−7.04, −2.85]) and $p < .001$ ($t(19) = -8.516$, CI [−5.54, −3.36])) with large effect sizes ($d = 1.76$, $d = 1.68$) and Digit Span Forward ($p = .002$ (CI [−2.67, −.83]) in the youngest group (Table 3). For the other tests, effect sizes ranged from very small to (low) medium.

Comparison between groups revealed no significant differences between left versus right versus bifrontal lateralization (based on EEG), age at seizure onset (young < 5 years vs. old ≥ 5 years), duration of FLE (short < 5 years vs. long ≥ 5 years), and drug load.

Working Memory Scale of the BRIEF

There were no significant differences on the working memory scale ratings between parents and teachers. Table 4 shows that approximately 40 to 50% of the scores of both sources are above average (almost a third scored 1.5 standard deviations above average norms). Correlation between both BRIEF measures was high ($r = .566$, $p < .001$).

Comparison between groups revealed no significant differences between left versus right versus bifrontal lateralization (based on EEG), age at seizure onset (young < 5 years vs. old ≥ 5 years), duration of Frontal Lobe Epilepsy (FLE) (short < 5 years vs. long ≥ 5 years), and drug load.

The working memory scale of the BRIEF for parents was only correlated with serially presented words ($r = -.44$, $p = .026$). For the teachers' scores the working memory scale was significantly associated with serially presented words ($r = -.74$, $p < .001$) and figures ($r = -.65$, $p = .001$).

Discussion

This study explored the auditory and visual domain of working memory in children with FLE. Working memory, assessed with performance-based measures (FePsy and Digit Span), was not impaired with the exception of two minor parts: Simultaneously Presented Figures, and Digit Span Forward for children aged 7 and 8 years. This negative finding concurs with other studies in children with FLE (Braakman et al., 2012, 2013; van Iterson & de Jong, 2018). Also, groups based on different epilepsy variables revealed no differences, which is consistent with previous studies (Braakman et al., 2013; Elger, Helmstaedter, & Kurthen, 2004; Gonzalez et al., 2014; Hernandez et al., 2002; Upton & Thompson, 1997; van Iterson & de Jong, 2018). The mean scores of the working memory tests in our small group show improving

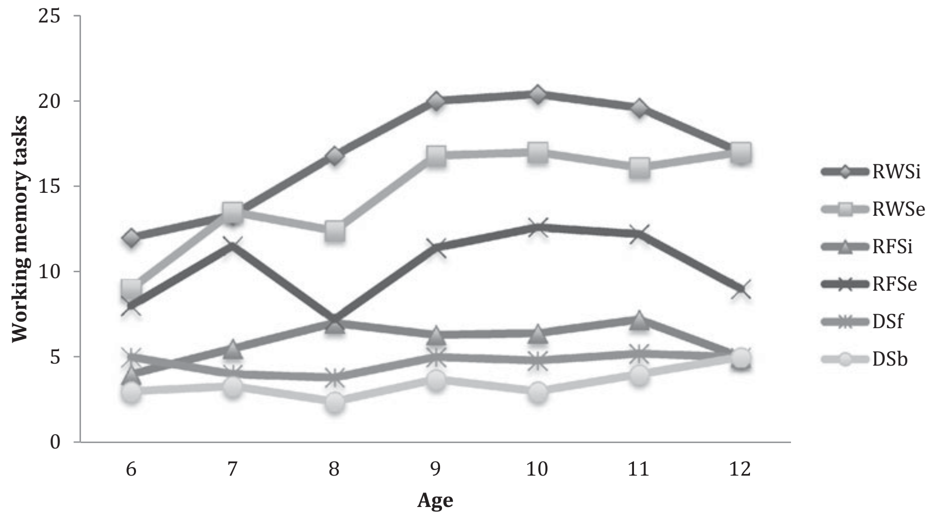

Figure 1. Mean score age groups.

Table 3. Neuropsychological scores: Participants and the reference group.

