Diagnostic and neuropsychiatric considerations in epilepsy and intellectual disability

DIAGNOSTIC AND NEUROPSYCHIATRIC CONSIDERATIONS IN EPILEPSY AND INTELLECTUAL DISABILITY

Psychological perspectives

Jans van Ool

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Promotor

Prof. dr. A. P. Aldenkamp

Copromotores

Dr. J.G.M. Hendriksen (Kempenhaeghe, Heeze)
Dr. H.J. Schelhaas (Kempenhaeghe, Heeze)

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Content

1

General introduction

Epilepsy and intellectual disability

Epilepsy is conceptually defined as a brain disease characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. Epileptic seizures imply the transient occurrence of signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain.[1] An updated operational clinical definition of epilepsy is provided by Fisher et al. in 2014.[2] Epilepsy is particularly common in people with intellectual disability (ID).[3] Whereas the prevalence of epilepsy in the general European population is around 1%,[4] the pooled prevalence among people with ID is 22.2% and increases with the severity of ID.[3] In 2016, around 181,100 individuals were registered as having epilepsy by reports of general practitioners in The Netherlands (0.85% of the Dutch population).[5]

ID is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) – 5 as having both reduced intellectual functioning and impaired adaptive abilities to cope with the daily demands of the social environment, and should manifest during the developmental period of an individual.[6] The impaired adaptive abilities refer to three general domains: conceptual, social, and practical. The conceptual domain refers to skills in reading, writing, mathematics, executive functioning, memory and knowledge; the social domain includes interpersonal communication skills, empathy, social judgement, emotional regulation and the ability to make and retain friendships; the practical domain refers to personal care, organizing school, work and domestic tasks, and money management.[6]

Compared to people without ID, the epilepsy among those with ID is often more severe, chronic, and refractory to treatment, which has a pervasive impact on their quality of life.[7,8] Nevertheless, this population is under-researched, as recognized by the International League Against Epilepsy (ILAE).[7] In the care for this population, there are many relevant clinical areas identified by experts, such as the impact of comorbidity, seizures, and antiepileptic drugs on behavior; treatment emergent behavioral difficulties, psychogenic nonepileptic seizures, and quality of life.[9] This emphasizes the need for multidisciplinary studies in order to bridge the knowledge gaps.

The triangle of epilepsy, ID and neuropsychiatry

Epilepsy and ID have each been linked to a variety of behavioral, affective, and psychiatric comorbidities.[10-12] For the full spectrum of challenging behavior, affective symptoms and psychiatric disorders, we will use the term “neuropsychiatric comorbidities” in this dissertation. Challenging behavior is defined by Emerson as “culturally abnormal behavior(s) of such an intensity, frequency or duration that the physical safety of the

person or others is likely to be placed in serious jeopardy, or behavior likely to seriously limit use of, or result in the person being denied acces to, ordinary community facilities".[11] These behaviors can result in a fear of harm or actual injury to the person or to others and might have adverse consequences for the individual's development and opportunities for community integration.[14] Psychiatric disorders are mental disorders that are usually defined by the standard criteria provided by the widely used classification systems DSM-5[6] or International Statistical Classification of Diseases and Related Health Problems (ICD) – 10.[15] Although the severity and symptomatology can vary significantly, psychiatric disorders are commonly stated as either present or not. Affective disorders, particularly depressive and anxiety disorders, are often indicated in gradations as well, however. This is especially useful among people with ID, as diagnosing depression or anxiety disorders can be complicated by limited cognitive and verbal abilities in people with ID. Hence, there are many instruments that are used to assess or screen for depressive symptoms or anxiety in people with ID.[16,17]

Nearly one-third of people with epilepsy has a depression or anxiety disorder, and epilepsy is also strongly associated with autism spectrum disorders.[18] Multiple reasons for the association between epilepsy and neuropsychiatry have been suggested, such as psychological factors (e.g., burden of epilepsy and perceived stigma) and neurobiological factors (e.g., seizure-related, adverse effects of antiepileptic drugs, same underlying pathophysiologic mechanism).[11,12,19] The prevalence of neuropsychiatric comorbidities among adults with ID depended strongly on the measurements and diagnostic criteria used, with point prevalence rates varying from 15.7% (DSM-IV-TR) to 40.9% (clinical diagnoses).[20] Challenging behaviors were most prevalent. Furthermore, neuropsychiatric comorbidities were significantly more common among people with a severe to profound ID compared to those with a mild ID.

Although epilepsy and ID seem to be a risk factor for neuropsychiatric comorbidities, the nature and extent of these comorbidities becomes more complicated in the population who have both epilepsy and ID. Especially when considering the many factors that are involved in epilepsy, such as etiology, epilepsy syndromes, seizure types and frequency, increased epilepsy severity in those with ID, and the more frequent use of psychotropic medication. In the current literature, people with ID are often excluded from studies on epilepsy and neuropsychiatry.[21] Conversely, studies on neuropsychiatry in people with ID often do not take into account epilepsy-related variables. A better understanding of the complex associations between neuropsychiatric comorbidities and epilepsy and ID can have important implications for good clinical practice and treatment of these individuals.

Still in the dark: a case report

Lisa is a young woman of 21 years of age who enjoys to listen to music, to dance, and to go for a stroll or bike ride; who makes other people laugh, who shows affection to others when her needs and desires are met, and who thrives best in close proximity of (professional) caregivers and in a positive atmosphere. When feeling well and fit.

Lisa has a severe epileptic encephalopathy with unknown etiology since the age of two. She has a combined epilepsy type with both focal and generalized seizures, including tonic, tonic-clonic, atonic, myoclonic and absence seizures, which occur daily (sometimes in clusters). Her epilepsy appears to be very difficult to treat. Over the years, pharmacological treatment with antiepileptic drugs was attempted with valproate, levetiracetam, zonisamide, topiramate, phenytoin, lacosamide, ethosuximide, rufinamide, gabapentin, and clobazam, all without sufficient effect. Also, treatment with vagus nerve stimulation did not lead to improvement. Since the age of 7-8, the social-emotional and cognitive development of Lisa has regressed and, at this time, her level of ID is severe to profound. Although Lisa can be lively and cheerful, she frequently exhibits challenging behavior, such as screaming, hitting and pinching of others, and biting and scratching herself. Her affective state is highly variable with periods of sadness and anxiety and, in addition, she is diagnosed with an autism spectrum disorder. There is a complex interaction between the epilepsy, ID, and her mood and behavior, which impacts on her well-being and affects social relationships between Lisa and her family, professional caregivers, and fellow clients.

Lisa lives at Kempenhaeghe since the age of 13 due to her severe epilepsy in combination with challenging behavior. Whereas she enjoyed day trips and overnight stays at her parents' during the first years while being admitted at Kempenhaeghe, nowadays such activities result in unpleasant and unsafe situations due to her unpredictable behavior and are therefore discontinued. Lisa's family as well as professional caregivers are often puzzled by her sudden changes in mood and behavior, which seem to be associated with epilepsy and epilepsy-related fatigue or confusion, but also with her deteriorated cognitive and social-emotional functioning and autism.

In the past years, several behavioral interventions have been implemented, including a behavioral alert plan for early intervention by which escalation is sometimes prevented. In addition, Lisa was treated with an antidepressant (citalopram), after which her mood stabilized initially. After several months, however, her mood deteriorated and behavioral outbursts increased. Citalopram was discontinued and treatment with antipsychotic medication (risperidone) was initiated, after which the seizure frequency increased immediately. Risperidone was replaced by pipamperon which seemed to have less adverse effects and a moderate effect on her behavior. The daily clinical care is aimed at preservations of her abilities and quality of life of Lisa.

The TRIANGLE study

In order to get a better understanding of neuropsychiatric comorbidities in people with epilepsy and ID, the TRIANGLE study is conducted by a multidisciplinary research team: **T**he **R**elation between epilepsy, **I**D, **A**nd **N**europsychiatric disorders in a **G**roup of adult patients in **L**ong-term care for **E**pilepsy. The TRIANGLE study is a cross-sectional study conducted in Kempenhaeghe, a tertiary epilepsy center, within the department of residential care. The overall aim of the TRIANGLE study was to explore the independent associations between neuropsychiatric outcomes and epilepsy and ID characteristics, while taking into account demographic factors and the other predictors. The study was undertaken by a multidisciplinary research team, including a neurologist, two clinical (neuro)psychologists, a physician for people with ID, a medical doctor, and a psychologist. TRIANGLE is approved by the medical-ethical committee of Kempenhaeghe (No. 15.01). The medical-ethical committee of Erasmus University medical center concluded that the rules laid down in the Medical Research Involving Human Subjects Act do not apply to this study (MEC-2016-408).

Patients were eligible to participate if they met the following criteria: 1) age ≥ 18 years, 2) diagnosis of epilepsy according to the clinical definition of the ILAE,[2] 3) diagnosis of ID or current adaptive functioning at level of ID as evaluated by the individual's psychologist, and 4) living at inpatient or outpatient tertiary care facilities of Kempenhaeghe for at least one year. A total of 189 out of 240 adults with epilepsy and ID participated in the TRIANGLE study. For all participants, the level of ID was (re-)assessed, epilepsy characteristics (as well as demographics) were retrieved from electronic patient files, and neuropsychiatric aspects were examined, including challenging behavior, mood, anxiety, and psychiatric classifications. The selection of diagnostic instruments is based on (internationally reported) validity and reliability, and feasibility of the instruments for use among people with ID.

The data collection took place from spring 2016 until the end of 2017, as participants were included on a rolling basis. In order to minimize the burden for patients and caregivers as much as possible, the assessment took place on-site at a location that is familiar to the person (e.g., the care unit or day care center). It was incorporated in the daily care if possible and, prior to assessment, the researcher discussed specific needs of the participant with the nursing staff. All participants received a small reward afterwards, irrespective of whether they had completed the assessments entirely or not.

Outline of this dissertation

In order to study the associations between epilepsy, ID, and neuropsychiatric comorbidities in a valid and reliable way, first a few methodological issues needed to be addressed. Therefore, this thesis is divided into two parts.

Part 1. Diagnostic processes: filling the gaps

In the first part, the studies focus on methodological aspects of the diagnostic processes within the fields of ID and assessment of mood and anxiety. The diagnostic criteria of ID have been revised in the DSM-5.[6] The DSM-5, which also includes criteria for psychiatric disorders, is officially implemented in the Dutch mental health care system since January 2017. Regarding the classification of ID, the criteria have shifted towards a tripartite model in which the severity of deficits, in terms of adaptive functioning, is to be addressed on three domains: conceptual, social and practical. This new classification gives the opportunity to define a concept of ID domain discrepancy, in which one domain is particularly more deficient than another, in a standardized way. In **chapter 2**, a method is described to assess each of these domains separately, as well as a method to identify an ID domain discrepancy. The associations between epilepsy characteristics and level of ID and between epilepsy characteristics and the presence of an ID domain discrepancy are explored. As the conceptual domain was assessed by using an intelligence test, **chapter 3** has built on this by studying the accuracy of abbreviated versions of the two most commonly used intelligence tests in The Netherlands: the Wechsler Intelligence Scale for Children – Third edition (WISC-III)[22] and the Wechsler Adult Intelligence Scale – Fourth edition (WAIS-IV).[2] Multiple abbreviated versions were created and their psychometric properties were examined in children and adults with neurological disorders, including epilepsy.

In **chapter 4**, the reliability and validity of the Dutch version of the Anxiety, Depression And Mood Scale (ADAMS) was investigated. Since the psychometric properties of the ADAMS were already examined in a Dutch population of older people with ID (aged 50 years or older),[24] this study focused particularly on adults with ID aged between 18 and 50. The reliability and validity was examined among adults with ID from multiple centers, including a subsample of adults with epilepsy.

Part 2. Epilepsy and ID in relation to neuropsychiatry: what's to blame?

In the second part, the studies focus on neuropsychiatric comorbidities in adults with epilepsy and ID. **Chapter 5** provides an overview of the literature in this area, by means of systematic review study. In **chapter 6**, the frequency and severity of self-injurious,

aggressive/destructive, and stereotyped behavior in adults with both epilepsy and ID is described. Associations between challenging behavior and epilepsy and ID characteristics are explored. In **chapter 7**, mood and anxiety in adults with epilepsy and ID, and self-reported quality of life in a subsample of adults with epilepsy and mild ID is examined. It is investigated whether epilepsy and ID characteristics are related to depressive symptoms, anxiety, and social withdrawal. In addition, associations between epilepsy and quality of life are explored. **Chapter 8**, reports on psychogenic nonepileptic seizures (PNES) in adults with epilepsy and ID. Clinical characteristics of PNES as well as associations with epilepsy severity, ID domain discrepancy, and psychosocial variables are studied.

Finally, **chapter 9** provides a general discussion of the results of the studies. Implications for clinical practice and recommendations for future research are discussed as well.

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Part 1

Diagnostic processes: filling the gaps

2

Classification of ID and ID domain discrepancy in adults with epilepsy

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Abstract

Background: In the DSM-5, the diagnostic criteria of intellectual disability (ID) include three domains of adaptive deficits: the conceptual, social and practical. Substantial intra-individual differences between domains can be considered an ID domain discrepancy.

Method: We explored the associations between ID domains, discrepancies, and epilepsy in 189 adults (mean age = 47.9; SD = 15.6). Each DSM-5 ID domain was assessed separately, using subscales of the Vineland II for the social and practical domains, and psychological instruments, including intelligence tests, for the conceptual domain. A set of standardised criteria is proposed to identify an ID domain discrepancy.

Results: An ID domain discrepancy seemed to be present in about one-third of subjects and was particularly present in subjects with moderate ID (53.4%). Impairment in the social domain was most often the reason for the discrepancy. The presence of a discrepancy was significantly related to a focal (localised) epilepsy type (OR = 2.3, $p = .028$) and a mixed seizure type (OR = 1.4, $p = .009$). Epilepsy characteristics that are indicative of a more severe and refractory epilepsy, including various seizure types, a high seizure frequency, a combined epilepsy type (both focal and generalised epilepsy) and an early age at onset, were significantly related to more severe impairments in conceptual, social and practical adaptive behaviour (all p-values < .01).

Conclusion: With a substantial proportion of the subjects who had both ID and epilepsy with an ID discrepancy, professionals should be aware of this and take all domains of ID into account when studying or working with this vulnerable population.

Background

The diagnostic criteria of intellectual disability (ID) have been revised in the Diagnostic and Statistical Manual of Mental Disorders – Fifth edition (DSM-5).[1] One of the most prominent changes is the shift towards a tripartite model in which the severity of deficits, in terms of adaptive functioning, is to be addressed on three domains: conceptual, social and practical. The conceptual domain refers to skills in reading, writing, mathematics, executive functioning, memory and knowledge; the social domain includes interpersonal communication skills, empathy, social judgement, emotional regulation and the ability to make and retain friendships; the practical domain refers to personal care, organizing school, work and domestic tasks, and money management.[1]

The new criteria require professionals to attribute a severity indication of deficits in each domain of adaptive functioning, i.e. mild, moderate, severe or profound deficits. As a consequence, the introduction of the DSM-5 has or will have implications for the diagnostic process, as each domain should be comprehensively assessed both clinically and using standardised instruments.[1] In the past, results from intelligence tests did have a prominent role in diagnostics of ID according to DSM-IV;[2] these tests, however, were essentially related to only one of the three domains: the conceptual domain.[1,3] The focus of the ID diagnostic criteria has now shifted towards assessing adaptive functioning by using standardised measures, such as the Vineland Adaptive Behavior Scales,[4,5] the Adaptive Behavior Assessment System,[6,7] and the Scales of Independent Behavior-Revised.[8]

The potential advantage of assessing the three DSM-5 domains of adaptive functioning separately is that one obtains a more accurate representation of the functioning of the individual. The new classification reveals an opportunity to define a concept of ID domain discrepancy in which one domain is particularly more deficient than another. Some instruments that measure adaptive behaviour, such as the Vineland-II, allow for between-domain comparisons that indicate whether standard scores between domains are significantly different. A person could, for example, demonstrate conceptual skills particularly worse than the social skills. With no other studies that have yet addressed ID discrepancies, increasing knowledge with respect to the relation between the three domains is relevant for both clinical care and research in this vulnerable population.

Deficits in specific domains of adaptive functioning might be related to impairments of specific brain structures, impaired neuronal networks or to comorbidity. For example, persons with autism spectrum disorder have poorer socialisation skills compared to other domains,[9] and traumatic brain injury, often affecting the prefrontal regions, can result in persistent executive dysfunction.[10] Among people with ID,

epilepsy is a particularly common comorbidity; it can be severe and have a pervasive impact.[11-13] Epilepsy is conceptually defined as a brain disease characterised by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. Epileptic seizures imply the transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[14] An operational clinical definition of epilepsy is provided by Fisher et al.[15] People with chronic epilepsy are at risk of altered brain development and accelerated ageing, which can result in cognitive deficits or deterioration.[16,17] In addition, some epilepsies have been linked to impaired practical adaptive behaviour, such as daily living skills.[18,19] One might speculate that the long-term impact of epileptic seizures might result in impairment of specific aspects of adaptive functioning, depending on the brain area affected by the seizures.

In the present study, we focus on three domains of ID in a clinical sample of adults with chronic epilepsy. The primary aims were to introduce a method to identify a between-domain discrepancy, to describe the point prevalence in this specific sample and to explore the associations between a discrepancy and epilepsy characteristics. The secondary aim was to examine associations between epilepsy characteristics and level of ID of each domain of adaptive functioning.

Methods

Participants and procedure

This cross-sectional study was conducted within a tertiary epilepsy centre with both inpatient and outpatient care facilities of Kempenhaeghe. All individuals who met the following criteria were invited for the study:

- age ≥18 years,
- diagnosis of epilepsy according to the clinical definition by Fisher et al.,[15]
- previous diagnosis of ID or current adaptive functioning at level of ID as evaluated by the individual's health care psychologist.

A total of 240 individuals were invited for the study, of whom 189 provided consent for the study (inclusion rate: 78.8%). The consent was provided by legal guardians in case individuals did not have the capacity, by individuals themselves if they were capacitated, or by both the individual and their legal guardian if the individual was lacking capacity but also had a legal guardian. Individuals who participated were significantly younger (mean difference = 6.04 years, $p = .015$) than non-participants and were using psychotropic medication less frequently (14.0% versus 41.3%, respectively, $p < .001$). Participants did not differ from non-participants with respect to gender or

level of ID. This study was approved by the local ethical committee of Kempenhaeghe (No. 15.01). The subjects could withdraw from the study at any time.

Instruments and procedure

Information with regard to demographics and epilepsy was collected from the subject's medical records. This included information about age, sex, age at epilepsy onset, daily use of anti-epileptic drugs, epilepsy type and seizure type and frequency in the last year. The epilepsy type was classified according to the guidelines of the International League against Epilepsy[20] and for seizure types the classification system of Lüders et al.[21] was applied.

The assessment of classification level of ID was based on the three domains of adaptive deficits as described in DSM-5: conceptual, social and practical.[1] These domains were assessed separately. The selection of instruments was based on psychometric qualities, feasibility, international use and availability in Dutch language.

Social and practical domain

The social and practical domains were addressed by the Vineland Adaptive Behavior Scales, second edition, Expanded Interview Form version (Vineland-II;[5] Dutch translation by Dijkxhoorn and Verhaar[22]), a clinical instrument to assess adaptive behaviour. For the purpose of this study, only the Daily Living Skills (DLS) and Socialisation subscales were administered by means of a semi-structured interview with a professional caregiver who is familiar with the subject for at least one year. The scoring procedure was performed according to the manual, resulting in an age-corrected standard score for both subscales (M = 100 and SD = 15), representing the social and practical domains.

Conceptual domain

As the Vineland-II has no subscale directly in accordance with conceptual functioning, the conceptual domain was assessed by other instruments. As many instruments are not suitable for all levels of ID, this assessment was adjusted to the subject's expected level of functioning. The instrument of choice was discussed with the subject's health care psychologist prior to administration. As the intelligence quotient (IQ) seems to be largely representative of the conceptual domain, this was the first-choice measure. The (full scale) IQ was obtained either from the subject's medical records, if administered within the past two years, or by administering a 4-subtest short form (SF) of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV).[22] This WAIS-IV-SF is a SF validated among people with neurological disorders and impaired intellectual functioning.[24] In cases of lower expected conceptual functioning, the Picture Peabody

Vocabulary Test – Third edition (PPVT-III)[25] was used, which results in an estimation of the developmental age. The PPVT-III is a measure of receptive vocabulary and is considered a valid screening tool for global cognitive functioning.[26,27]

If neither the WAIS-IV-SF nor PPVT-III were suitable and no psychological reports on intellectual functioning were available, an expert opinion about the level of conceptual functioning was formulated based on DSM-5 criteria.[1] This expert opinion was provided by a qualified health care psychologist who treated the person for at least one year. This procedure was also applied in cases where the legal representative did not give consent for the assessment of conceptual measures (n = 3) or if subjects expressed signs of objection during the individual assessment, after which the assessment was aborted (n = 2).

Level of ID and ID domain discrepancy

The results on each domain were converted into a classification of mild, moderate, severe or profound deficits. Internationally applied cut-off points, described by DSM-IV,[2] the International Statistical Classification of Diseases – tenth edition (ICD-10)[28] and Vineland II[3], were retained, all using cut-off points of 70 – 50/55 for mild deficits, 50/55 – 35/40 for moderate deficits, 35/40 – 20/25 for severe deficits and below 20/25 for profound deficits. The lower values were applied and all classifications were validated by the subject's health care psychologist.

An ID profile was considered as discrepant when there was a substantial difference in level of adaptive functioning between two domains, indicating that one domain is considerably more or less deficient than the other(s). As different measures were used to assess the domains, multiple criteria could be applied to determine whether a discrepancy was present. An ID domain discrepancy was attributed if one of the following criteria was met:

- Social versus practical domain: a difference between the Socialization and DLS standard scores with significance level of .01, according to the Vineland II manual[3]
- Social or practical domain versus conceptual domain:
  - a difference of at least 15 points (= 1 SD) between the Short Form IQ of the WAIS-IV-SF and the Socialization or DLS standard score; or
  - if the conceptual domain was determined by the PPVT-III or expert opinion: a difference of at least one complete classification level between the conceptual domain and the social or practical domain.

Statistical analyses

Associations between epilepsy and ID domain discrepancy were explored using logistic regression analysis. The backwards stepwise method was applied to remove nonsignificant factors from the model, i.e., $p > .15$, based on Wald's test. The associations between epilepsy characteristics and domain or average level of ID and ID domain discrepancy were explored using IBM SPSS Statistics version 24. For associations between level of ID and epilepsy characteristics, Chi-square tests were performed for categorical data and nonparametric tests were conducted for continuous data (including Kruskal-Wallis and Mann-Whitney U) as the continuous data did not meet the assumption of normal distribution. Subjects with a severe or profound ID classification were combined into one subgroup in the analyses. Results were considered significant if $\alpha < .05$.

Table 2.1: Clinical characteristics of the study sample (N = 198)

Characteristics	**Values**
Age at onset of epilepsy (years)	Mdn = 2.0, IQR = 0–5.5, range 0–53
Infancy (< 1 yr)	32.8%
Childhood (1 - 12 yr)	54.0%
Adolesence (12 - 18 yr)	10.1%.
Adulthood (18+ yr)	3.2%
Epilepsy type	
Generalised	10.6%
Focal	41.3%
Both generalised and focal	44.4%
Unknown	3.7%
Number of seizure types (semiology)	Mdn = 3.0, IQR = 1–4, range 0–8
Seizure frequency (last year)	Mdn = 70.0, IQR = 11.5–153.0, range 0–1206
Seizure-free	12.7%
Yearly	12.2%
Monthly	19.6%
Weekly	43.9%
Daily	11.6%
Daily use of anti-epileptic drugs	Mdn = 3.0, IQR = 2.5–4.0, range 0–6
0	0.5%
1	7.9%
2	16.4%
3+	75.1%

Note. Mdn = median, IQR = interquartile range.

Results

Sample characteristics

A total of 189 subjects met our inclusion criteria. See Table 2.1 for a complete overview of clinical characteristics. The majority of subjects were inpatients (76.2%); the others lived in community settings. The mean age was 47.9 years (SD = 15.6; range 18.3-85.9 years) and 58.7% were male. The epilepsy originated in childhood in more than half of subjects (54.4%). Most subjects had focal epilepsy or a combination of focal and generalized epilepsy (41.3% and 44.4%, respectively), with a seizure frequency of at least once a week (55.5%). Nearly all subjects were using anti-epileptic drugs (99.5%) and 41.5% were prescribed psychotropic medication on a daily basis.

The average level of ID varied from mild to profound deficits; most subjects were classified as having moderate (30.7%) or severe (29.1%) deficits.

ID domain discrepancy

An ID domain discrepancy – a substantial difference in level of adaptive functioning between two domains of adaptive functioning – was present in 32.8% of subjects (see Table 2.2). An ID domain discrepancy was significantly more often present in subjects with moderate ID (53.4%) and significantly less often present in subjects with a profound level of ID (5.3%; χ^2 (3) = 24.7, p < .001). With respect to the three adaptive domains, it appeared that an ID domain discrepancy was most often characterised by a more impaired social or practical domain (in 59.7% and 38.7% of cases, respectively), and less often by a more impaired conceptual domain (16.2% of cases). Thus, the social adaptive skills were relatively often particularly poorer than the subject's practical and/or conceptual adaptive skills. Seven subjects had two out of three adaptive domains being particularly more impaired than the other.

Table 2.2: Level of ID and ID domain discrepancy.

Level of ID	Conceptual domain	Social domain	Practical domain	Overall level of ID	ID domain discrepancy present
Mild	17.5%	17.5%	21.2%	n = 38 (20.1%)	34.2%
Moderate	39.2%	24.9%	29.6%	n = 58 (30.7%)	53.4%
Severe	23.3%	36.0%	30.2%	n = 55 (29.1%)	29.1%
Profound	20.1%	21.7%	19.0%	n = 38 (20.1%)	5.3%
Total sample					32.8%

Note. ID = intellectual disability

Associations between ID domain discrepancy and epilepsy

The associations between epilepsy characteristics and ID domain discrepancy, taking the average level of ID into account, were explored using logistic regression. A stepwise backward regression procedure was applied to obtain a parsimonious model (see Table 2.3). Predictors were stepwise removed according to their odds ratio, starting with the lowest associations. The final model included the level of ID, number of seizure types, and epilepsy type, is significantly associated to the presence of an ID domain discrepancy (model: χ2 (4) = 32.1, p < .001). While adjusting for level of ID, a higher number of seizure types and a diagnosis of a focal epilepsy type significantly increased the likelihood of having an ID domain discrepancy (OR = 1.4, 95%- confidence interval (CI) = 1.1 – 1.7, p = .009; OR = 2.3, 95%-CI = 1.1 – 4.9, p = .028, respectively). In addition, both a mild or moderate level of ID increase the likelihood of having an ID domain discrepancy, with an odds ratio of 3.6 (95%-CI = 1.3 – 10.3, p = .014) and 8.0 (95% CI = 3.2 – 19.7, p < .001), respectively.

Table 2.3: Factors associated with ID domain discrepancy using stepwise backward logistic regression analysis.

Model parameters	Predictors	Odds ratio	95% CI
Adjusted model			
χ^2 (4) = 32.11***	Mild level of ID	3.64*	1.30–10.25
Nagelkerke R^2 = .226	Moderate level of ID	8.00***	3.22–19.70
	Number of seizure types	1.35**	1.08–1.68
	Focal epilepsy type	2.33*	1.10–4.94

Note. ID = intellectual disability; CI = confidence interval. * p < .05; ** p < 0.01; *** p < .001.

Associations between levels of adaptive deficits and epilepsy

Analyses of direct associations between epilepsy characteristics and the average level of ID revealed that a more severe level of ID was significantly associated with an earlier age at epilepsy onset and a higher number of seizure types and seizure frequency (all p values < .001, see Table 2.4). There was also a significant association between the level of ID and the epilepsy type. Subjects with a severe-profound level of ID had more often a combined generalised and focal epilepsy type and less often a focal epilepsy type only (χ^2 (4) = 13.5, p = .009, see Table 2.4). There was no association between the level of ID and daily use of antiepileptic drugs.

Post hoc Mann-Whitney U tests showed that significant differences were particularly present between subjects with a mild level of ID and subjects with a severe-

profound level of ID (all *p* values < .001) and between subjects with a moderate level of ID and severe-profound level of ID (all *p* values < .001). When comparing subjects with a mild level of ID and those with a moderate level of ID, only the age of onset was significantly different (median = 5.0 years versus 3.0 years, respectively, *p* = .007).

With regard to each of the three DSM-5 domains, conceptual, social and practical adaptive functioning, Kruskal-Wallis and Chi Square tests showed a similar pattern of significant associations compared to the average level of ID. For each domain, a more severe level of deficits was significantly related to an earlier age at epilepsy onset (all *p* values < .001), more often a combined epilepsy type (*p* values = .019 – .009), a higher number of seizure types (all *p* values < .001), and a higher seizure frequency (*p* values = .002 – < .001).

Table 2.4: Associations between epilepsy characteristics and average level of ID.

Epilepsy characteristics	**Overall level of ID**			**Statistic**
	Mild Mdn, [IQR]	**Moderate** Mdn, [IQR]	**Severe-profound** Mdn, [IQR]	
Age at onset of epilepsy	5.0 [2.8–13.0]	3.0 [0.8–6.0]	1.0 [0.0–3.5]	H (2) = 25.07***
Number of seizure types	2.0 [0.0–3.0]	2.0 [1.0–3.0]	4.0 [3.0–5.0]	H (2) = 42.04***
Seizure frequency	18.0 [2.0–56.0]	58.5 [4.3–127.3]	106.0 [35.0–272.0]	H (2) = 24.59***
Daily use of anti-epileptic drugs	3.0 [3.0–4.0]	3.0 [2.0–4.0]	3.0 [2.0–4.0]	H (2) = 1.20 (*p* = .549)
Epilepsy type				χ^2 (4) = 13.48**
Generalized only	4 (10.5%)	8 (15.1%)	8 (8.8%)	
Focal only	22 (57.9.2%)	27 (50.9%)	29 (31.9%)	
Both generalised and focal	12 (31.6%)	29 (31.9%)	54 (59.3%)	

Note. ID = intellectual disability, Mdn = Median, IQR = interquartile range. * *p* < .05; ** *p* < 0.01; ***; *p* < .001.

Discussion

In the present study, the associations between epilepsy characteristics and the revised DSM-5 classification of ID, in terms of three domains of adaptive functioning, were explored in a clinical sample of 189 adults with both epilepsy and ID. Each of the three domains of adaptive functioning (conceptual, social, practical) was addressed separately, as well as an overall measure of ID. We introduced a set of criteria for

identifying a discrepancy between domains in an ID profile, and investigated associations between epilepsy and ID discrepancies.

Nearly one-third of our sample demonstrated a discrepancy in their ID profile. Impairment in the social domain was most often the reason for the discrepancy, indicating that the social skills were more impaired than practical and/or conceptual adaptive behaviour. This ID profile might be associated with the high prevalence of autism and autistic-like features among people with ID and/or epilepsy,[29] which is characterised by deficiencies in social communication and social interactions.[1] In addition, social impairments may also relate to the lack of opportunity to develop such skills, due to the combination of having an ID as well as living in the more protective and less demanding environment of the residential setting when compared to living in the community. Although no other studies have yet been published regarding ID discrepancies with respect to the three domains of adaptive functioning as far as we are aware, this proportion seems clinically relevant. Addressing an ID domain discrepancy in daily clinical practice could, for example, have implications for the treatment strategies to meet both the strengths and needs of the individual.

An ID discrepancy was particularly present in those with a moderate level of ID (53%) and less often in individuals with a profound level of ID (5.3%). This might be related to the broader spectrum of self-care skills and (social) activities in which individuals with a moderate ID are regularly engaged, by which personal specific strengths and needs become more visible. In addition, a lower rate of ID discrepancies could be explained by a floor effect in those with a profound level of ID, as this is the lowest level. While controlling for the level of ID, the odds of having an ID discrepancy was significantly associated with a focal epilepsy type (i.e., a form of epilepsy that originates from an area on one side of the brain) and, regarding types of seizures, with a mixed seizure type. It is tentative to speculate that the reason for the increased ID discrepancy in patients with a focal form of epilepsy is explained by a focal lesion causing both the epilepsy and ID. As a mixed seizure type is more often observed in a (multi)focal form of epilepsy, this might also explain the increased ID discrepancy in patients with these types of seizures. In addition, a methodological confounding effect should be considered as well, as the probability of having focal seizures increases with a higher number of different seizure types. To further clarify the working mechanisms, future research should focus on associations between specific brain areas that are regularly affected by epilepsy, for example the temporal lobe, and adaptive functioning, using neuroimaging.

A secondary finding was that a refractory and more severe epilepsy, including a higher seizure frequency, mixed seizure types, and an earlier age at epilepsy onset, was significantly associated with a more severe overall ID. These characteristics were also related to a more severe impairment of each of the domains: conceptual, social

and practical adaptive behaviour. Also, having a form of both generalized and focal (localized) epilepsy was associated with a more severe overall ID. This subgroup might reflect a large number of patients with epileptic encephalopathy, which is often accompanied by developmental slowing or regression.[30] Although it is well known that the prevalence of epilepsy increases with the severity of ID,[11] the increase in epilepsy severity among people with severe ID is less well documented. Causal inferences cannot be made, as both severe epilepsy and ID can reflect a highly affected brain or brain networks, or have the same underlying cause, such as genetically determined syndromes.[31] Longitudinal research of epilepsy characteristics is needed to clarify the long-term impact on aspects of cognitive and adaptive functioning, while taking into account the aetiology of epilepsy.

The present study has some limitations. Although the subjects came from one tertiary care facility, which increases homogeneity and reliability of data sampling, the majority lived at a residential care facility. Therefore, our findings require validation in a more representative sample of persons with epilepsy and ID, preferably with a control group without epilepsy when studying ID domain discrepancies. In addition, only instruments available in the Dutch language could be used. The Adaptive Behavior Assessment System–Third Edition[7] and the Diagnostic Adaptive Behavior Scale, which is under development by the American Association on Intellectual and Developmental Disabilities (AAIDD), are promising instruments that match the ID domain structure of DSM-5. These have, however, not yet been adapted to the Dutch language; our data might, therefore, have a lower content validity.

This exploratory study is, to our knowledge, the first to specifically focus on each domain of ID and to derive possible ID domain discrepancy, which might have great implications for clinical practice and research. With nearly one-third of individuals with epilepsy having an ID domain discrepancy emphasizes the relevance of this concept and the importance of assessing each domain of adaptive functioning. In order to minimize the risk of overestimating or underestimating an individual, it is important for professionals to take into account the full spectrum of ID and to be aware of the possibility of an ID domain discrepancy. Also, regular follow-up of both epilepsy and ID is recommended, as treatment and services should take into account both epilepsy and ID in personal plans and evaluations to improve the social care and health of this population.[11]

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3

Accuracy of WISC-III and WAIS-IV short forms in people with neurological disorders

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J.S. van Ool, P.P.M. Hurks, F.M. Snoeijen-Schouwenaars, I.Y. Tan, H.J. Schelhaas, A.P. Aldenkamp, S. Klinkenberg, J.G.M. Hendriksen (2018). Accuracy of WISC-III and WAIS-IV short forms in patients with neurological disorders. *Developmental Neurorehabilitation, 21,* 101-107.

Abstract

Background: The assessment of intellectual abilities is intensive, time-consuming, and might be considered burdensome for patients.

Methods: We examined psychometric qualities of short forms (SFs) of the Wechsler Intelligence Scales for Children (WISC-third edition) and for adults (WAIS-fourth edition), in children (n = 986; mean age = 10.9) and adults (n = 324; mean age = 40.9) with neurological disorders. SF estimates were compared with Full Scale IQ (FSIQ), obtained by a complete administration, for the entire sample and for the subgroups FSIQ < 80 and FSIQ ≥ 80.

Results: The FSIQ was correctly identified within ± 7 points in 86% of children and 87% of adults. There were, however, some differences regarding the optimal SF subtest combination between subgroups.

Conclusion: Although clinical inferences should not be made, SFs may be useful in research settings to obtain a global estimate of intelligence, and in clinical settings to screen periodically for possible intellectual deterioration.

Introduction

The Wechsler intelligence scales are widely used for assessing the intellectual abilities of children and adults, and are often incorporated as standard components in diagnostic batteries for neuropsychological evaluations.[1] The most recent versions available in the Dutch language are the Wechsler Intelligence Scale for Children-Third Edition, published in 2002 (WISC-III)[2,3], and the Wechsler Adult Intelligence Scale-Fourth Edition, published in 2012 (WAIS-IV)[4,5]. The assessment of intellectual abilities is believed to be fundamental for, for example, the diagnosis of intellectual disability (ID), along with a measure of adaptive functioning,[6] or the evaluation of cognitive abilities associated with neurological disorders. Periodic re-evaluation of these abilities is recommended,[7] which is especially relevant for individuals with co-morbid neurological disorders, such as epilepsy, who are at risk of possible deterioration.[8]

Each Wechsler intelligence scale consists of multiple subtests that are used to obtain the summary score full scale IQ (FSIQ) and specific index scores. For instance, the Dutch WISC-III indices include Verbal Comprehension, Perceptual Organization, and Processing Speed, whereas the original WISC-III has an additional index labeled Freedom from Distractibility. The WAIS-IV indices include Verbal Comprehension, Perceptual Reasoning, Processing Speed, and Working Memory. The FSIQ as well as each index score follow a normal distribution with a mean of 100 and standard deviation of 15 IQ points. According to the Wechsler classification system, a FSIQ in the range of 70–79 is labeled as borderline and a FSIQ below 69 as extremely low.[9]

Administration times for the WISC-III and WAIS-IV are approximately 60 minutes and 60–90 minutes, respectively.[10,11] Research on the administration time of the WAIS-III in a clinical sample found an increase of up to 136 minutes, with a mean of 91 minutes.[12] Also, although the discontinue rule applies earlier in individuals who perform more poorly (e.g. individuals with ID), the overall administration times for WISC-III and/or WAIS-IV subtests are not reduced as these individuals often take more time to respond to items and/or need more time in between subtest administrations.[13] In people with ID and/or neurological disorders, the intensive and timeconsuming assessment might lead to frustration or fatigue, or might be affected by seizure activity and medication side-effects. Consequently, the validity and reliability of the test outcome might be jeopardized. Briefer methods for estimating global intelligence might, therefore, be desirable, in particular when reassessing patients for screening or rehabilitation purposes, in research settings.[14,15]

To meet the demand for a shortened, but reliable and valid measure of intelligence, the Wechsler Abbreviated Scale of Intelligence (WASI) was developed for individuals aged 6;0–90;11 and later adjusted (WASI-II).[15] The WASI-II consists of four subtests that are similar, although not identical, to their WISC-IV and WAIS-IV counterparts,

which measure both verbal and non-verbal abilities. The WASI-II provides accurate and reliable estimates of general intellectual abilities, while reducing administration time to 30 minutes. The WASI-II is, however, a separate instrument, only available in certain languages: English, Norwegian, and Lithuanian.[16] Hence, various shortened versions – hereafter referred to as short forms – have been created, mostly based on a specific combination of subtests of Wechsler intelligence scales that are subsequently converted into an estimation of the FSIQ.