Test	N	FLE participants' mean (±*SD*)	Reference mean (±*SD*)	Cohen's d	*p*-value
Corsi Block (CB)					
≤ 9 years	15	3.73 (±0.93)	4.24 (±0.55)[a]	.67	.051
> 9 years	14	4.75 (±0.79)	4.69 (±0.75)[a]	−.07	.779
Recognition figures serial (RFSE)					
≤ 10 years	18	10.40 (±3.80)	10.70 (±3.30)	.08	.737
> 10 years	7	11.70 (±5.10)	13.10 (±2.70)	.34	.498
Recognition figures simultaneous (RFSI)					
≤ 10 years	20	6.30 (±2.30)	10.70 (±2.90)	1.68	.000*
> 10 years	7	6.90 (±2.30)	11.80 (±3.20)	1.76	.001*
Recognition words serial (RWSE)					
≤ 10 years	21	14.80 (±4.20)	16.60 (±4.80)	.40	.091
> 10 years	8	16.30 (±6.60)	11.00 (±4.10)	−.96	.061
Recognition words simultaneous (RWSI)					
≤ 10 years	21	17.50 (±4.30)	16.60 (±5.00)	−.19	.336
> 10 years	8	19.30 (±6.60)	18.40 (±3.30)	−.17	.725
Digit-span forward (DSF)[b]					
≤ 8 years	10	5.10 (±1.30)	6.85		.002*
9 years	6	6.67 (±1.40)	7.26		.336
10 years	4	7.00 (±1.80)	7.53		.602
11 years	8	7.00 (±2.10)	7.84		.303
Digit-span backward (DSB)[b]					
≤8 years	10	3.20 (±1.20)	4.01		.067
9 years	6	4.50 (±1.00)	4.22		.542
10 years	4	3.80 (±1.70)	5.00		.239
11 years	8	4.63 (±2.10)	5.01		.614

Note. [a]Reference group consists of only people with epilepsy. [b]*SD* not available and therefore also no *d*.
*p = significant.

working memory across the age span, but this growth seems to levels off at around 11 years. An explanation for this could be that demands on executive function increases with brain maturation (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002) and with frontal disturbances, executive dysfunction emerges over time (Braakman et al., 2011; Dinkelacker et al., 2016) resulting in long-term developmental "lagging behind" or a delayed development of working memory, as previously suggested (Hernandez et al., 2003).

Preliminary findings in this same group and other studies on children with FLE imply that inhibition as well as shifting problems are more frequently found (Holtmann et al., 2006; MacAllister et al., 2018; Rzezak et al., 2018). Also, attention problems are reported extensively in children with epilepsy (e.g., Williams

Table 4. Ratings working memory scale BRIEF.

BRIEF working memory scale	*N* (%)
Parents' ratings	
<= percentile 83 (< 1 *SD*)	19 (60)
percentile 84–93 (1 *SD*)	3 (9)
=> percentile 93 (> 1,5 *SD*)	10 (31)
Teachers' ratings	
<= percentile 83 (< 1 *SD*)	15 (50)
percentile 84–93 (1 *SD*)	6 (20)
>= percentile 93 (> 1,5 *SD*)	9 (30)

Note. BRIEF = Behavior Rating Inventory of Executive Functions.

et al., 2016). Additionally, there is evidence that working memory seems to rely on the frontoparietal network and is not a frontal function per se (Braakman et al., 2013; Curtis & D'Esposito, 2003; Kane & Engle, 2002) and might depend on motor control (Rietbergen, Roelofs, den Ouden, & Cools, 2018). As the neuroanatomical basis of executive functions has been suggested to be in different cortical and subcortical regions (Armbruster, Ueltzhoffer, Basten, & Fiebach, 2012; Bari & Robbins, 2013; Botvinick & Todd, 2015; Dajani & Uddin, 2015), a variety of cognitive problems and interactions can be expected under the influence of (frontal) epileptic discharges (Braakman et al., 2011; Dinkelacker et al., 2016; Smith, 2016). The subtle working memory deficits we detected could, therefore, originate from, or interact with other cognitive problems and might not be an isolated deficit.

Overall, with scores at the lower end of the normal distribution, the current study finds that working memory is relatively intact in primary-school aged children with FLE, as far as the objective cognitive tests are concerned. In contrast with these performance-based measurements, teacher and parents ratings showed that 40 to 50% of the participating sample scored at least 1 *SD* above average, and a third scored above the clinical criteria of the working memory scale of the BRIEF. Although the precise seizure frequency in our group is unknown and there is lack of imaging, we do know that all participants in our sample have frontal disturbances as confirmed by EEG registration. As mentioned earlier, there is evidence that working memory processes are related to the prefrontal areas (e.g., Østby et al., 2011) and that FLE can lead to structural and functional disorders (e.g., Braakman et al., 2011). Therefore, it might be safe to conclude that the working memory deficits in daily life in our participants can be, at least for some part, linked to their frontal lobe epilepsy. The unique availability of both parent and teacher ratings improves the reliability of this association.