Many studies have been conducted to evaluate the accuracy of such short forms and have reported promising results.[17-19] Several studies have, however, indicated possible differences in appropriateness of short forms across populations,[20-22] probably due to population-specific cognitive profiles. Short forms, therefore, need to be validated in specific populations. Furthermore, research on short forms among the population of children and adults with neurological disorders and/or ID has been scarce. As ID and cognitive deterioration are relatively common among people with e.g. epilepsy,[23] gaining insights into the accuracy of short forms in this population would be very useful in order to obtain a valid and reliable screening tool to estimate intelligence.

Van Duijvenbode et al. examined a WASI-based short form,[24] consisting of the four WASI subtests of the WAIS-III, in a sample of adults with mild to borderline ID (n = 117) and concluded that this short form is sufficiently accurate in estimating the FSIQ. Axelrod et al. compared the WASI and the WASI-based short form of the WAIS-III in a sample with neurological disorders (n = 72) and found that the WASI-based short form outperformed the WASI.[25] Hrabok et al. investigated the accuracy of multiple short forms, varying from two to seven subtests, extracted from the more recent WISC-IV (which has not been adapted to Dutch language) in an epilepsy sample (n = 104).[26] There were some differences in short form accuracy between children with FSIQ ≤ 80 and FSIQ > 80, with higher classification rates obtained for subjects with FSIQ ≤ 80 than with FSIQ > 80. This pattern requires validation in an extensive sample of children and should also be investigated in adults, as results are rarely compared in subsamples divided by IQ performance. Also, there is a paucity of index-based short forms which are known to have greater construct validity and provide more clinically relevant information.[27]

The aims of the present study were (1) to investigate the psychometric qualities of the Dutch version of the WISC-III and WAIS-IV short forms in patients with a neurological disorder and (2) to determine which specific short form had the best psychometric qualities for the entire sample as well as for specific subgroups based on FSIQ performance, e.g. FSIQ < 80 (extremely low to borderline[9]) and FSIQ ≥ 80.

Methods

Subjects

The subjects were patients assessed in Kempenhaeghe, a tertiary referral center for epilepsy and other neurological disorders in The Netherlands. We used archival data of clinical referrals to the Department of Behavioral Sciences of Kempenhaeghe to whom the core subtests of the Dutch version of the WISC-III or WAIS-IV had been administered. Data were available for 986 children, collected between May 2009 and December 2014, and for 324 adults, collected between January 2013 and December 2014. The subjects included heterogeneous samples of patients with a variety of epilepsy classifications and congenital and acquired neurological disorders, of which neurofibromatosis, traumatic brain injury, prematurity, and chromosomal abnormalities were most common.

The mean age of subjects who completed the WISC-III was 10.9 years (SD = 2.8, range 6–16) and comprised 57.5% males. Mean FSIQ scores were 89.1 (SD = 17.1, range 45–137). The subjects were divided into two FSIQ-categories, resulting in the following distribution: extremely low to borderline FSIQ (FSIQ < 80, n = 274) and average to high FSIQ (FSIQ ≥ 80, n = 712). The mean age of subjects who completed the core subtests of the WAIS-IV was 40.9 (SD = 16.3, range 16–78) and comprised 49.4% males. They had a mean FSIQ of 83.0 (SD = 16.1, range 46–129). Again, the subjects were divided into three FSIQ-categories: 145 subjects had an extremely low to borderline FSIQ (FSIQ < 80), and 179 had average to high FSIQ (FSIQ ≥ 80).

Procedure

Subjects completed the age-appropriate Wechsler Intelligence Scale as part of a more extensive neuropsychological evaluation of regular medical care. The scales were administered and scored by qualified diagnostic staff members of the Department of Behavioral Sciences according to the standardized procedures outlined in the manuals,[8,9] resulting in age-corrected FSIQ and scaled subtest scores. Prior to this study, the data from patient files were de-identified in order to ascertain anonymous data analyses, and the use for research purposes was approved by the local ethical committee of Kempenhaeghe.

All short form estimates were derived by applying the formulae described by Tellegen and Briggs,[28] using tables B-10 and B-11 from Sattler and Ryan.[29] This method is based on a linear scaling method to yield deviation quotients that maintain the FSIQ's distribution (i.e., M = 100, SD = 15), and has been used in recent studies on short

form accuracy.[26,30] The lower bound of the original WISC-III and WAIS-IV, i.e. FSIQ = 45, was applied if a short form yielded an estimate below 45.

Table 3.1: Overview of short forms of the WISC-III and WAIS-IV.

Name	Subtest included	Formula[a]	Specification
WISC-III			
SF1_PcInBdVc	Picture Completion, Information, Block Design, Vocabulary	$\Sigma_{subtests} * 1.7 + 32$	[31]
SF2_PcSiBdAm	Picture Completion, Similarities, Block Design, Arithmetic	$\Sigma_{subtests} * 1.7 + 32$	[18]
SF3_PcSiBdVc	Picture Completion, Similarities, Block Design, Vocabulary	$\Sigma_{subtests} * 1.6 + 36$	[32]
SF4_PcInBdVcCo	Picture Completion, Information, Block Design, Vocabulary, Coding	$\Sigma_{subtests} * 1.5 + 25$	[33-35]
SF5_BdVcCo	Block Design, Vocabulary, Coding	$\Sigma_{subtests} * 2.2 + 34$	One subtest per WISC-III-NL index[b]
WAIS-IV			
SF6_BdMrVcSi	Block Design, Matrix Reasoning, Vocabulary, Similarities	$\Sigma_{subtests} * 1.6 + 36$	Based on WASI-II[15]
SF7_MrSsVcSi	Matrix Reasoning, Symbol Search, Vocabulary, Similarities	$\Sigma_{subtests} * 1.7 + 32$	[26,36]
SF8_MrSsVcCo	Matrix Reasoning, Symbol Search, Vocabulary, Coding	$\Sigma_{subtests} * 1.7 + 32$	[26,36]
SF9_MrSsVcAm	Matrix Reasoning, Symbol Search, Vocabulary, Arithmetic	$\Sigma_{subtests} * 1.7 + 32$	One subtest per WAIS-IV index[c]
SF10_VpSsVcAm	Visual Puzzles, Symbol Search, Vocabulary, Arithmetic	$\Sigma_{subtests} * 1.7 + 32$	One subtest per WAIS-IV index[d]
SF11_BdVcCo	Block Design, Vocabulary, Coding	$\Sigma_{subtests} * 1.7 + 32$	Combination similar to SF5

Note. SF = Short form version; $\Sigma_{subtests}$ = sum of subtest scaled scores.
[a]The formulae used to derive short form IQ estimates were based on a linear equating method described by Tellegen and Briggs.[28]
[b]Selection of subtests was based on highest correlation with the corresponding indices and the FSIQ.
[c]Selection was based on highest correlation with the FSIQ.
[d]Selection was based on highest correlation with the corresponding indices.

Selection of short forms

For both the WISC-III and WAIS-IV, short form versions were created consisting of a unique combination of subtests. See Table 3.1 for an overview of the short forms, in which abbreviations are explained. As multiple studies have shown that the accuracy of Wechsler short forms decreases when fewer subtests are included,[19,26] two-subtest

combinations were not considered in this study. Taking into account both accuracy and administration time, three- to five-subtest combinations were used. The subtest combinations were a priori selected, primarily based on psychometric results from earlier studies on clinical samples and the WASI-II. This resulted in Short Form 1 (SF1) to SF4 with regard to the WISC-III[18,31-35] and in SF6 – SF8 for the WAIS-IV.[15,26,36]

For SF5, SF9 and SF10, the selection of subtests was index-based. As the short forms described above do not perfectly match the index structure of the Dutch WISC-III and WAIS-IV, i.e., one subtest per index, short forms were added by selecting a subtest for each index based on the highest correlation between the subtest and the FSIQ (corrected $r = 0.50–0.69$) or its index (corrected $r = 0.55–0.79$). This resulted in SF5, SF9 and SF10. In this way, each subtest itself would still provide information about one's abilities on the corresponding index, which increases the clinical relevance of the short forms by providing more detailed diagnostic information and increases the construct validity.[27,30] In order to compare short form accuracy between the WISC-III and WAIS-IV, a WAIS-IV short form (SF11) was added that included the same subtests as SF5.

Analyses

Psychometric properties of the short forms were evaluated separately for the entire WISC-III and WAIS-IV samples in the study, and were repeated, per Wechsler scale, for the subgroups with a FSIQ < 80 and FSIQ ≥ 80. The results were interpreted according to the minimal criteria set by Donders and Axelrod:[37] (1) a reliability coefficient of the short form ≥ 0.90 (calculated using the methods described by Sattler and Ryan[29]); (2) a correlation coefficient between short form and FSIQ ≥ 0.82, corrected for redundancy;[38] and (3) a proportion of short form estimates that fell within the 90% confidence interval of the FSIQ (i.e., within ± 7 IQ points) ≥ 0.81. Additionally, the agreement between short form estimates and FSIQ was calculated using intra-class correlations (ICC) and the differences inmean scores were compared by means of paired t-tests. All analyses were performed using IBM SPSS Statistics 21.

Results

The means, standard deviations and ranges of the FSIQ and the estimated short form IQ scores are presented in Table 3.2. The IQ scores of all separate IQ categories (e.g., < 80 and ≥ 80) were normally distributed (WISC-IIII: Skewness = –0.75 – 0.65; Kurtosis = –0.85 – 0.04; WAIS-IV: Skewness = –0.65 – 0.52; Kurtosis = –0.88 – 0.09). The psychometric properties of each short form are summarized in Table 3.2 for all subjects and in Table 3.3 for the subgroups.

Table 3.2: Descriptive statistics and results of the WISC-III and WAIS-IV short forms for all subjects.

				All subjects (N = 986)				
WISC-III	**M**	**SD**	**Range**	**r_{sf}**	**r´**	**p (±7)**	**ICC**	**95%-CI**	**$M_{difference}$**
FSIQ	89.13	17.10	45-137						
SF1_PcInBdVc	**90.23**	**18.09**	**45-139**	**0.91**	**0.86**	**0.81**	**0.94**	**0.92-0.96**	**1.11*** **
SF2_PcSiBdAm	90.23	17.97	45-136	0.92	0.86	0.80	0.93	0.85-0.96	1.80***
SF3_PcSiBdVc	92.22	16.93	45-137	0.91	0.86	0.77	0.96	0.96-0.97	3.09***
SF4_PcInBdVcCo	**88.82**	**18.90**	**45-135**	**0.92**	**0.88**	**0.86**	**0.92**	**0.92-0.93**	**0.31**
SF5_BdVcCo	89.37	17.75	45-135	0.94	0.87	0.74	0.95	0.94-0.95	0.21
WAIS-IV									
	M	**SD**	**Range**	**r_{sf}**	**r´**	**p (±7)**	**ICC**	**95%-CI**	**$M_{difference}$**
FSIQ	83.04	16.21	45-129						
SF6_BdMrVcSi	**83.86**	**15.29**	**47-122**	**0.94**	**0.88**	**0.80**	**0.80**	**0.73-0.86**	**0.81***
SF7_MrSsVcSi	**84.64**	**17.39**	**45-127**	**0.93**	**0.87**	**0.74**	**0.74**	**0.45-0.86**	**1.60*** **
SF8_MrSsVcCo	82.86	18.24	45-126	0.93	0.85	0.74	0.74	0.16-0.89	0.18
SF9_MrSsVcAm	**83.66**	**16.97**	**45-129**	**0.93**	**0.88**	**0.77**	**0.77**	**0.69-0.83**	**0.62***
SF10_VpSsVcAm	**82.62**	**16.12**	**47-132**	**0.93**	**088**	**0.81**	**0.81**	**0.74-0.86**	**-0.42**
SF11_BdVcCo	83.61	16.13	47-122	0.92	0.86	0.80	0.80	0.73-0.86	0.57

Note. FSIQ = Full Scale Intelligence Quotient; SF = Short form version; r_{sf} = reliability of short form; *r´* = correlation corrected for redundancy; ICC = intra-class correlation; CI = confidence interval; p(±7) = proportion of estimated scores that fell within ± 7 points of the FSIQ; $M_{difference}$ = mean difference from FSIQ; Am = Arithmetic; Bd = Block Design; Co = Coding; In = Information; Mr = Matrix Reasoning; Pc = Picture Completion; Si = Similarities; Ss = Symbol Search; Vc = Vocabulary; Vp = Visual Puzzles. Short forms that meet the minimal criteria set by Donders & Axelrod[37] are displayed in bold. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

WISC-III

Entire sample

All short forms met the reliability criterion of $r_{sf} \geq 0.90$ with coefficients varying between 0.91 and 0.94 (see Table 3.2). The corrected correlations between the short form and FSIQ met the criterion of $r' \geq 0.82$ for each short form ($r' = 0.86 – 0.88$). Only SF1 (Picture Completion, Information, Block Design and Vocabulary) and SF4 (Picture Completion, Information, Block Design, Vocabulary and Coding) met the criterion of at least 81% of the short form estimates falling within the 90% confidence interval of the FSIQ. SF1 met this criterion with 81% and SF4 met this criterion with 86%.

Table 3.3: Descriptive statistics and results of the WISC-III short forms for the subgroups FSIQ < 80 and FSIQ ≥ 80.

				FSIQ < 80 (n = 274)				
	M	**SD**	**Range**	***r´***	**p(±7)**	**ICC**	**95%-CI**	**$M_{difference}$**
FSIQ	67.86	8.39	45-79					
SF1_PcInBdVc	69.40	11.22	45-92	0.78	0.84	0.86	0.82–0.88	0.65*
SF2_PcSiBdAm	69.33	11.28	45-95	0.77	0.84	0.84	0.79-0.87	1.47***
SF3_PcSiBdVc	72.09	10.99	45-89	0.77	0.73	0.78	0.42-0.89	4.23***
SF4_PcInBdVcCo	65.21	11.29	45-88	0.81	0.82	0.85	0.71-0.91	-2.65***
SF5_BdVcCo	67.78	11.29	45-91	0.76	0.78	0.80	0.76-0.84	-0.08
				FSIQ ≥ 80 (n = 712)				
	M	**SD**	**Range**	***r´***	**p(±7)**	**ICC**	**95%-CI**	**$M_{difference}$**
FSIQ	97.31	11.70	80-137					
SF1_PcInBdVc	98.59	12.38	71-139	0.80	0.81	0.89	0.87-0.91	1.28***
SF2_PcSiBdAm	99.24	12.24	71-136	0.80	0.79	0.87	0.83-0.90	1.93***
SF3_PcSiBdVc	99.96	11.60	71-137	0.80	0.78	0.86	0.77-0.91	2.65***
SF4_PcInBdVcCo	97.91	12.24	72-135	0.84	0.88	0.93	0.91-0.94	0.60**
SF5_BdVcCo	97.68	11.79	65-135	0.76	0.73	0.82	0.80-0.85	0.37

Note. FSIQ = Full Scale Intelligence Quotient; SF = Short form version; *r´* = correlation corrected for redundancy; ICC = intra-class correlation; CI = confidence interval; p(±7) = proportion of estimated scores that fell within ± 7 points of the FSIQ; $M_{difference}$ = mean difference from FSIQ; Am = Arithmetic; Bd = Block Design; Co = Coding; In = Information; Mr = Matrix Reasoning; Pc = Picture Completion; Si = Similarities; Ss = Symbol Search; Vc = Vocabulary; Vp = Visual Puzzles. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The ICC coefficients indicated very strong agreement between the FSIQ and each short form (ICC ≥ 0.92; $p < 0.001$). Paired t-tests suggested significant overestimations of the FSIQ by SF1, SF2 and SF3 (SF1: $M_{difference} = 1.11$, t (985) = 6.37, $p < 0.001$; SF2: $M_{difference} = 1.80$, t (985) = 9.90, $p < 0.001$; SF3: $M_{difference} = 3.09$, t (985) = 17.53, $p < 0.001$).

SF4 is the only short form that met the minimal criteria set and whose estimates did not significantly differ from the FSIQ.

Sample FSIQ < 80 and FSIQ ≥ 80

Psychometric properties for the subgroups FSIQ < 80 and FSIQ ≥ 80 are presented in Table 3.3. The second criterion is only met by SF4, subgroup FSIQ ≥ 80 (r' = 0.84). The corrected correlations for SF4, subgroup FSIQ < 80, and SF1, SF2 and SF3, subgroup FSIQ ≥ 80, fell just short (r' = 0.80 – 0.81), whereas the correlation coefficients for all other groups were insufficient (r′ = 0.76 – 0.78). For both SF1 and SF4, the third criterion was met in each subgroup (percentage of short form estimates that fell within ± 7 IQ points = 81 – 88%), leaving SF4 being the only short form that met the minimal criteria set in subgroup FSIQ ≥ 80 and having values that were closest toward meeting the minimal criteria in subgroup FSIQ < 80.

ICC coefficients indicated strong agreement between short form estimates and the FSIQ for all subgroups (ICC = 0.78– 0.93). Except for SF5, paired t-test revealed a significant overestimation or underestimation of the FSIQ for all subgroups and short forms ($M_{difference}$ = –2.65–2.65; *p* values = 0.044 – < 0.001).

WAIS-IV

Entire sample

All short forms met the reliability criterion of $r_{sf} \geq 0.90$ with coefficients varying between 0.92 and 0.94 (see Table 3.2). The corrected correlations between the short form and FSIQ met the criterion of $r' \geq 0.82$ for each short form (r' = 0.85 – 0.88). SF6, SF7, SF9, and SF10 also met the criterion of at least 81% of the short form estimates falling within the 90% confidence interval of the FSIQ (percentage of estimated scores within ± 7 IQ points). The percentages varied between 82% and 87%.

The ICC coefficient indicated a very strong agreement between the FSIQ and SF6, SF10 and SF11 (ICC = 0.80 – 0.81; $p < 0.001$) and a strong agreement between FSIQ and SF7, SF8 and SF9 (ICC = 0.74 – 0.77; $p < 0.001$). Paired t-test suggested significant overestimations of the FSIQ by SF6, SF7, and SF9 (SF6: $M_{difference}$ = 0.81, t (323) = 2.50, p = 0.013; SF7: $M_{difference}$ = 1.60, t (323) = 5.09, $p < 0.001$; SF9: $M_{difference}$ = 0.62, t (323) = 2.30, p = 0.022). SF10 (Visual Puzzles, Symbol Search, Vocabulary, and Arithmetic) is the only short form that met the minimal criteria set and whose estimates did not significantly differ from the FSIQ.

Table 3.4: Descriptive statistics and results of the WAIS-IV short forms for the subgroups FSIQ < 80 and FSIQ ≥ 80.

				FSIQ < 80 (n = 145)				
	M	**SD**	**Range**	***r′***	**p(±7)**	**ICC**	**95%-CI**	**$M_{difference}$**
FSIQ	68.41	8.11	46-79					
SF6_BdMrVcSi	70.79	8.98	47-89	0.77	0.83	0.65	-0.03-0.86	2.38***
SF7_MrSsVcSi	69.65	10.64	45-88	0.77	0.83	0.82	0.61-0.90	1.24**
SF8_MrSsVcCo	67.05	12.11	45-92	0.78	0.75	0.84	0.78-0.88	-1.35**
SF9_MrSsVcAm	69.09	10.12	45-90	0.80	0.88	0.85	0.69-0.91	0.68
SF10_VpSsVcAm	68.85	9.16	47-90	0.78	0.90	0.83	0.69-0.90	0.44
SF11_BdVcCo	69.79	9.78	47-100	0.73	0.84	0.80	0.73-0.86	1.37**
				FSIQ ≥ 80 (n = 179)				
	M	**SD**	**Range**	***r′***	**p(±7)**	**ICC**	**95%-CI**	**$M_{difference}$**
FSIQ	94.90	10.37	80-129					
SF6_BdMrVcSi	94.44	10.35	66-129	0.77	0.78	0.78	058-0.87	-0.46
SF7_MrSsVcSi	96.79	11.21	73-127	0.77	0.78	0.83	0.76-0.88	1.89***
SF8_MrSsVcCo	95.67	10.78	69-126	0.77	0.72	0.80	0.74-0.85	0.77
SF9_MrSsVcAm	95.46	11.26	69-129	0.82	0.87	0.90	0.86-0.92	0.56
SF10_VpSsVcAm	93.78	11.14	69-132	0.82	0.87	0.89	0.85-0.92	-1.12**
SF11_BdVcCo	94.81	10.60	69-122	0.75	0.76	0.83	0.78-0.87	-0.09

Note. FSIQ = Full Scale Intelligence Quotient; SF = Short form version; r′ = correlation corrected for redundancy; ICC = intra-class correlation; CI = confidence interval; p(±7) = proportion of estimated scores that fell within ± 7 points of the FSIQ; $M_{difference}$ = mean difference from FSIQ; Am = Arithmetic; Bd = Block Design; Co = Coding; In = Information; Mr = Matrix Reasoning; Pc = Picture Completion; Si = Similarities; Ss = Symbol Search; Vc = Vocabulary; Vp = Visual Puzzles. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Samples FSIQ < 80 and FSIQ ≥ 80

With regard to the subgroups FSIQ < 80 and FSIQ ≥ 80, the second criterion is only met by SF9 and SF10, subgroup FSIQ ≥ 80 (r' = 0.82; see Table 3.4). The corrected correlation in subgroup FSIQ < 80 fell just short for SF9 (r' = 0.80) and was insufficient for all other groups (r' = 0.73 – 0.78). The third criterion was met for SF9 and SF10, for both subgroups (percentage of short form estimates that fell within ± 7 IQ points = 87 – 90%). For SF6, SF7, and SF11, the cut-off was only met for subgroup FSIQ < 80 (83 – 84%) and not for subgroup FSIQ ≥ 80. SF9 and SF10 both met the minimal criteria set in subgroup FSIQ ≥ 80 and SF9 had values that were closest toward meeting the minimal criteria in subgroup FSIQ < 80.

ICC coefficients indicated a very strong agreement between FSIQ and SF7, SF8, SF9, SF10 and SF11 (ICC = 0.82 – 0.90, both subgroups). With respect to SF6, the ICC was moderate for subgroup FSIQ < 80 (ICC = 0.65; $p < 0.001$) and strong for subgroup FSIQ

≥ 80 (ICC = 0.78; $p < 0.001$). For subgroup FSIQ < 80, paired t-tests revealed significant overestimation or underestimations of the FSIQ by SF6, SF7, SF8, and SF11 ($M_{difference}$ = −1.35–2.38; *p*s = 0.009–< 0.001). For subgroup FSIQ ≥ 80, paired t-tests revealed significant differences between the FSIQ and SF7 and SF10 (SF7: $M_{difference} = 1.89$, t (178) = 4.24, $p < 0.001$; SF10: $M_{difference} = -1.12$, t (178) = −2.95, $p = 0.004$).

Comparison of short forms across samples

Only two short forms included an identical subtest combination (BdVcCo) for both the WISC-III and WAIS-IV, i.e. SF5 and SF11. Although statistically driven comparisons could not be made, it appeared that the short forms' results followed a slightly similar pattern overall (see Tables 3.3 - 3.5). Both short forms did not meet the third criterion of at least 81% of the short form estimates falling within the 90% confidence interval of the FSIQ for the entire sample. Regarding the subgroups, ICC and corrected correlation coefficients were similar for both subgroups. Although paired t-tests yielded no significant difference between the short forms and the FSIQ in subgroup FSIQ ≥ 80, SF11 significantly overestimated the FSIQ in subgroup FSIQ < 80.

Discussion

In the present study, we examined the psychometric qualities of multiple WISC-III and WAIS-IV short forms in heterogeneous clinical samples of children and adults with neurological disorders, with a specific focus on subsamples with FSIQ < 80 (extremely low to borderline) and FSIQ ≥ 80.

Regarding the WISC-III, only two out of five short forms met the minimal criteria set:[37] SF1 and SF4. With respect to the full sample, SF4 was superior to SF1 as SF1 significantly overestimated the FSIQ with approximately 2 IQ points. Based on results per subgroup, SF4 is still recommended as this short form met the minimal criteria set for subgroup FSIQ < 80 and is very close to meeting the criteria for subgroup FSIQ ≥ 80 (r' = 0.81, instead of ≥ 0.82). As described by Evers, Sijtsma, Lucassen and Meijer,[39] a reliability coefficient of ≥ 0.70 of a test is considered sufficient when less important decisions are to be made, for example in research settings. We only encourage the use of short forms in such "less important" situations.

When comparing our results to Hrabok et al.,[26] who have used a similar methodology with the WISC-IV in a sample of children with epilepsy, it appears that mean differences between short form estimates and the FSIQ are in general smaller in our sample and subgroups. Also, the classification accuracy of four-subtest short forms across subgroups appears higher in our subsamples (percentage ± 7 points: 73 – 86% versus percentage ± 5 points: 33 – 71%). Regarding the WAIS-IV, four out of five short forms met the minimal criteria set: SF6, SF7, SF9, and SF10. With respect to the full

sample, SF10 seems superior to all others, as the short form estimates of the other short forms significantly differed from the FSIQ. The differences for SF6 and SF9, however, were rather small (0.8 and 0.6 IQ points, respectively). When taking a closer look to the psychometric qualities of these short forms in each subgroup, some differences are noted. Both SF9 and SF10 outperformed SF6 and SF7 in the subgroup FSIQ < 80, and are thus recommended for adults who are expected to have poor intellectual abilities. Although both SF9 and SF10 met the minimal criteria in the subgroup FSIQ ≥ 80, SF10 significantly underestimated the FSIQ with approximately 1 IQ point. SF9 is therefore recommended for adults with average intellectual abilities.

When comparing our results to Girard et al.,[30] who have created two-subtest WAIS-IV short forms based on the same methodology in a sample of clinical referrals, it appears that most of the psychometric properties in our sample are higher. The corrected correlations are slightly higher in our sample (r' = 0.85 – 0.88 versus 0.76 – 0.86) as well ass the classification accuracy (percentage ± 7 points: 72 – 87% versus percentage ± 10 points: 66 – 84%), whereas ICC coefficients are generally slightly higher in the sample of Girard et al. (ICC = 0.73 – 0.87 versus 0.74 – 0.81).

The differences in psychometric qualities across subgroups are especially relevant when re-evaluating a patient of whom previous results are already known, as it can guide the choice for most optimal short form in individual cases. Such differences might be due to variation in reliability coefficients between subtests[10,40] or to an inconsistent subtest profile within subjects. An inconsistent subtest profile is characterized by a significantly better or poorer performance on one or several subtests relative to the other subtests, possibly indicative of strengths and weaknesses in the individual. In our study population, there are several factors known to affect cognitive aspects, such as type of neurological condition, epilepsy characteristics (e.g., seizure type and seizure frequency), use of antiepileptic drugs and co-morbid deficits.[41-43] One might speculate that these factors result in a different subtest profile in individuals with both a neurological condition and ID, compared to subjects without ID, which might explain why some subtests are more representative of the FSIQ than others.

When comparing results from post-hoc paired t-tests for the subgroups FSIQ < 80 and FSIQ ≥ 80, with Bonferroni correction applied, it appeared that with regard to the WISCIII, only subjects with FSIQ < 80 performed significantly lower on Block Design and higher on Similarities ($M_{difference}$ = −0.6 and 1.4, respectively, $p < 0.001$) and only subjects with FSIQ ≥ 80 performed significantly higher on Information, Vocabulary, and Similarities ($M_{difference}$ = 0.2 – 1.2, p = 0.004 –< 0.001). Regarding the WAIS-IV, subjects with FSIQ < 80 appeared to perform significantly lower on Symbol Search and Coding ($M_{difference}$ = −1.1 and −0.8, respectively, $p < 0.001$) and higher on Vocabulary ($M_{difference}$ = 0.9, $p < 0.001$) and subjects with FSIQ ≥ 80 performed significantly higher on Matrix

Reasoning and Similarities ($M_{difference}$ = 0.9 and 0.6, $p < 0.001$) and significantly lower on Symbol Search ($M_{difference}$ = –1.1, $p < 0.001$).

An interesting finding of this study is that the index-based WAIS-IV short forms (SF9, and SF10) yielded stronger psychometric qualities than the short forms based on previous literature (SF6–SF8, including the WASI-based short form). In SF9 and SF10, the four-index structure has been maintained, providing more clinically relevant information and increasing the construct validity of the short form.[27,30] Against our hypothesis, the WASI-based short form overestimated the FSIQ in subgroups FSIQ < 80 with 2.4 IQ points. The overestimation by a WASI-based short form compared to FSIQ was also found in previous studies conducted in a clinical sample of adults with neurological disorders[25] and a sample with mild to borderline ID,[24] indicating that these subtests might overshadow a poorer performance on other cognitive aspects in these populations.

Limitations

Our study is limited by several factors. The subjects comprised convenience samples of children and adults with heterogeneous neurological conditions. As the overall mean FSIQ was approximately 89 for WISC-III and 83 for WAIS-IV, the results should not be generalized to children and adults with above-average intellectual functioning and only to a limited extent for average intellectual functioning. Furthermore, the short form estimates were derived from a complete scale administration; it is uncertain what results would have been in a stand-alone version. It could be hypothesized that because of the shorter attention span required, short forms may lead to better performance than would be obtained with the complete scale administration. Results may also be influenced by individual characteristics such as (less) fatigue, (less) frustration or (better) motivation. Future research should re-examine psychometric qualities of short forms administered independently of all FSIQ subtests of the WISC-III or WAIS-IV. Finally, as the present study included the currently available Dutch WISC-III, the results should be validated for the updated Dutch version of the WISC-V.

Conclusion

To conclude, the results of the present study support the use of WISC-III and WAIS-IV short forms in children and adults with neurological conditions in specific situations. We recommend that, where possible, professionals select the short form that yielded highest psychometric results for the specific intelligence category, e.g., if ID is suspected or has previously been determined, one should select a different short form than if one expects average intellectual functioning. The short form IQ obtained should be treated

very cautiously and be reported as a global estimation of the FSIQ in clinical situations. Professionals should bear in mind the critique of using short forms,[44,45] especially when evaluating a single individual rather than a group performance. A short form should not be used to make clinical inferences, but can be useful in research settings or in clinical settings to screen for possible deterioration in patients with epilepsy or other neurological disorders.

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4 Reliability and validity of the Dutch ADAMS in adults aged < 50 years with ID

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Abstract

Background: Reliable and valid screening instruments for depression and anxiety are needed for adults with intellectual disabilities (ID).

Method: Internal consistency (n = 198), interrater reliability (n = 41), test-retest reliability (n = 37) and criterion validity (n = 43) were studied in adults aged between 18-49 years. Internal consistency was also studied in a sample with epilepsy (n = 98).

Results: Internal consistencies of the Dutch ADAMS total scale and subscales were satisfactory to good (*α*: 0.76 to *α*: 0.92), as well as in the subgroup with epilepsy (α: 0.74 to α: 0.88). Interrater reliability and test-retest reliability were fair to excellent for the total scale (ICC's: 0.57 - 0.84) and subscales (ICC's: 0.43 – 0.86). The criterion validity of the Dutch ADAMS Depressive Mood subscale was good with a sensitivity of 88% (95% CI: 53 - 98%) and a specificity of 80% (95% CI: 64 - 90%).

Conclusion: Our study shows that the Dutch ADAMS is a reliable and valid instrument for adults aged between 18-49 years with ID (and comorbid epilepsy).

Background

In the population of adults with intellectual disabilities (ID), the prevalence of depression ranges from 2.2% to 8.3%, and the prevalence of anxiety disorder varies from 1.7% to 7.8%, depending on the study population and which (clinical) diagnostic criteria are used.[1-5] Depressive symptoms can be hard to recognize and are often missed in people with ID.[3] Limited cognitive and verbal abilities make diagnosing depression challenging. Therefore, accurate screening and diagnostic instruments, specifically developed for the ID population, are important for detecting depressive symptoms and also to monitor the effectiveness of interventions. Unfortunately, the number of reliable and valid screening instruments to detect psychopathology, such as depression, in the adult ID population is limited.[6,7]

Depression and epilepsy are both highly prevalent in adults with ID.[2,3,8,9] and having epilepsy is associated with more depressive symptoms in adults with ID.[10] Moreover, Van Ool and colleagues suggest that more severe epilepsies are risk factors for behavioral problems and psychiatric disorders.[10] Depressive and anxiety symptoms may result from epilepsy due to seizure-related or psychosocial factors, such as increased dependence, experienced stigma, restrained activity, and poor seizure control,[11,12] or may come from the same underlying neurobiological mechanism.[13] Depression in patients with epilepsy seems under diagnosed[14] and depressive symptoms may be partly hard to distinguish from epilepsy related symptoms, such as fatigue and concentration problems. Therefore, it is important to pay attention to proper screening instruments for adults with ID and epilepsy as well.

In 2003, Esbensen and colleagues published the Anxiety, Depression And Mood Scale (ADAMS) which is specifically developed for the ID population.[15] Hermans and colleagues[16] investigated the reliability and validity of the Dutch translation in adults with ID, aged 50 years and older (Healthy Ageing and Intellectual Disabilities Study, HA-ID study).[16] The authors concluded that the feasibility, test-retest reliability and internal consistency of the Dutch translation of the ADAMS are fair to good, with exception of a poor interrater reliability of the Social Avoidance subscale in the borderline and mild ID subgroup. The clinical manual of the Dutch ADAMS was published in 2013, including new data and reordered subscales.[17] Currently, this version of the Dutch ADAMS is used in many different care provider services of people with ID in the Netherlands. As the HA-ID study focused on people of 50 years and older, no conclusions can be drawn about the reliability and validity of the Dutch ADAMS within a younger adult population (18-49 years). Therefore, the aim of this study is to investigate the validity and reliability of the Dutch ADAMS in adults with ID in a sample of adults younger than 50 years of age.

Methods

Study population

Participants were recruited by behavioral scientists, psychologists and physicians of different care provider services for adults with ID in the Netherlands. The only exclusion criterion of this study was age below 18 or above 49 years. The legal guardians of the participants gave informed consent to participate if the participant was not able to give informed consent. Adapted information letters were used for the people with ID who gave permission themselves. The questionnaires in this study were completed by professional caregivers of the participants who knew the participants for at least 3 months. For the reliability analyses, we calculated that the sample size must be at least 39 participants (minimal 95% confidence interval (CI)).[15,16,18] In order to be able to examine the reliability for subgroups based on the degree of ID (mild, moderate, severe/profound), we need at least 117 participants. Before the start of this study, the Medical Ethical Testing Committee of the Erasmus University Medical center concluded that the rules laid down in the Dutch Medical Research Involving Human Subjects Act (WMO) do not apply to the current study (MEC-2015-587 and MEC-2016-408).

Instrument characteristics

ADAMS

The Anxiety, Depression And Mood Scale (ADAMS) is a by proxy instrument for adults with ID.[15] This instrument consists of 28 items (4-point scale) and five subscales ('Manic/Hyperactivity Behaviour', 'Depressive Mood', 'Social Avoidance', 'General Anxiety' and 'Obsessive/Compulsive behaviour'). The minimum total score is 0 and the maximum score is 84.

In 2012, the ADAMS was translated into Dutch and feasibility, reliability and validity of the Dutch version of the ADAMS was studied as part of the HA-ID study.[16] In total, 975 participants of 50 years and older were screened with the ADAMS. Internal consistency was tested in a sample of 127 participants and was good (Cronbach's alpha: 0.80 - 0.88 for the five different subscales). Test-retest reliability was tested in a sample of 93 participants and was good as well (ICC total ADAMS: 0.83, ICC subscales: 0.75 - 0.86). The test-retest reliability of the total score and subscales was also studied in different subgroups based on level of ID. Good test-retest reliability was found in all level of ID subgroups, with exception of a fair test-retest reliability in the severe/profound ID group (0.52, 95% CI: 0.11 - 0.78). Interrater reliability, measured in a sample of 83 participants, was fair to good for all subscales (ICC total ADAMS: 0.76, ICC subscales: 0.57 - 0.78). Within the level of ID subgroups, interrater reliability was fair to

good for all ID subgroups except for the borderline/mild ID subgroup where a poor interrater reliability was found (0.38, 95% CI: 0.02-0.66). Criterion validity of the ADAMS Depressive Mood Subscale was tested in a sample of 288 participants by studying the sensitivity and specificity rates compared to the outcome of the PAS-ADD interview.[19] Sensitivity and specificity ranged from sufficient to good.[16]

After the study of Hermans et al. was published in 2012, more data has been collected in clinical practice. In 2013, Hermans and colleagues published the manual of the Dutch ADAMS which included this new data.[17] In response to an explorative factor analyses and to what extent a subscale is indicative of a depression or anxiety disorder, the 'Depressive Mood' subscale was extended with six items, the 'Manic/Hyperactivity Behaviour' and 'Obsessive/Compulsive behaviour' subscales have been removed and a subscale labeled 'Other problems' has been added. The anxiety subscale and social avoidance subscale are unchanged. The current 'Depressive Mood' subscale covers the following topics: 'Sleeps more', 'Depressed', 'Sad', 'Worried', 'Attention', 'Fatigued/Lacks energy', 'Distracted', 'Facial expression', 'Starting routine tasks', 'Listless', 'Trembles' and 'Tearfull'. The Anxiety subscale includes the original topics: 'Nervous', 'Does not relax', 'Tense', 'Worried', Anxious', 'Panic attacks' and 'Trembles'. As the previous subscale, the 'Social Avoidance' subscale covers the same topics as the original subscale: 'Communication', 'Withdraws', 'Shy', 'Avoids others', 'Facial expression', 'Avoids eye contact', 'Avoids peers'. The fourth subscale of the Dutch ADAMS, 'Other Problems', consists of some items included in the 'Manic/Hyperactive Behavior' and the 'Compulsive Behavior' subscales of the original ADAMS complemented by other items. The following topics are included in the 'Other Problems' subscale of the Dutch ADAMS: 'Communication', 'Overactive', 'Ritualistic behavior', 'Attention', 'Checker', 'Distracted', 'Rituals', 'Facial Expression', 'Starting routine tasks', 'Panic attacks', 'Avoid eye contact'.

PAS-ADD

The Psychiatric Assessment Schedule for Adults with Developmental Disability (PAS-ADD) is a semi-structured clinical interview which provides full diagnoses under both ICD-10 and DSM-IV (TR) for several disorders, including depression and anxiety disorders.[19] The PAS-ADD can be used for the patient, as well as with an informant when the patient's language or verbal level is poor.[19] The test-retest and interrater reliability analysis of the PAS-ADD show moderate to high kappa values.[20] The PAS-ADD has a good interrater reliability as well (mean Kappa of 0.65 for individual items).[21] Criterion validity of the PAS-ADD was investigated with psychiatric diagnoses of experts. The validity of the PAS-ADD in relation to depressive symptoms was good.[22]

Procedure

After informed consent, the main professional caregiver of the participant was asked to fill out the Dutch ADAMS (baseline, T1, N = 198). For the participants in sample A, a second professional caregiver of the participant was asked to fill out the Dutch ADAMS at baseline as well, independent of the main professional caregiver (interrater reliability sample). In sample A, the main professional caregivers was also asked to fill out the Dutch ADAMS four weeks after baseline (T2) (test-retest sample). Further, a random part (n = 43) of sample A was assessed with the PAS-ADD interview as well (only the Depression section). Personal characteristics (gender, age, level of ID) and type of care setting of the participants were retrieved from the personal files. The interrater reliability, test-retest reliability and criterion validity were not studied at the tertiary epilepsy center (sample B).