In general, BRIEF scores in many clinical populations, rarely correlate with cognitive tests (e.g., Anderson et al., 2002; Smidts & Huizinga, 2009). The present study also reports few associations between performance-based measures and the BRIEF, confirming the outcome of other studies in epilepsy (Gross, Deling, Wozniak, & Boys, 2015; Hernandez et al., 2002; MacAllister et al., 2012). The strongest associations are found with the teachers' reports; this has not previously been studied in this population. Explanations for this inconsistency often mentioned in the literature are the lack of ecological validity for neuropsychological tests, the problems with computerized testing (Witt, Alpherts, & Helmstaedter, 2013) and the response bias of teachers and parents (Gross et al., 2015; Rodenburg, Meijer, Dekovic, & Aldenkamp, 2007). Reported everyday behavioral and tested measures appear to tap different elements of executive functioning, however, confirming that the BRIEF reflects more daily "real-life" behavior, while performance in neuropsychological tests primarily predicts behavior in a controlled assessment setting (Hessen et al., 2018; Huizinga & Smidts, 2011; MacAllister et al., 2012). Our results suggest that teachers report slightly more problems than parents. Another study in the same population confirms this tendency using the whole BRIEF (van den Berg et al., 2018) and strengthens the theory that executive function demands vary across settings.

Although the explanations about the limited associations previously discussed above sound valid and plausible, it is worthwhile considering an alternative explanation in (frontal lobe) epilepsy: working memory and attention are closely related (Fougnie, 2008; Rensink, 2002) and teachers and parents could confuse the domains while rating. Another possibility is that teacher and parent ratings are based on observing children with epilepsy showing huge variations in their behavior and cognitive skills (e.g., impaired attention) due to the epileptic activity itself (Auclair, Jambaque, Dulac, LaBerge, & Sieroff, 2005; Centeno, Thompson, Koepp, Helmstaedter, & Duncan, 2010; Hernandez et al., 2002, 2003; Oostrom, Schouten, Kruitwagen, Peters, & Jennekens-Schinkel, 2001), to epilepsy as a stressor thus releasing Dopamine (Kodama, Hikosaka, Honda, Kojima, & Watanabe, 2014; Lee & Goto 2015) and to fluctuating sleep quality, a main characteristic in our target group (Barnett & Cooper, 2008; Holley et al., 2014). The impact of parental stress and reporting bias (Rodenburg et al., 2007), as well as the use of anti-epileptic medication (Brandt, Lahr, & May, 2015; Burns, Ludwig, Tajiri, & DeFilippis, 2018; deGroot et al., 2013) on the results remain unknown, but may also contribute. Correlating subjective opinions based on variations in behavior and cognitive capacity with performance based measures such as neuropsychological assessment in children with FLE, is difficult and calls for systematic future studies on this issue.

There are several limitations to this study to acknowledge. The group as a whole is very heterogeneous in terms of epilepsy variables and overall neuropsychological deficits. In addition, the sample size is smaller than that necessary to show significant differences, according to the power analysis we conducted (38 participants). This was however based on determining a difference (of 2 *SD*) between an epilepsy group and ADHD group (with 80% power, two-sided alpha of 0.05). Unfortunately, there were no children with only ADHD enrolled in the study. Furthermore, there is a normative reference group, but this group lacks age-appropriate data, which reduces the reliability of our data. Expanding the clinical group and adding a control group and possibly another clinical group would increase the power of the study. Expanding age groups to investigate possible delayed development is also necessary. Moreover, there might be a selection bias due to our setting. All children were referred for neuropsychological examination by the pediatric neurologist. The results can, therefore, not be fully generalized to a broader epilepsy sample.

Conclusions

Working memory in children with FLE is minimally affected compared to a normative reference sample, as assessed with performance-based measures. Parents and teachers, however, find the working memory deficits in daily life behavior. Therefore, FLE can be associated with working memory problems on a daily life level rated by both parents and teachers. Future research is needed to differentiate further between daily life behavior and clinical behavior in children with FLE.

Declaration of interest

The authors declare no conflicts of interest.

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