Statistical analyses

IBM SPSS Statistics version 22 was used to perform the statistical analyses with a significance level of α = 0.05. Missing data was not imputed or included in the analyses. Differences on baseline in means of the total Dutch ADAMS score and four Dutch ADAMS subscales were studied in the whole sample with t-tests for gender and two age groups (18-34 and 35-49) and with One-way ANOVA for level of ID. Differences between sample A and sample B were studied with Pearson's Chi-square tests for independence for gender, the two age groups and level of ID. The Yates Continuity Correction is used with 2 by 2 tables. Besides, we used a two-way between-groups ANOVA to explore the impact of two independent variables (level of ID and sample A/B) on the total Dutch ADAMS score.

Pearson's Chi-square tests for independence were used to study if the three subsamples (the interrater reliability sample, test-retest reliability sample and criterion validity sample) are representative for sample A. The Yates Continuity Correction is used with 2 by 2 tables. The following characteristics of the participants were used to determine representativeness: gender, age and level of ID. Our hypothesis was that the participants in sample A and the interrater reliability, test-retest reliability and criterion validity are not significantly different.

Cronbach's alpha was used to analyze internal consistency of the Dutch ADAMS (total scale and the subscales). Correlations below 0.40 are considered to be poor, correlations between 0.40 and 0.59 are fair and correlations between 0.60 and 0.74 are considered as good. Excellent correlations are those correlations above 0.75.[23] With item analysis we studied if one or more items decreased the internal consistency. Test-retest reliability was used to measure the stability and reliability of the Dutch ADAMS

over time. Two scores (T1 and T2) from the main professional caregivers were used to examine if these scores were correlated (Intraclass Correlation Coefficients (ICCs)). The scores of the Dutch ADAMS can be influenced by an occurrence of a major event. If a major event occurred between T1 and T2, the scores of the participant was not included into the analyses. To measure the interrater reliability, the T1 scores of the main professional caregiver and the second professional caregiver were examined. ICCs were used to measure the interrater reliability. Both test-retest reliability and interrater reliability were measured for the total test-retest and interrater reliability samples as well as for subgroups (mild ID, moderate ID and severe / profound ID). The criterion validity of the Dutch ADAMS Depressive mood subscale was studied by measuring the sensitivity and specificity rates. The PAS-ADD interview (Depression section) was used as the gold standard.

Results

Participants

The total study population consisted of 198 adults aged 18 - 49 years (mean age: 34.8 years) with mild, moderate, severe or profound ID and were recruited from different care provider services in the Netherlands. The participants of sample A (n =100) lived in different care provider services for people with ID. The participants of sample B (n=98) lived in residential facilities of a tertiary epilepsy center. All the participants of sample B had epilepsy. Details of the participants characteristics can be found in Table 4.1.

In the total sample (n=198), we did not find significant differences in mean total score and subscale scores for gender, age and level of ID. There were no significant differences in gender and age between sample A and sample B. There were significant differences in level of ID between sample A and sample B: less participants with mild ID and more participants with profound ID were included in sample B. The interaction effect between group (sample A/B) and level of ID was not significant, F (3, 177) = 2.11, p = .10. A significant main effect was found for 'group' (F (1, 177) = 4.96, p = .027), but the effect size was small (partial eta squared = 0.03). The main effect of level of ID was not significant (F (3, 177) = 0.58, p = .632).

Representativeness

Interrater reliability sample

No significant differences in gender ($\chi^2(1) = .329$, $p = .566$) and age ($\chi^2(1) = .661$, $p = .416$) between sample A and the interrater reliability sample were found. There were significant differences in level of ID between sample A and the interrater reliability

sample ($\chi^2(3) = 39.626$, $p < .001$), because no adults with mild ID were included in the interrater reliability sample.

Table 4.1: Participants characteristics.

	Total sample* N = 198	Sample A n = 100	Sample B n = 98	Interrater reliability sample** n = 41	Test-retest reliability sample** n = 37	Criterion validity sample** n = 43
Gender						
Male/Female	108/90	51/49	57/41	19/22	25/12	17/26
Age (%)						
18-34	97 (49.0)	50 (50.0)	47 (48.0)	18 (43.9)	18 (51.4)	19 (44.2)
35-49	101 (51.0)	50 (50.0)	51 (52.0)	23 (56.1)	19 (48.6)	24 (55.8)
Level of ID (%)						
Mild ID	44 (22.2)	28 (28.0)	16 (16.3)	0 (0.0)	13 (35.1)	9 (20.9)
Moderate ID	46 (23.2)	21 (21.0)	25 (25.5)	11 (26.8)	8 (21.6)	11 (25.6)
Severe ID	57 (28.8)	30 (30.0)	27 (27.6)	18 (43.9)	13 (35.1)	12 (27.9)
Profound ID	41 (20.7)	11 (11.0)	30 (30.6)	11 (26.8)	2 (5.4)	11 (25.6)
Unknown	10 (5.1)	10 (10.0)	0 (0.0)	1 (2.4)	1 (2.7)	0 (0.0)
Residential setting (%)						
Central location	129 (65.2)	53 (53.0)	76 (77.6)	41 (100)	25 (67.6)	32 (74.4)
Community-based	33 (16.7)	15 (15.0)	18 (18.3)	0 (0.0)	7 (18.9)	8 (18.6)
Independent with support	12 (6.1)	8 (8.0)	4 (4.1)	0 (0.0)	5 (13.5)	3 (7.0)
Unknown	24 (12.1)	24 (24.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epilepsy (%)						
Diagnosis of epilepsy	98 (49.5)	0 (0.0)	98 (100)	0 (0.0)	0 (0.0)	0 (0.0)
Epilepsy data not collected	100 (50.5)	100 (100)	0 (0.0)	41 (100)	37 (100)	43 (100)

Note. Total sample = sample A + sample B, ** Part of sample A.

Test-retest reliability sample

There was a significant difference in gender (less women) ($\chi^2(1) = 5.441$, $p = .020$) and no significant differences in age ($\chi^2(1) = .000$, $p = 1.000$) between sample A and the test-retest reliability sample. There were also no significant differences in level of ID between sample A and the test-retest reliability sample ($\chi^2(3) = 2.835$, $p = .418$).

Criterion validity sample

The were no significant differences in gender ($\chi^2(1) = 3.204$, $p = .073$) and age ($\chi^2(1) = .653$, $p = .419$) between sample A and the criterion validity sample. Further, there were significant differences in level of ID between sample A and the criterion validity

sample ($\chi^2(3) = 15.672$, $p = .001$) due to less adults with mild ID and more adults with profound ID included in the criterion validity sample.

Table 4.2: Reliability of the Dutch ADAMS (N = 198).

	Total Dutch ADAMS	Depressive mood	Anxiety	Social Avoidance	Other Problems
Descriptives					
Mean score (SD)	24.69 (14.24)	10.95 (7.88)	6.28 (4.48)	5.34 (4.26)	10.07 (5.88)
Min-max score	0–69	0–34	0–20	0–19	0–24
Internal consistency (Cronbach's alpha)					
Total Sample (n=198)	0.91	0.87	0.83	0.80	0.76
Sample A (n=100)	0.92	0.90	0.84	0.81	0.77
Sample B (n=98)	0.88	0.84	0.76	0.77	0.74
Interrater reliability (ICC (95%-CI))*					
Total subsample (n = 41**)	0.64 (0.42–0.79)	0.77 (0.61–0.87)	0.64 (0.42–0.79)	0.69 (0.49–0.82)	0.66 (0.45–0.81)
Moderate ID (n = 11)	0.70 (0.19–0.91)	0.68 (0.17–0.90)	0.78 (0.35–0.93)	0.59 (0.01–0.87)	0.74 (0.28–0.93)
Severe/profound ID (n = 29)	0.57 (0.28–0.77)	0.81 (0.64–0.91)	0.49 (0.16–0.72)	0.60 (0.31–0.79)	0.62 (0.34–0.80)
Test-Retest reliability (ICC (95% CI))*					
Total subsample (n=37**)	0.71 (0.51–0.84)	0.72 (0.52–0.84)	0.75 (0.57–0.87)	0.79 (0.63–0.89)	0.72 (0.53–0.85)
Mild ID (n=13)	0.64 (0.15–0.87)	0.59 (0.07–0.86)	0.77 (0.41–0.92)	0.61 (0.11–0.87)	0.43 (-0.17 -0.79)
Moderate ID (n=8)	0.59 (-0.11–0.90)	0.82 (0.35–0.96)	0.58 (-0.20–0.90)	0.52 (-0.15–0.88)	0.75 (0.22–0.94)
Severe/profound ID (n=15)	0.84 (0.58–0.94)	0.75 (0.40–90)	0.85 (0.61–0.95)	0.86 (0.63–0.95)	0.85 (0.60–0.95)

Note. * Analyzed in sample A, ** one participant's level of ID is missing, ICC = intraclass correlation, CI = confidence interval.

Reliability

In the total sample (N = 198), the alpha coefficient of the total Dutch ADAMS scale was 0.91. The alpha coefficients of the four subscales ranged from 0.76 to 0.87. The internal consistency was also calculated for sample A. The alpha coefficient of the total Dutch ADAMS scale in sample A was 0.92. The alpha coefficients of the four subscales of sample A ranged from 0.77 to 0.90. The internal consistency was calculated for the subgroup with epilepsy as well (sample B). The alpha coefficient for the total Dutch

ADAMS in this subgroup was 0.88 and the alpha coefficient for the four subscales ranged from 0.74 to 0.84. Details of the internal consistency results can be found in Table 4.2.

For the interrater reliability, 41 second professional caregivers also completed the Dutch ADAMS at baseline. The interrater reliability, measured with Intraclass Correlation Coefficients (ICCs), of the total Dutch ADAMS was 0.64 (95% CI: 0.42 - 0.79). The interrater reliability of the four subscales ranged from 0.64 to 0.77. Interrater reliability was also measured for the different levels of ID. These, and the details of the overall interrater reliability, are presented in Table 4.2. To measure the stability and reliability of the Dutch ADAMS over time (test-retest reliability), professional caregivers completed the Dutch ADAMS at T1 and T2. Sixteen participants who experienced major life events between T1 and T2 were not included into the test-retest analyses, resulting in a sample of 37 participants. The test-retest period (T1-T2) ranged from 27 to 72 days. ICCs were used to examine the test-retest reliability. The test-retest reliability of the whole Dutch ADAMS was 0.71 (95% CI: 0.51 - 0.84). The test-retest reliability of the four subscales varied from 0.72 to 0.79. The details of the test-retest reliability of the Dutch ADAMS, as well as the results in the level of ID subgroups, can be found in Table 4.2.

Validity

The criterion validity was studied in a sample of 43 participants. A cut-off score of ≥14 on the Depressive Mood subscale was used for the sensitivity and specificity analyses based on the manual of the Dutch ADAMS.[17] When a participant was diagnosed with a Major Depressive Disorder (MDD) according to the DSM criteria in the PAS-ADD clinical interview, this participant was marked as 'positive' on the PAS-ADD. When a participant did not reach the required number of symptoms on the PAS-ADD clinical interview to be diagnosed with a MDD, the participant was marked as 'negative' on the PAS-ADD. Of the 43 participants, 28 participants scored negative on the PAS-ADD clinical interview as well as on the ADAMS Depressive Mood subscale (true negatives). Seven out of the 43 participants scored positive on the PAS-ADD Clinical interview (MDD diagnosed) and also positive on the ADAMS Depressive Mood subscale (true positives). Seven out of the 43 participants were not diagnosed with an MDD according to the PAS-ADD Clinical interview, but scored above the cut-off point of the ADAMS Depressive Mood subscale (false positives). One of the 43 participants had a MDD according to the PAS-ADD Clinical interview, but did not have a score above the cut-off point of the ADAMS Depressive Mood subscale (false negative).

The sensitivity of the Dutch ADAMS Depressive Mood subscale is 88% (95% CI: 53 - 98%). The specificity of the Dutch ADAMS Depressive Mood subscale is 80% (95% CI: 64 - 90%). As the criterion validity sample is small, sensitivity and specificity rates

of the Dutch ADAMS Depressive Mood subscale were not measured for the level of ID groups separately.

Discussion

Depressive and anxiety symptoms can be difficult to recognize in adults with ID. Therefore, reliable and valid screening instruments are needed for this population. Prior to this study, the reliability and validity of the Dutch translation of the Anxiety, Depression And Mood Scale were not investigated in adults with ID below the age of 50 years (and with comorbid epilepsy). The results of our study show a good internal consistency of the Dutch ADAMS total scale and satisfactory to good internal consistency of the subscales, for adults younger than 50 years of age. In the subgroup of participants with epilepsy (sample B), the internal consistency of the Dutch ADAMS total scale is good and the internal consistency of the subscales is satisfactory to good. Thus, even including participants with epilepsy did not have consequences for the internal consistency of the Dutch ADAMS.

Furthermore, our results suggest a good interrater reliability of the total Dutch ADAMS scale and a good to excellent interrater reliability for the subscales. In the level of ID subgroups, the interrater reliability is fair to good for the total scale and fair to excellent for the subscales.[23] The stability over time of the Dutch ADAMS (measured with test-retest reliability), is good for the total scale and good to excellent for the subscales. In the level of ID subgroups, the test-retest reliability of the total scale is excellent for the severe/profound subgroup and fair to good for the mild and moderate subgroups. The test-retest reliability of the subscales in the ID subgroups ranges from fair tot excellent.[23] The criterion validity of the Dutch ADAMS Depressive Mood subscale, measured with sensitivity and specificity rates, is good.

Previous research by Hermans and colleagues in an elderly sample (mean age 62.2 years) showed a good internal consistency of all subscales of the Dutch ADAMS.[16] Moreover, they also found a good test-retest reliability for the total group and good test-retest reliability in the level of ID subgroups (except for the Social avoidance subscale in their severe/profound ID subgroup, which had a fair test-retest reliability).[16] Furthermore, they also mentioned a fair to good interrater reliability for the total scale and subscales. In their level of ID subgroups, the interrater reliability was fair to good, with exception of a poor interrater reliability in the borderline/mild ID subgroup.[16]

Furthermore, their criterion validity analyses of the Dutch ADAMS showed a sufficient to good sensitivity and specificity. Rojahn and colleagues mention in their study an excellent internal consistency of the total ADAMS, which is comparable to ours.[24] The French version of the ADAMS was evaluated in 2004.[25] They found a satisfactory to excellent internal consistency and an excellent test-retest reliability. The

results in the studies of Hermans and colleagues[16] and Rojahn and colleagues[24] are based on the ADAMS with five subscales, and the study of Methot and colleagues[25] is based on an ADAMS with three subscales. As the Dutch ADAMS in the present study has four subscales, results of the previous studies are not completely comparable with the current study.

The first strength of the present study is the large sample used in the internal consistency analyses. A second strength of the current study is the significant amount of adults with ID and comorbid epilepsy who are included. Third, the mean age of the participants of the current study (34.8 years) is almost 30 years below the mean age of the previous study in 2012 by Hermans and colleagues (62.2 years). As a result, the current study adds valuable information to the existing literature about the reliability and validity of the Dutch ADAMS.

The small sample sizes of the subgroups used in the reliability and validity analyses is a limitation of this study. A second limitation of this study is that the three subsamples of this study (interrater reliability sample, test-retest reliability sample and criterion validity samples) do not completly represent sample A. There was a difference between the interrater reliability sample and sample A because no adults with mild ID were included in the interrater reliability sample. In the test-retest reliability sample there was a underrepresentation of women and in the criterion validity sample, the overrepresentation of participants with profound ID and the underrepresentation of participants with mild ID caused significant differences. A third limitation is the rather large range of the test-retest period.

In conclusion, the Dutch ADAMS is a reliable and valid screening instrument which can be used to screen for depressive symptoms and anxiety symptoms in the adult population with ID in clinical practice and to monitor the effectiveness of interventions. Routinely screening is recommended in order to prevent underdiagnosis, especially among those with epilepsy. In the future, larger subgroups based on level of ID are needed, and more research can be done in analyzing the underlying factors in the Dutch ADAMS in the ID population aged 18 - 50 years.

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Part 2

Epilepsy and ID in relation to neuropsychiatry: what's to blame?

5

A systematic review of neuro-psychiatric comorbidities in people with epilepsy and ID

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Abstract

Background: Epilepsy is a neurological condition that is particularly common in people with intellectual disability (ID). The care for people with both epilepsy and ID is often complicated by the presence of neuropsychiatric disorders, defined as psychiatric symptoms, psychiatric disorders, and behavioral problems. The aim of this study was to investigate associations between epilepsy or epilepsy-related factors and neuropsychiatric comorbidities in ID patients and between ID and neuropsychiatric comorbidities in epilepsy patients.

Method: We performed a systematic review of the literature, published between January 1995 and January 2015, retrieved from PubMed/Medline, PsychInfo, and ERIC, and assessed the risk of bias using the SIGN-50 methodology. Forty-two studies were identified of which fifteen were assessed as having a low or acceptable risk of bias evaluation. Neuropsychiatric comorbidities were examined in relation to epilepsy in nine studies, in relation to epilepsy-related factors, such as seizure activity, seizure type, and medication in four studies, and in relation to the presence and degree of ID in five studies.

Results and conclusion: We can conclude that the presence of epilepsy only was not a clear determinant of neuropsychiatric comorbidity in patients with ID, although a tendency towards negative mood symptoms was identified. Epilepsy-related factors indicating a more severe form of epilepsy were associated with neuropsychiatric comorbidity as was the presence of ID as compared to those without ID in patients with epilepsy, although this should be validated in future research. A large proportion of the studies in this area are associated with a substantial risk of bias. There is a need for high-quality studies using standardized methods to enable clear conclusions to be drawn that might assist in improving the quality of care for this population.

Introduction

Epilepsy is a neurological condition that is particularly common in people with intellectual disability (ID). For the ID population, the epilepsy prevalence rates range from 20 to 30%, increasing with severity of ID,[1] whereas rates of around 1% are reported for the general European population.[2] For the epilepsy population, 16% of individuals with epilepsy also have some degree of ID (e.g. mild, moderate, severe, or profound),[3] which is much higher than the prevalence of < 1% reported for the population overall.[4] The population with both epilepsy and ID has a high rate of complex needs and comorbid behavioral difficulties; these have important implications for good clinical practice and treatment of these patients.[5]

Eplepsy can be associated with a variety of behavioral, cognitive, and psychiatric comorbidities.[6-8] The nature of these comorbidities is complicated, as many factors are involved, such as etiology and factors related to epilepsy, seizures and anti-epileptic drugs (for an overview, see[6]). In children with epilepsy, the most prevalent comorbidities 6include attention deficit hyperactivity disorder (ADHD), mood and anxiety disorders, autism spectrum disorders, and behavioral problems.[8] Adults with epilepsy are most often diagnosed with mood and anxiety disorders and social difficulties.[7]

Behavioral and psychiatric comorbidities are also common in the ID population.[9-11] Most common are psychotic, affective and anxiety disorders, autism spectrum disorders, and behavioral problems .[9] The specific group of patients with both epilepsy and ID might present even more complicated neuropsychiatric features, since both ID and epilepsy are risk factors for such conditions. Against this background, we carried out a systematic review in order to determine which neuropsychiatric comorbidities are typical for patients who have both epilepsy and ID and which factors are associated with the neuropsychiatric comorbidities in this population. A better understanding of neuropsychiatric comorbidities in patients with both epilepsy and ID is important to improve appropriate management of epilepsy, and could eventually enhance the quality of life. As far as we are aware, no review study with this goal has been performed.

Methods

Search strategy

The present systematic review was carried out in keeping with the guidelines of the PRISMA statement.[12] The electronic databases Medline/PubMed, PsychInfo, and ERIC were searched for relevant articles on neuropsychiatric outcomes in patients with epilepsy and ID. Our search was limited to articles in the English language, published between January 1995 and January 2015. The search terms and strategy

were customized for each electronic database, using Medical Subject Heading (MeSH) and title/abstract words for Medline/PubMed, and Subject Headings and keywords for PsychInfo and ERIC. The search terms for neuropsychiatric outcomes were broadly selected to ensure all relevant articles were retrieved. For each database, search terms for epilepsy, ID, and neuropsychiatric outcomes were combined in the final search (Table 5.1).

Table 5.1: Search strings for Epilepsy, ID and Neuropsychiatric Comorbidities[a]

Medline/PubMed	
Epilepsy	epilepsy[MeSH] OR epilep*[TIAB]) OR (seizures[MeSH] OR seizure[TIAB] OR seizures[TIAB]
ID	"Intellectual Disability"[Mesh] OR (intellectual*[TIAB] AND (disabil*[TIAB] OR handicap*[TIAB] OR impair*[TIAB] OR retard*[TIAB])) OR (mental*[TIAB] AND (retard*[TIAB] OR disable*[TIAB] OR deficienc*[TIAB])) OR 'Mentally Disabled Persons'[Mesh]
Neuro-psychiatry	"mental disorders"[MeSH] OR psychiatric[TIAB] OR depress*[TIAB] OR manic[TIAB] OR bipolar[TIAB] OR adhd[TIAB] OR anxi*[TIAB] OR autis*[TIAB] OR psychosis[TIAB] OR psychot*[TIAB] OR schizophren*[TIAB] OR mood[TIAB] OR affective[TIAB] OR emotional*[TIAB] OR phob*[TIAB] OR psychopatholog*[TIAB] OR behavior*[TIAB] OR behaviour*[TIAB] OR 'self-injury'[TIAB] OR aggress*[TIAB] OR conduct[TIAB] OR violence[TIAB] OR externali*[TIAB] OR internali*[TIAB] OR (Stereotyp*[TIAB] AND behavior[TIAB])
PsychInfo	
Epilepsy	epilepsy[SH] OR seizures[SH]
ID	"Intellectual development disorder"[SH] OR "cognitive impairment"[SH] OR "intellectual disability"[KW]
Neuro-psychiatry	"mental disorders"[SH] OR psychopathology[SH] OR "psychiatric symptoms"[SH] OR "emotional disturbances"[SH] OR "emotional state"[SH] OR "emotion regulation"[SH] OR "behavior disorders"[SH] OR "behavior problems"[SH] OR "conduct disorder"[SH] OR "attention deficit disorder"[SH] OR "aggressive behavior"[SH] OR "antisocial behavior"[SH] OR "oppositional defiant disorder"[SH] OR comorbidity"SH] OR "stereotyped behavior"[SH] OR "self-destructive behavior"[SH] OR "coping behavior"[SH] OR externalization[SH] OR internalization[SH]
ERIC	
Epilepsy	epilepsy[SH] OR seizures[SH]
ID	"mental retardation"[SH] OR "learning problems"[SH]
Neuro-psychiatry	"mental disorders"[SH] OR psychopathology[SH] OR psychiatry[SH] OR "mental health"[SH] OR depression[SH] OR "behavior disorder"[SH] OR "behavior problems"[SH] OR "attention deficit hyperactivity disorders"[SH] OR aggression[SH] OR comorbidity[SH] OR "self destructive behavior"[SH] OR coping[SH]

Note. MeSH = Medical Subject Heading, TIAB = Title and Abstract, KW = Keyword, SH = Subject heading., ID = intellectual disability. [a] Search terms for epilepsy, intellectual disability, and neuropsychiatric outcomes were combined in the final search (i.e. epilepsy AND intellectual disability AND neuropsychiatric comorbidity).

We used the following definitions for our key terms:

- *Epilepsy*: Studies that reported on the presence of epilepsy or seizure disorders in their study sample. There were no restrictions on epilepsy type or seizure activity.
- *Intellectual disability*: According to ICD-10 and DSM-5, ID is defined as having both reduced intellectual functioning (IQ below 70) and impaired adaptive abilities to cope with the daily demands of the social environment, and should manifest during the developmental period of an individual.[13,14] However, as this level of intellectual functioning is not always reported in articles and the terminology for ID is often inconsistent, we included the following: articles that reported IQ levels below 70, clearly impaired adaptive abilities of individuals, or any levels of ID (or a similar term) in accordance with ICD-10 or DSM-5.
- *Neuropsychiatric comorbidity*: In order to obtain a clear and comprehensive overview of neuropsychiatric comorbidity, we included a variety of behavioral and affective problems, psychiatric symptoms and psychiatric disorders. We based our search terms on symptoms of common ICD-10 and DSM-5 diagnoses in the ID literature and aspects of psychological instruments (see Table 5.1).

Titles and abstracts of records were screened by one author (JO). Full-text versions of relevant articles were retrieved and assessed for eligibility. In addition, references of included articles were screened for relevance; this resulted in one additional article that met the inclusion criteria. Inclusion criteria according to type of study, type of study population, and type of outcome were:

- *Type of study*: Empirical and observational studies written in English, published in peer-reviewed journals. We excluded case reports, psychometric studies, commentaries, and reviews.
- *Type of study population*: Humans with both epilepsy and ID included in at least part of the study sample. All types of epilepsy, levels of ID, and types of residential setting were included.
- *Type of outcome*: Any type of behavioral difficulties or psychiatric symptoms, specifically reported for those with both epilepsy and ID.

Studies were excluded if they did not meet the inclusion criteria or if the focus was on neuropsychiatric characteristics related to a specific intervention or to the etiology, as these topics are beyond the scope of this review. Reasons for exclusion were noted. A blinded standardized double-check of 10% of included and excluded articles was carried out by a second author (JH). They disagreed on 6.7% of the double-checked studies; this was resolved by consensus. As a result, a total of 42 articles were considered eligible for the present review.

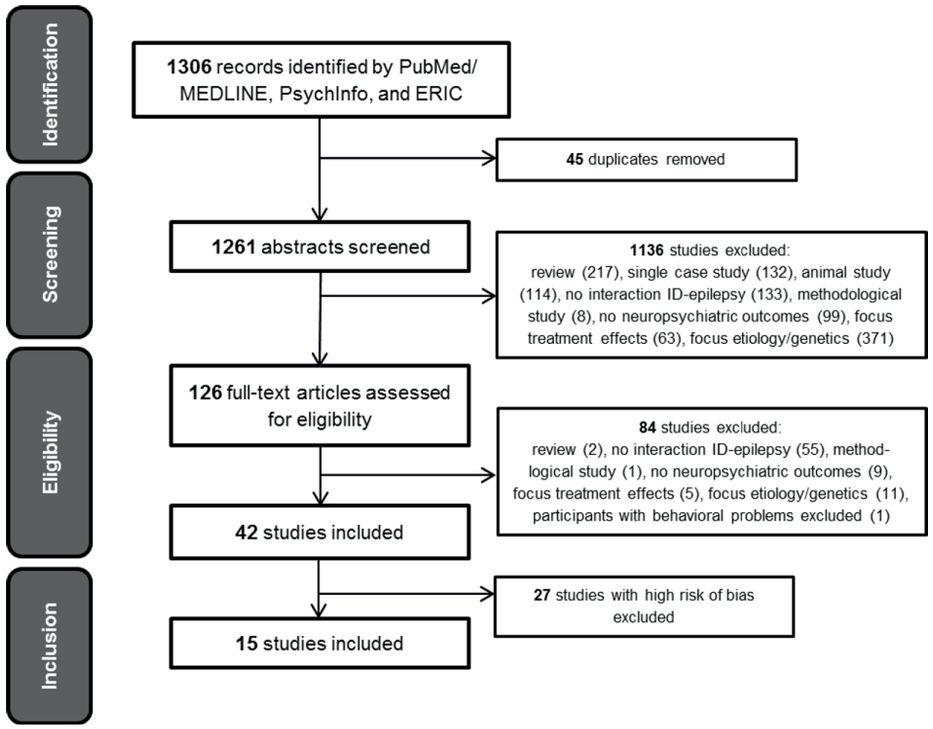
Next, the study quality and risk of bias were analyzed according to the SIGN-50 methodology.[15] SIGN has developed checklists that can be used as a tool to assess the level of evidence of a study, and that include items regarding selection bias (e.g. 'The study indicates how many of the people asked to take part did so'), attrition bias (e.g. 'Comparison is made between full participants and those lost to follow-up'), detection bias (e.g. 'Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable'), and confounding (e.g. 'The main potential confounders are identified and taken into account in the design and analysis'). The principles of GRADE processes were incorporated in the development of these checklists.[16] According to SIGN-50, studies are allocated to one of four categories based on their level of evidence (LE), with LE1 indicating the lowest risk of bias. As there is no checklist for cross-sectional studies, we followed the procedures of De Winter, Jansen, and Evenhuis[17] and Van de Wouw, Evenhuis, and Echteld[18] and adapted the SIGN methodology checklist for cohort studies in order to enable assessment of cross-sectional studies. Accordingly, the level of evidence of cross-sectional studies was considered to be LE2, and cross-sectional studies without statistical analyses as non-analytical studies (LE3). The LE can be further specified as either high-quality (++), well-conducted (+) or high risk of bias (-). Our assessment of LE was only performed on the questions related to our review area. Two of the authors (JO and FS) independently analyzed the included studies according to SIGN criteria. Disagreements (21%) were resolved by consensus. After excluding the studies with a high risk of bias, a total of 15 studies remained to be included in this systematic review (the excluded studies are described in Supplementary Table 5.7 in the Appendix). See Figure 5.1 for an overview of the selection procedure.

Data collection and analysis

Study characteristics of the included articles were reviewed and the following characteristics noted, if sufficient information was available:

1. Study design, size of total sample, and number with epilepsy and ID;
2. Participants: sex, age range, and study population;
3. Level of ID and method of assessment;
4. Seizure type and method of assessment of epilepsy;
5. Neuropsychiatric outcomes and method of assessment;
6. Relevant results and conclusion.

Figure 5.1. Overview of the selection procedure.



Results

The 15 included articles varied in their scope, and were subdivided into three categories with respect to the relation between neuropsychiatric comorbidities and: (1) the presence or absence of epilepsy in patients with ID, (2) differences in epilepsy-related factors in patients with both epilepsy and ID, and (3) the presence or absence, or degree of ID in epilepsy patients. If an article addressed more than one category, it was allocated to both. There were nine studies in category 1, four studies in category 2, and four studies in category 3. The study characteristics and results are presented by category in Tables 5.2 – 5.4. In order to provide a complete overview of the literature, the excluded studies with a high risk of bias are presented in Supplementary Table 5.7 and the methods of assessment of epilepsy, level of ID and neuropsychiatric outcomes for all studies are described in Supplementary Table 5.6.

To avoid complexity in the text, individual statistical results are not presented here but the data are available in Tables 5.2 – 5.4, to which reference should be made. Only statistically significant results are presented. It should be noted that, in some cases where statistically significant associations were not established, these studies may have been underpowered, implying that statistically significant results might have been obtained if larger numbers had been included; detailed discussion of the power of each of these studies to determine statistically significant differences is not presented in this paper.

Presence or absence of epilepsy

We identified nine articles that studied the association between the presence or absence of epilepsy and neuropsychiatric comorbidities in people with ID (Table 5.2). Only one study was of high quality;[19] the rest were well-conducted. The studies consisted of participants from heterogeneous populations with respect to their age, epilepsy, level of ID, and etiology of epilepsy and ID. N varied from 90 to 3065 participants. Information about seizure type and seizure activity was often lacking.

Presence of epilepsy and psychiatric symptoms and disorders

The high quality study compared adults with ID with and without epilepsy with regard to psychiatric disorders, matched according to level of ID.[19] When controlling for age, type of living environment, and sex, adults with epilepsy had more symptoms of depression and unspecified disorders (such as dementia and organic problems) than those without epilepsy. This is in line with results from Fitzgerald et al.,[20] who found more negative mood symptoms in adults with seizures than in those without, after controlling for level of ID and age. In addition, McGrother et al.[21] reported that, after

controlling for age, sex, and level of intellectual understanding, adults with epilepsy and ID had higher rates of lack of empathy, mood swings, and poor speech than adults without epilepsy.

In contrast, Cooper et al.[22] found that adults with epilepsy were less likely to have psychosis, after adjustment for age and level of ability. There were two studies that did not report associations between the presence of epilepsy and psychiatric symptoms. More specifically, Matthews et al.[23] concluded that having epilepsy was not associated with any psychopathology in adults with ID and Lewis et al.[24] reported that having epilepsy was not associated with emotional disturbances in individuals aged 8 to 22, after correcting for cognitive level.

Presence of epilepsy and behavioral problems

The presence of epilepsy was associated with higher rates of being uncooperative, seeking attention, and disturbing others at night in adults with ID, after controlling for age, sex, and level of intellectual understanding.[21] Didden et al.[25] found that children and adolescents with epilepsy had more severe sleep problems than those without epilepsy, which were related to more irritability. Challenging behavior and social impairments appeared to be more prevalent in adults with epilepsy and ID, compared to adults without epilepsy.[23] These differences, however, became non-significant when comparisons were restricted to a subgroup of patients with ID with adaptive behavior levels similar to levels of patients with epilepsy and ID. Tyrer et al.[26] find a similar trend; epilepsy was associated with aggression in adults with ID, but this effect became non-significant after controlling for demographic and comorbid factors. Having epilepsy was not related to behavioral disturbances in individuals aged 8 to 22,[24] nor to social skills in adults.[27]

Epilepsy-related factors

We identified four studies that investigated the role of epilepsy-related and other factors on neuropsychiatric outcomes in adolescents and adults with both epilepsy and ID (Table 5.3).

Seizure type

Three studies revealed a relationship between neuropsychiatric outcomes and seizure type, number of seizure types, or seizure severity.[28-30] Steffenburg et al.[30] found that children and adolescents with autism spectrum disorder and ID were more likely to have more than two seizure types than ID patients without autism spectrum disorder. They did not, however, find a difference in number of seizure types between ID patients with autism spectrum disorder and ID patients with other psychiatric disorders.

Table 5.2: Characteristics of studies on the effect of the presence of epilepsy on neuropsychiatric outcomes in patients with ID (n = 9).

Study; design	Participants	N	Seizure type	Neuropsychiatric outcome	Outcomes determined by	Results & conclusion
Cooper et al.[22] Cohort study	16-83 yr Mild-rofound ID	1023 with ID, of whom 49% with epilepsy	Not reported	Pychosis	Psychiatrist, based on DC-LD, ICD-10, DSM-IV-TR	Backwards logistic regression: Not having epilepsy was related to psychosis (p<.01), while adjusting for gender and level of ability.
Didden et al.[25] Cross-sectional study	1-19 yr Mild-profound ID	286 with ID, of whom 16% with epilepsy	Not reported	Sleep problems, daytime problem behavior	Sleep questionnaire, Aberrant Behavior Checklist	Mann-Whitney U: Having epilepsy related to severe sleep problems (X^2=6.550, p<.01). Multivariate logistic regression: Irritability was a risk factor for severe sleep problems (Wald X^2=10.32, p<.01), while correcting for age and level ID.
Fitzgerald et al.[20] Cross-sectional study	20-88 yr Severe-profound ID	115 with ID and epilepsy and 206 with ID only	Not reported	Symptoms of psycho-pathology	DASH-II	MANCOVA: Having seizures related to negative mood symptoms (F=8.67, p<.01), while controlling for level ID and age.
Lewis et al.[24] Cross-sectional study	8-22 yr Borderline-profound ID	392 with ID, of whom 29% with epilepsy	Not reported	Behavioral and emotional disturbances	Develop-mental Behavioral Checklist	MANCOVA: Epilepsy not related to behavioral and emotional disturbances, while correcting for cognitive level.
Matthews et al.[23] Case control study	17-86 yr Level ID not reported	55 with ID and epilepsy and 260 with ID only, of which 55 matched on level of adaptive behavior	All	Challenging behavior, social impairment, psychiatric status	Aberrant Behavior Checklist, Disability Assessment Schedule, PIMRA	Mann-Whitney U: Epilepsy related to challenging behavior (U=4.64; p<.001) and social impairments (U=5.38, p=.001), but results became non-significant after matching control group on level of adaptive behavior. Epilepsy not related to psychopathology. Chi-square: Epilepsy not related to possible psychiatric disorder.
McGrother et al.[21] Population based prevalence study	20-70+ yr Moderate-profound ID	2393 with ID, of whom 26% with epilepsy	Not reported	Psychological symptoms, autistic traits, behavior problems	Structured carer interview, Disability Assessment Schedule	Multivariate logistic regression: Having epilepsy related to poor speech (OR 2.2), lack of empathy (OR 1.5), mood swings (OR 1.5), being uncooperative (OR 1.6), seeking attention (OR 1.7), and disturbing others at night (OR 1.9) (p<.0001 for all), while adjusting for age, sex, and level of understanding.
Smith et al.[27] Case control study	29-72 yr profound ID	25 with ID, 25 with ID and epilepsy, 25 with ID and ASD, 25 with ID, ASD and epilepsy	Not reported	Social skills	MESSIER	MANOVA: Epilepsy not related to social skills.
Turky et al.[19] Prospective case control study	18-70 yr Mild- profound ID	45 with ID and epilepsy and 45 with ID only, matched on level of ID	Not reported	Psychiatric disorders	Mini PAS-ADD	RM ANCOVA: Epilepsy related to depressive symptoms (F=5.858, p=.017) and unspecified disorders (F=11.107, p=.001), while controlling for sex, age, and type of living environment.
Tyrer et al.[26] Cross-sectional study	19-92 yr Mild-profound ID	3065 with ID, of whom 27% with epilepsy	Not reported	Physical aggression	Structured carer interview, Disability Assessment Schedule	Logistic regression: Epilepsy risk factor for aggression (OR 1.55, p<.001), but effect disappeared after controlling for demographic and comorbid factors.

ASD = Autism Spectrum Disorder; DASH-II = Diagnostic Assessment for the Severely Handicapped-II; DC-LD = Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities/ Mental Retardation; DCR-ICD-10 = Diagnostic Criteria for Research-International Classification of Disease-10; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision; ICD = International Classification of Disease; MESSIER = Matson Evaluation of Social Skills in Individuals with sEvere Retardation; PAS-ADD = Psychiatric Assessment Schedule for Adults with Developmental Disabilities; PIMRA = Psychopathology Instrument of Mentally Retarded Adults. a The terminology of neuropsychiatric outcome as used in each article is maintained.

Andrews et al.[28] found that adult and elderly patients with generalized epilepsy showed more hyperactivity and non-compliance than those with localized epilepsy. Furthermore, greater seizure severity was an independent risk factor for a possible psychiatric disorder in adults with ID.[29]

Seizure activity

Only two studies investigated associations between seizure activity and neuropsychiatric outcomes; the results of these two studies were not consistent.[24,29] Espie et al.[29] showed that having more seizures in the past month was an independent risk factor for psychiatric disorders in adults with ID. Lewis et al.[24] did not, however, find a relation between active versus non-active epilepsy and behavioral or emotional disturbances in individuals aged 8 - 22, after adjusting for cognitive level.

Other factors

Four well-conducted studies examined associations between other factors and neuropsychiatric comorbidities. Irritability, agitation, and crying appeared to be more prevalent in women compared to men and in adults who had a history of febrile convulsions.[28] Steffenburg et al.[30] found that children and adolescents with autism spectrum disorder and ID had a higher age of epilepsy onset than those without autism spectrum disorder. Furthermore, a lower tendency to loss of consciousness during seizures was an independent risk factor for having a possible psychiatric disorder and having a sensory disability was positively related to behavioral problems in adults.[29] More specifically, speech impairment was associated with lethargy, whereas a visual impairment was associated with stereotypical behavior. Adverse events due to antiepileptic drugs were positively associated with behavioral problems in adults. More specifically, double/blurred vision and sleepiness were risk factors for irritability, weight gain was a risk factor for lethargy, shaky hands and double or blurred vision were risk factors for hyperactivity, and shaky hands was a risk factor for inappropriate speech.[29] These studies might have identified important factors that interact with other variables in explaining neuropsychiatric outcomes. Their findings are not, however, validated by other studies and should therefore be interpreted carefully.

Presence and level of ID

Our search revealed five studies that examined the presence or level of ID on neuropsychiatric outcomes in epilepsy patients (Table 5.4). One study received a high quality evaluation;[31] the results of the remaining four studies had an acceptable risk of bias.

Table 5.3: Characteristics of studies on the effect of epilepsy-related and other factors on neuropsychiatric outcomes (n = 4).

Study; design	Age; level of ID	N	Seizure type	Neuropsychiatric outcomes	Results & conclusion
Andrews et al.[28] Cross-sectional study	18–93 yr, mild to profound ID	116 with ID and epilepsy	All	Maladaptive behavior, determined by ABC	Mann–Whitney U: More hyperactivity/noncompliance in those taking psychotropic medication (Z = –2.32, p < .05) and in those with generalized epilepsy compared to localized epilepsy (p b .01). More irritability/agitation/crying in females than males (p b .05) and in those with febrile convulsions (Z = 2.49, p < .05)
Espie et al.[29] Cross-sectional study	35.5 ± 10.1 yr, mild to profound ID	186 with ID and epilepsy	All	Behavioral problems, screening for psychiatric disorders, determined by ABC and PAS-ADD checklist	Logistic regression: Greater seizure severity (p < .01), more seizures in the past month (p < .05), and lower tendency to loss of consciousness during seizures (p < .01) are risk factors for possible psychiatric disorder. Speech impairment (p b .001) and visual impairment (p < .05) are risk factors for lethargy and stereotypic behavior, respectively. Side effects of AEDs related to behavioral problems: double/blurred vision and sleepiness are risk factors for irritability (p < .01), weight gain is a risk factor for lethargy (p b .01), shaky hands and double/blurred vision are risk factors for hyperactivity (p <.01), and shaky hands are a risk factor for inappropriate speech (p < .05).
Lewis et al.[24] Cross-sectional study	8–22, yr borderline-profound ID	392 with ID, of whom 29% had epilepsy	Not reported	Behavioral and emotional disturbances, determined by DBC	MANCOVA: No differences in behavioral and emotional disturbances between patients with epilepsy taking AEDs and those not on AEDs and between those with active epilepsy and nonactive epilepsy, while correcting for cognitive level.
Steffenburg et al.[30] Population based cross-sectional study	8-16 yr, mild to severe ID	90, of whom 38% with ASD or autistic-like condition	All, mostly genera-lized	Psychiatric disorders, determined by HBSS, CARS, Autism Behavior Checklist, psychiatrist	T-Test: Median age at onset of epilepsy higher in ASD group than in non-ASD (2.2 vs 0.9 years, p < .001), but did not differ from non-ASD with psychiatric disorders. The ASD group had more often >2 seizure types than the non-ASD group (59% vs 39%), but did not differ from non-ASD with psychiatric disorders.

*Note*ABC = Aberrant Behavior Checklist, ASD = autism spectrum disorder, DBC = Developmental Behavior Checklist, CARS=Childhood Autism Rating Scale, HBSS = Handicaps, Behavior, and Skills Schedule, PAS-ADD = Psychiatric Assessment Schedule for Adults with Developmental Disabilities.

Table 5.4: Characteristics of studies on the effect of the presence and role of ID on neuropsychiatric outcomes (n = 5)

Study; design	Age	N	Level of ID	Seizrue type	Neurpsychiatric outcomes	Restuls & conclusion
Andrews et al.[28] Cross-sectional study	18–93 yr	116 with ID and epilepsy	80% mild, 13% moderate, 6% severe, and 1% profound	All	Maladaptive behavior, determined by ABC	ANOVA: More hyperactivity/non-compliance (X^2 = –8.6, p < .05) and inappropriate speech (X^2 = 15.7, p < .001) in those with moderate ID than with mild ID
Espie et al.[29] Cross-sectional study	35.5 ± 10.1 yr	186 with ID and epilepsy	8% borderline, 11% mild, 4% moderate, and 69% profound	All	Behavioral problems, determined by ABC	Stepwise linear regression: Level of ID was arisk factor for lethargy (p < .001) and stereotypic behavior (p < .01).
Hilger et al.[33] Case-control study	41.3 ± 11.4 yr	248 with TLE, of whom 5% had ID	Not reported	Mostly genera-lized	Postictal psychosis, ictal fear, witnessed during EEG, or from psychiatric, patient, and informant reports	Chi-square: Postictal psychosis was associated with impaired intellectual functioning (p < .05) and ictal fear (p < .01).
Matsuura et al.[32] Cross-sectional study	6–76 yr	398 with epilepsy, of whom 23% had ID	47% mild, 22% moderate, 14% severe, and 8% profound	All	Psychiatric disorders, determined by self-developed 5-axial scheme, based on ICD-10	Chi-square: Having ID was a risk factor for nonpsychotic and psychotic disorders (X^2 = 22.02, p < .001).
Reilly et al.[31] Prospective community based study	5-15 yr	85 with epilepsy, of whom 40% with ID	Not reported, mostly mildb	All	Psychiatric disorders, based on psychological assessment, psychiatrist, based on DSM-IV-TR	Multivariate logistic regression: Having ID was a risk factor for ASD (OR 14.1, p < .01), while adjusting for epilepsy duration, seizure type, and known/unknown etiology.

Note. ABC =Aberrant Behavior Checklist, DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders — IV-Text Revision, ICD-10=International Classification of Disease-10, ASD= autism spectrum disorder.

It should be noted that the study samples of three studies predominantly included participants with mild ID and that none of the studies corrected for epilepsy characteristics in the analyses.

Presence of ID and neuropsychiatric outcomes

The high quality study examined psychiatric disorders in children with epilepsy, 40% of whom were diagnosed with ID.[31] They found significantly higher rates of autism spectrum disorder in children with ID compared to those without, while adjusting for epilepsy duration, seizure type, and known/unknown etiology. Having ID was not related to ADHD, depression, developmental coordination disorder, or anxiety. Matsuura et al.[32] investigated psychiatric disorders in a mixed sample of children and adults with epilepsy. Of these, 23% had ID, predominantly of a mild level. They showed that the presence of ID was the strongest predictor for having a psychiatric disorder. Hilger et al.[33] studied postictal psychosis in adults with temporal lobe epilepsy of whom 5% had impaired intellectual functioning. Postictal psychosis was associated with impaired intellectual functioning and ictal fear.

Level of ID

Two studies examined associations between level of ID and behavioral problems.[28,29] Andrews et al.[28] found that adults with a moderate level of ID showed more hyperactivity/non-compliance and used more inappropriate speech than adults with a mild ID. Espie et al.[29] found that a more severe level of ID was a risk factor for lethargy and stereotypic behavior in adults. Thus, both studies concluded that patients with more severe ID have more behavioral problems, although the specific type of problematic behavior differed. To our knowledge, these are the only studies that examined the relation between level of ID and neuropsychiatric outcomes in epilepsy patients.

Discussion

This systematic review aimed to clarify whether there are significant associations between epilepsy or epilepsy-related factors and neuropsychiatric comorbidities in the ID population and between ID and neuropsychiatric comorbidities in epilepsy patients. From an initial total of 1306 records, we included 15 studies with a high quality or acceptable risk of bias evaluation,[15] comprising 461 children and adolescents, 7742 adults and elderly, and 392 patients of mixed age groups. An overview of results is presented in Table 5.5. As most studies had a cross-sectional design, it is not possible to draw firm conclusions about causality.

With respect to the relation between the presence or absence of – any type of – epilepsy and neuropsychiatric outcomes in ID, there was an indication that having

epilepsy was significantly related to higher rates of negative mood symptoms in adults and elderly with ID,[19-21] including depressive symptoms, negative mood, and mood swings. Having epilepsy was, however, not associated with emotional disturbances.[24] The association between epilepsy and mood symptoms would be in line with results from a systematic review and meta-analysis on active and lifetime depression rates in epilepsy patients (including patients without ID), demonstrating increased odds in epilepsy patients compared to those without.[34] As far as behavioral problems are concerned, the results were inconsistent. Most studies did not, however, demonstrate a significant association between the presence of epilepsy and behavioral problems.[23,24,26,27]

The role of epilepsy-related and other factors on neuropsychiatric comorbidities in ID patients were examined in only five studies. Generally, the results indicate that more severe epilepsies, including generalized seizures, greater seizure severity, higher seizure frequency, and higher number of seizure types, were risk factors for behavioral problems and psychiatric disorders.[29,30,33] These epilepsy factors can generate a negative impact on cognitive processes and brain development,[6,7] and might, therefore, result in the development of neuropsychiatric problems.

Finally, four studies looked into the relation between the presence and degree of ID and neuropsychiatric outcomes in epilepsy patients and showed a significant association. More specifically, having ID was related to higher rates of autism spectrum disorder, postictal psychosis, and both psychotic and non-psychotic disorder.[31-33] The degree of the ID seemed relevant with respect to behavioral problems, a more severe ID being significantly associated with more behavioral problems in adults with epilepsy.[28,29] These tentative results on the associations between ID and neuropsychiatric comorbidities in epilepsy patients should, however, be validated by future research.

The main limitation of this review is that many of the included studies examined highly heterogeneous patient groups, with different types of epilepsies and seizures, multiple levels of ID combined, a wide age range, and a lack of information regarding the etiology of epilepsy and ID. In addition, the terminology used to describe similar conditions was not consistent, such as behavioral problems, maladaptive behavior, behavioral disturbances, and challenging behavior, even in studies in which the same instrument was used. This makes it very difficult to compare and generalize results from multiple studies on similar conditions in order to draw firm conclusions. Also, in the designs of several studies, potential confounding variables, such as the effects of antiepileptic drugs and known etiology of ID and epilepsy, were not included. Finally, the wide variety of instruments to assess psychiatric disorders or symptoms, often with poor psychometric properties, are of concern as they might weaken or bias the results. We highly recommend the use of validated instruments or assessment by

trained professionals, based on the most recent editions of ICD or DSM and following structured guidelines developed primarily for the ID population.[35]

This review illustrates the wide range of neuropsychiatric problems among patients with ID and epilepsy, but also identifies major gaps and limitations in the literature. As most studies in the present review had a cross-sectional design, several questions remained unanswered, and future studies should study patients with both epilepsy and ID longitudinally, ideally along with a matching control group of patients without ID and a comparison group without epilepsy. A focus on epilepsy-related factors is recommended. Also, studying more homogenous groups of patients, both with regard to epilepsy syndrome and degree of ID, might help to clarify remaining issues. More attention should be paid to potential confounding variables. We encourage researchers to use validated and internationally-used methods in order to promote high quality research and generalized conclusions, and to try to use the same terminology.

Table 5.5: Summary of findings.

Presence of epilepsy	
Psychiatric characteristics + Negative mood[20] + Depressive symptoms and unspecified disorders[19] + Lack of empathy, mood swings[21] – Less psychosis[18] No association with emotional disturbances[24] and psychopathology[23]	*Behavioral problems* + Poor speech, being uncooperative, disturbing others at night[21] + Severe sleep problems, which were related to irritability[25] No association with behavioral disturbances,[24] behavioral problems and social impairment,[23] social skills[27] and physical aggression[26]
Epilepsy-related factors	
Seizure type + Generalized epilepsy: hyperactivity, non-compliance[28] + More than 2 seizure types: ASD[30] + Seizure severity: possible psychiatric disorder[29] *Seizure frequency* + Higher seizure frequency: possible psychiatric disorder[29] No association between active epilepsy and behavioral and emotional disturbances[24]	*Other* + Higher age at onset: ASD[30] + Febrile convulsions, females: irritability, agitation, crying[28] – Loss of consciousness: fewer psychiatric disorders[29] + Sensory disabilities: behavioral problems[29] + AED adverse events: behavioral problems[29]
ID	
Presence of ID + Non-psychotic and psychotic disorders[32] + Autism Spectrum Disorder[31] + Postictal psychosis[33]	*Level of ID* + Moderate ID (vs. mild ID): hyperactivity, non-compliance and inappropriate speech[28] + More severe ID: lethargy, stereotypic behavior[29]

Note. (+): statistically significant positive association, (–): statistically significant negative association.
AED = antiepileptic drugs, ASD = autism spectrum disorder, ID = intellectual disability.

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Appendices

Supplementary Table 5.6: Assessment methods of epilepsy and ID of all studies.

	Asssessment method	
	Epilepsy	**Level of ID**
Andrews et al.[28]	EEG and CT data	IQ tests, clinical notes
Arshad et al.[36]	*Not reported*	Psychiatrists specialized in people with ID
Brylewski et al.[37]	Parent/patient interview	*Not reported*
Buono et al.[38]	*Not reported*	*Not reported*
Chadwick et al.[39]	*Not reported*	Reported by special need schools
Chadwick et al.[40]	EEG and CT data	Reported by special need schools
Chung et al.[41]	Parent/patient interview	Rated by keyworkers
Cooper et al.[9]	*Not reported*	Vineland Adaptive Behavior Scale, results previous IQ tests

Supplementary Table 5.6 continued.

Study	**Asssessment method**	
	Epilepsy	**Level of ID**
Cooper et al.[22]	*Not reported*	Reported by family physician or general practitioner
Cowley et al.[10]	*Not reported*	*Not reported*
Deb[44]	*Not reported*	*Not reported*
Deb[45]	Clinical features	*Not reported*
Deb et al.[46]	Interview with patients and carers, medical case-notes	Interview with patients and carers, medical case- notes
Deb et al.[47]	Interview with subjects and carers	Interview with subjects and carers
Didden et al.[25]	Parent questionnaire	Results from standardized instrument from child's dossier
Espie et al.[29]	Ratings by experienced epileptologists	Vineland Adaptive Behavior Scales
Fitzgerald et al.[20]	*Not reported*	*Not reported*
Hilger et al.[33]	*Not reported*	Attendance special school (relating to IQ<70)
Johnson et al.[46]	Child neurologist	*Not reported*
Jones et al.[47]	Reports by teacher and parent	*Not reported*
Koskentaus et al.[11]	*Not reported*	Psychological assessment or case reports
Lacey et al.[48]	Epilepsy specialist	*Not reported*
Lewis et al.[24]	Parent interview	Cognitive tests administered by psychologists
Matson et al.[49]	Neurologist	*Not reported*
Matsuura et al.[50]	Self-developed 5-axial scheme	Medical records, interview patient and family
Matsuura et al.[32]	*Not reported*	WAIS-R
Matthews et al.[23]	Data from epilepsy research nurse, evaluated by doctors	Medical notes and records
McGrother et al.[21]	Structured home interview with carers by trained interviewers	Identified by Leicester Learning Disability Register
Molteno et al.[51]	*Not reported*	*Not reported*
Pawar et al.[52]	Case notes	*Not reported*
Piazzini et al.[53]	Patient interview	*Not reported*
Reilly et al.[31]	Pediatric neurologists	Psychological assessment
Ring et al.[54]	Clinical notes or EEG and imaging data	Mostly WAIS
Roberts et al.[55]	*Not reported*	*Not reported*
Smith et al.[56]	Neurologist	Psychologist
Smith et al.[26]	Neurologist	Psychologist
Smith et al.[57]	Neurologist	Psychologist
Steffenburg et al.[58]	*Not reported*	Psychological assessment
Steffenburg et al.[30]	Interview with patients, parents, nursing staff and teachers	Psychological assessment
Turkistani et al.[59]	Case notes	Case notes
Turky et al.[19]	Medical records	Clinical and psychometric reports, Adaptive Behavior Scales
Tyrer et al.[27]	Structured home interview with carers by trained interviewers	Identified by Leicester Learning Disability Register

Supplementary Table 5.7: Characteristics of studies with a high risk of bias evaluation

Study	Participants	N	Seizure type	Neuropsychiatric outcome	Outcome assessed by	Results & conclusion
Arshad et al..[36]	<24-55+ yr Mild-severe ID	156 with ID and epilepsy and 596 with ID only	All, mostly generalized	Psychiatric disorders	Psychiatrist specialized in ID, based on ICD-10	Chi-square: Having epilepsy negatively related to rates of psychiatric disorders (X^2=33.20, p<.001), although groups differed in ID level and type of housing.
Brylewski et al.[37]	21-83 yr, Mild-profound ID	205 with ID, of whom 24.4% with epilepsy	Not reported	Sleep disorders and behaviors	Modified questionnaire of Simonds & Parraga (1982)	Chi-square: Having epilepsy positively related to excessive bedtime rituals (X^2=5.59, p<.05) and more nocturnal incontinence (X^2=17.32, p<.01).
Buono et al.[38]	1-85 yr Mild-profound ID	69 with ID and epilepsy and 69 with ID only	All, mostly partial	Self-injurious behavior (SIB)	Scale for the assessment of SIB	Chi-square: No relation between SIB and presence of epilepsy.
Chadwick et al.[39]	4-11 yr Severe ID	114 with ID, of whom 22.8% with epilepsy	Not reported	Behavior problems	Disability Assessment Schedule, Aberrant Behavior Checklist	T-test: Epilepsy not related to behavior problems.
Chadwick et al.[40]	11-17 yr Severe ID	82 with ID, of whom 18.3% with epilepsy	Not reported	Behavior problems, autism symptoms	Disability Assessment Schedule, Autism Screening Questionnaire	Univariate regression: Epilepsy not related to behavior problems or autism symptoms.
Chung et al.[41]	21-47 yr ID level n.r.	14 with ID and epilepsy and 14 with ID only	All, mostly generalized TC	Challenging behavior	Disability Assessment Schedule, Aberrant Behavior Checklist	T-test: Having epilepsy positively related to irritability (t=2.99, p<.01). Pearson correlation: Inappropriate speech positively related to partial seizures (r=0.512, p<.05) and to seizure frequency (r=0.652, p<.01 4th year, r=.500, p<.05 5th year).
Cooper et al.[9]	16-83 yr Mild-profound ID	1023 with ID, % with epilepsy not reported	Not reported	Mental ill-health	Psychiatrist, based on DC-LD, ICD-10, DSM-IV-TR	Binary logistic regression: Epilepsy not related to mental ill-health (values not reported)
Cowley et al.[10]	80% <44 yr Mild-severe ID	752 with ID, of whom 48% with epilepsy	Not reported	Psychopathology	Psychiatrists, based on ICD-10	Binary logistic regression: Not having epilepsy was a risk factor for psychopathology (β=-0,66, p<.01) and schizophrenia spectrum disorder (β=-0.81, p<.05).
Deb[42]	20-77 yr Mild-severe ID	150 with ID and epilepsy and 150 with ID only	All	Maladaptive behavior, psychiatric illness (ICD-9)	Profile of Abilities and Adjustment, case notes, psychiatric interview, patient observation	Chi-square: Having epilepsy negatively related to rates of psychiatric illness (X^2=4.04, p<.05), specifically to manic illness.
Deb[43]	20-77 yr, mild to severe ID	100 with ID and epilepsy	All	Maladaptive behavior, psychiatric disorders	Profile of Abilities and Adjustment, psychiatric interview, based on DSM-III-R	35% had psychiatric disorder. Chi-square: Seizure type not related to psychiatric disorders.
Deb et al.[44]	20-83 yr , borderline to severe ID	143 with ID and epilepsy	Not reported	Behavioral problems, psychiatric disorders	Medical case notes, based on ICD-10	Chi-square: Generalized TC seizures positively related to behavioral problems (X^2=5.9, p=.01). Higher rates of psychiatric disorders in those aged 64+ than in those aged 18-64 (X^2=4.56, p<.05). Seizure activity, AED treatment not related to behavioral problems or psychiatric disorders. Higher rates of psychiatric disorders in those with mild ID than in those with severe/moderate ID (X^2=6.8, p<.01).
Deb et al.[45]	16-64 yr Mild-severe ID	101 with ID, of whom 25% with epilepsy	Not reported	Behavior disorders	Disability Assessment Schedule	Chi-square: History of epilepsy positively related to severe behavior problems (X^2=4.83, p<.05).
Johnson et al.[46]	4-19 yr Borderline-profound ID	42 with ID and epilepsy and 42 with epilepsy only	All, mostly complex partial	Psychiatric disorders	Child psychiatrist, based on DSM –III	Chi-square: Having seizure disorder positively related to ADHD (X^2=2,183, p<.05) and organic brain syndrome NOS (X^2=3.578, p<.001).
Jones et al.[47]	5-19 yr, Severe ID	14 with ID and epilepsy and 14 with epilepsy only	All	Maladaptive behavior, behavior disturbances	Adaptive Behavior Scales, Rutter Behavior Scale	MANOVA: Having epilepsy positively related to hyperactivity (F=8.39, p<.05).

Supplementary Table 5.7 continued.

Study	Participants	N	Seizure type	Neuropsychiatric outcome	Outcome assessed by	Results & conclusion
Koskentausta et al.[11]	6-13 yr Mild-profound ID	155 with ID, of whom 35% with epilepsy	Not reported	Psychiatric disorders	Case files, based on ICD-10	Fisher's exact test: Epilepsy not related to psychiatric disorders.
Lacey et al. [48]	13-102 yr, mostly mild ID	554 with epilepsy, of whom 5% with ID	All	Psychological distress	K-10 questionnaire	Multivariate regression: Presence ID was a risk factor for more psychological distress (F=7.1, p<.1), while adjusting for age and gender.
Matson et al.[49]	37.85 ± 14.15 yr Mostly profound ID	353 with ID and epilepsy and 353 with ID only	Not reported	Psychopathology, behavioral problems, social functioning	DASH-II, Aberrant Behavior Checklist, MESSIER	Most prevalent in those with ID and epilepsy: SIB (25%), stereotypies (15%), aggression (15%), tantrums (15%) and mouthing (8%). ANOVA: Having epilepsy negatively related to psychopathology (F=10.7, p<.001) and aberrant behavior (F=19.1, p<.001), but positively related to poor social skills (F=87.2, p<.001).
Matsuura et al.[50]	With ID: 27.8 ± 9.8 Without ID: 33.1 ± 12.2; ID level n.r.	298 with epilepsy, of whom 13% with ID	Not reported	Psychiatric disorders	Self-developed 5-axial scheme, Operational Criteria Checklist for Psychotic Illness	60% psychiatric disorder. Chi-square/ANOVA: Those with ID had more organic psychiatric disorders (p<.05), psychotic disorders (p<.01) and personality disorders (p<.01) than those without.
Molteno et al.[51]	6-18 yr Mild-profound ID	355 with ID, of whom 24% with epilepsy	Not reported	Psychopathology	Developmental Behavioural Checklist – Teacher version	Chi-square: Having epilepsy positively related to higher levels of psychopathology (X^2=4.854, p<.05): more self-absorbed and autistic relating behavior.
Pawar et al.[52]	17-65+ yr, Level ID n.r.	53 with ID and epilepsy, 124 with ID only	Not reported	Challenging behavior, psychiatric disorders	Case notes	No statistical analyses: challenging behavior was present in 59% of those with epilepsy and ID. Depression was most common psychiatric disorder (19%)
Piazzini et al.[53]	39.6 ± 14.2 Mild-severe ID	503 with epilepsy, of whom 18% with ID	Not reported	Aggressive behavior	Aggression Questionnaire	Multivariate ANOVA: More overall aggressive functioning (p<.05), physical aggression (p<.05), anger (p<.01), and hostility (p<.05) in patients with compromised intellectual functioning while adjusting for age and gender.
Ring et al.[54]	16-72 yr Mild-profound ID	175 with ID and epilepsy	All	Psychopathology	Clinical notes or descriptions from healthcare professional, based on ICD/DSM	Fisher's exact test: More psychopathology in those with no seizures in past 3 months (p<.01).
Roberts et al.[55]	27-46 yr, Moderate-severe ID	3 with ID and epilepsy	Genera-lized	(Aggressive) problem behavior	Behavioral observations	Yale's Q: positive correlation between absence seizures and problem behavior (pre-ictal within 2.2 minutes) in 2 of 3 patients (z=5.82, p<.05; z=5.49, p<.05). Positive correlation between TC seizures and problem behavior (pre-ictal within 1 minute) in 1 of 1 patient (Z=7.08, p<.05).
Smith et al.[56]	29-72 yr profound ID	25 with ID, 25 with ID and epilepsy, 25 with ID and ASD, 25 with ID, ASD and epilepsy	Not reported	Behavior problems	Autism Spectrum Disorders – Behavior Problems – Adults version	MANOVA: Epilepsy not related to behavioral problems.
Smith et al.[57]	As above	As above	Not reported	Psychopathology	Autism Spectrum Disorders – Comorbidity – Adults version	ANOVA: Epilepsy not related to psychopathology.
Steffenburg et al.[58]	8-16 yr, Mild-severe ID	90	All	Psychiatric disorders	Handicaps, Behaviour, and Skills Schedule, Childhood Autism Rating Scale, Autism Behavior Checklist, child psychiatrist	No statistical analyses: 57% had at least 1 psychiatric diagnosis, most common was ASD.
Turkistani et al.[59]	42.06 yr Mild-profound ID	108 with ID and epilepsy and 132 with ID only	All, mostly mixed	Mental illness, behavioral disturbances	Case notes, based on ICD-10	Chi-square: Epilepsy positively related to rate of depression (X^2=14.68, p=.001). Epilepsy not related to behavioral disturbances.

6 Challenging behavior in adults with epilepsy and ID

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Abstract

Purpose: The study aimed to describe the frequency and severity of self-injurious, stereotyped, and aggressive/destructive behavior in adults with both epilepsy and intellectual disability (ID) who reside at a tertiary epilepsy center and to investigate the associations between challenging behavior and epilepsy and ID characteristics.

Method: The frequency and severity of self-injurious, (motoric) stereotyped, and aggressive/destructive behavior among 189 patients was assessed using the Behavior Problem Inventory. Comparisons were made with an adult reference population with ID, based on gender, to determine whether the behavior was clinically deviant. Epilepsy characteristics, including age at onset, epilepsy type, seizure types, seizure frequency, and use of antiepileptic drugs (AEDs), were retrieved from patient files. The level of ID was classified using the Diagnostic and Statistical Manual of Mental Disorders — Fifth Edition (DSM-5) and an ID domain discrepancy was allocated if there was a substantial difference between two domains of adaptive behavior within a subject.

Results: Self-injurious behavior was present in 35% of subjects, stereotyped behavior in 60%, and aggressive/destructive behavior in 63%. The behavior exceeded clinical norms in 7%, 18%, and 12%, respectively. Aggression was the behavior evaluated most often as being problematic, despite its reported frequency being the lowest. When adjusting for level of ID and use of psychotropic medication, logistic regression analyses showed that self-injurious behavior was significantly associated with a lower number of AEDs (odds ratio (OR = 0.4); that stereotyped behavior was significantly associated with a higher number of seizure types (OR = 1.4) and a lower number of AEDs (OR = 0.4); and that aggression was significantly associated with the presence of an ID domain discrepancy (OR = 3.1).

Conclusion: Challenging behavior is a serious issue among adults with epilepsy and ID. Although some of the epilepsy and ID characteristics seemed to contribute independently to these types of challenging behavior, the effects of epilepsy-related characteristics are modest when compared with ID.

Introduction

Challenging behavior is a serious concern among people with epilepsy and intellectual disability (ID).[1] It is defined by Emerson as "culturally abnormal behavior(s) of such an intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy, or behavior likely to seriously limit use of, or result in the person being denied access to, ordinary community facilities".[2] Various types of challenging behavior are encountered in the daily care for this population, such as aggression, self-injury, noncompliance, hyperactivity, and stereotyped mannerisms. These behaviors can result in a fear of harm or actual injury to the person or to others and might have adverse consequences for the individual's development and opportunities for community integration.[3]

The prevalence of challenging behavior among people with ID was studied in multiple large population studies, which resulted in point prevalence rates between 10 and 22.5%.[4-7] The prevalence in those with both epilepsy and ID is less well-documented. Two systematic review studies on challenging behavior in this population concluded that people with epilepsy and ID did not clearly exhibit more challenging behavior when compared with those without epilepsy,[8,9] although the results were inconclusive. More specifically, having epilepsy was not associated with aggression, behavioral disturbances, social impairments, or challenging behavior in people with ID.[10-13] McGrother et al.,[14] however, found higher rates of being uncooperative, seeking attention, and disturbing others at night in people with epilepsy and ID compared with those without epilepsy, after adjusting for gender, age, and level of intellectual understanding. Studies comparing ID populations with and without epilepsy might oversimplify the association between epilepsy and challenging behavior, considering epilepsy is a very heterogeneous disorder with variability in localization, syndromes, etiology, seizure types and frequency, and treatment strategies often including polypharmacy in people with ID.

The literature on the impact of specific epilepsy-related characteristics on challenging behavior in people with ID is scarce. Espie et al.[15] explored associations between epilepsy factors as well as nonepilepsy concerns and challenging behavior and psychiatric symptoms. They concluded that psychiatric symptoms were most strongly related to epilepsy characteristics, such as seizure frequency and severity, whereas behavioral outcomes were most strongly predicted by nonepilepsy concerns, including sensory, intellectual, andmotor impairments, as well as adverse effects of drugs.[15] Other studies on behavioral changes associated with antiepileptic drugs (AEDs) show that effects vary among different AEDs, with positive as well as negative effects, although high quality evidence in people with ID is lacking.[1]

The aim of the study was to describe the frequency and severity of self-injurious,

stereotyped, and aggressive/destructive behavior in adults with both epilepsy and ID who reside at a tertiary epilepsy center and to investigate the associations between challenging behavior and epilepsy and ID characteristics.

Method

Study design and participants

This study had a cross-sectional design and was part of the TRIANGLE study (The Relation between epilepsy, ID, And Neuropsychiatric comorbidities in a Group of patients in Long-term care for Epilepsy), which was conducted within the tertiary care facility of Kempenhaeghe, the Netherlands. The TRIANGLE study is approved by the medical-ethical committee of Kempenhaeghe (No. 15.01), and the medical-ethical committee of Erasmus University Medical Center concluded that the rules laid down in the Medical Research Involving Human Subjects Act do not apply to this study (MEC-2016-408). The inclusion criteria were as follows: 1) age ≥ 18 years, 2) diagnosis of epilepsy according to the clinical definition by Fisher et al.,[16] 3) diagnosis of ID or current adaptive functioning at the level of ID as evaluated by the individual's psychologist, and 4) currently living at the residential care facilities of Kempenhaeghe for at least 1 year. The consent was provided by individuals themselves if they were capacitated, by their legal guardian in case individuals did not have the capacity, or by both the individual and their legal guardian if the individual was capacitated but also had a legal guardian.

Instruments and procedure

Challenging behavior

To assess challenging behavior, the Dutch version of the Behavioral Problem Inventory-01 (BPI)[3] was completed by a professional caregiver who had been familiar with the subject for at least 1 year. The BPI consists of three subscales: self-injurious behavior (SIB; 15 items), stereotyped behavior (25 items), and aggressive/destructive behavior (11 items). Self-injurious behavior was defined as behavior that may cause damage to the person's body and that occurred repeatedly in an unvarying manner (e.g., head-hitting); stereotyped behavior included peculiar or inappropriate voluntary acts that occurred repetitively and habitually (e.g., rocking); and aggressive/destructive behavior referred to deliberate, abusive attacks against others or objects (e.g., hitting others). For each item, the caregiver was asked to evaluate the frequency and severity of the particular behavior in a subject during the past two months. Frequency was rated on a five-point scale (never, monthly, weekly, daily, or hourly) and – if the item occurred at least monthly – the severity was rated on a three-point scale (slight problem, moderate problem, or severe problem). The sum of items yields a continuous (nonstandardized) frequency and severity score per subscale, with a higher score representing more frequent or severe challenging behavior. In addition, whether the scores were clinically deviant was examined by comparing the subject's score with clinical norms of an international population with ID (USA, UK, the Netherlands, and Romania).[17] A score was considered clinically deviant if it exceeded the mean score plus 1.5 standard deviation (≥ 93rd percentile) of the adult group with the corresponding gender.

The BPI is found to have good psychometric properties.[3,18] Reliability analyses in this study showed Cronbach's alpha values ranging from 0.684 – 0.858 (internal consistency) and split-half reliability values of 0.557 – 0.864. The BPI was also found to have good factor and criterion validity.[3]

Epilepsy characteristics

Epilepsy characteristics, including age at onset, epilepsy type and etiology, seizure type, number of seizures (including nocturnal seizures) in the past year, and the use of AEDs, were retrieved from the subject's medical records. With respect to all aspects of epilepsy, the patients are regularly followed up by a neurologist specialized in epilepsy. Seizures were recorded by the direct support staff and relied therefore on direct or secondary observations. Nonepileptic events, such as psychogenic nonepileptic seizures,were excluded. Non-EEG seizure-detection systems were used to detect nocturnal seizures if applicable. The epilepsy type was classified according to the most recent classification system by the International League Against Epilepsy (ILAE).[19]

ID

Regarding the ID, there were two variables of interest: overall level of ID and ID domain discrepancy. The level of ID was based on the three domains of adaptive deficits as described in the Diagnostic and Statistical Manual of Mental Disorders — Fifth Edition (DSM-5): the conceptual, social, and practical domains.[20] Each domain was assessed separately. The conceptual domain was assessed using a psychological test in combination with an expert opinion by the subject's psychologist. The psychological test applied was either a 4-subtest version of the Wechsler Adult Intelligence Scale — Fourth Edition (WAIS-IV),[21] in case of expected mild to (high-) moderate level of ID (n = 79), or the Peabody Picture Vocabulary Test — Third Edition (PPVT-III),[22] in case of (low-) moderate to severe level of ID (n = 57). The remaining 53 subjects were classified by expert opinion of the subject's psychologist. The WAIS-IV short form was validated among people with neurological disorders and impaired intellectual functioning.[23] The PPVT-III is a measure of receptive vocabulary and is considered a valid screening tool

for global cognitive functioning.[24,25] The social and practical domains were assessed using the corresponding Daily Living Skills and Socialization subscales of the Vineland-II Expanded Interview Form[26] (Dutch translation by Dijkxhoorn and Verhaar[27]), which were completed on all subjects.

The results for each domain were converted into a classification of mild, moderate, severe, or profound deficits. Internationally used cut-off points, described by the Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition (DSM-IV), the International Statistical Classification of Diseases — tenth edition (ICD-10), and Vineland-II, were applied, all using cut off points of 70–50/55 for mild deficits, 50/55–35/40 for moderate deficits, 35/40–20/25 for severe deficits, and below 20/25 for profound deficits.[26,28,29] The lower-end values were applied. An ID profile was considered to be discrepant when there was a substantial intra-individual difference between two DSM-5 domains, indicating that one domain is considerably more or less deficient than the other(s). An ID domain discrepancy was attributed if one of the following criteria was met: (1) a difference between the Vineland-II subscales Daily Living Skills and Socialization with a significance level of .01[25] or (2) a difference of at least one complete classification level between the conceptual domain and the social or practical domain (if the conceptual domain was determined by the PPVT-III or expert opinion).

Analyses

Descriptive statistics were calculated for each subscale of the BPI as well as the most reported items and the number of subjects with clinically deviant challenging behavior. Associations between subscales were examined using Kendall's tau-b rank correlation analyses, as the subscale variables violated the normality assumption and had a high number of tied ranks (e.g., both subscales with scores of 0). In order to examine the extent to which the frequency scores were predictive of the severity scores, separate regression analyses were performed. Each score was standardized to adjust for unequal item numbers so that slopes could be compared between subscales.

As the frequency and severity subscales were highly correlated, subsequent analyses were performed using only the frequency variables, as this is the more objective measure. Multiple binary logistic regression analyses were performed to examine direct associations between predictors and clinically deviant behavior, as well as multivariate logistic regression including all predictors and controlling for the use of psychotropic medication. Categorical variables were only included if they had sufficient statistical power. Hence, the level of ID was divided into mild/moderate and severe/profound, and the type of epilepsy included only focal epilepsy or a combined type with both generalized and focal epilepsy, as the number of subjects with

generalized epilepsy only was small (n = 20). Results were considered significant if $p < .05$. All analyses were conducted in IBM SPSS Statistics version 24.

Table 6.1: Clinical characteristics of the study sample (N = 198).

Characteristics	**Values**
Age at onset of epilepsy (years)	Mdn = 2.0, IQR = 0–5.5, range 0–53
Infancy (< 1 yr)	32.8%
Childhood (1 - 12 yr)	54.0%
Adolesence (12 - 18 yr)	10.1%.
Adulthood (18+ yr)	3.2%
Epilepsy type[a]	
Generalized	10.6%
Focal	41.3%
Both generalized and focal	44.4%
Unknown	3.7%
Number of seizure types (semiology)[a]	Mean = 3.8, SD = 1.9, range 0–8
Seizure frequency (last year)	Mdn = 70.0, IQR = 11.5–153.0, range 0–1206
Seizure-free	12.7%
Yearly	12.2%
Monthly	19.6%
Weekly	43.9%
Daily	11.6%
Etiology of epilepsy[a]	
Structural	28.6%
Generic	20.1%
Infectious	6.3%
Metabolic	1.1%
Unknown	43.9%
Daily use of anti-epileptic drugs	Mean = 3.1, SD = 1.1, range 0–6
Daily use of psychotropic drugs	41.8%
Psychiatric classification (DSM-IV)	20.6%

Note. [a]Based on ILAE 2017 criteria[18], Mdn = median, IQR = interquartile range, SD = standard deviation.

Results

Sample characteristics

A total of 240 patients were invited for the study, 189 of whom provided consent (inclusion rate: 78.8%). Participants were significantly younger than nonparticipants (mean difference = 6.04 years, $p = .015$) and were using psychotropic medication more often (41.8% versus 14.0%, respectively, $p < .001$). Individuals who participated did not differ from nonparticipants with respect to level of ID or gender.

The sample comprised 58.7% males, and mean age was 47.9 years (SD = 15.6; range: 18.3 – 85.9 years). The majority of subjects resided in residential facilities of Kempenhaeghe (76.2%); the others lived in community settings. The epilepsy originated in childhood in more than half of the subjects (54.4%). Most subjects experienced focal epilepsy or a combination of focal and generalized epilepsy (41.3% and 44.4%, respectively), with a seizure frequency of at least once a week (55.5%). Those who were seizure-free in the past year were currently using AEDs. Nearly all subjects were using AEDs (99.5%), and 41.3% were prescribed psychotropic medication on a daily basis. The level of ID was mild in 20.1%, moderate in 30.7%, severe in 29.1%, and profound in 20.1%, and an ID domain discrepancy was present in 32.8%. Clinical characteristics are depicted in Table 6.1.

Table 6.2: Kendall's tau-b correlation coefficients between BPI subscales.

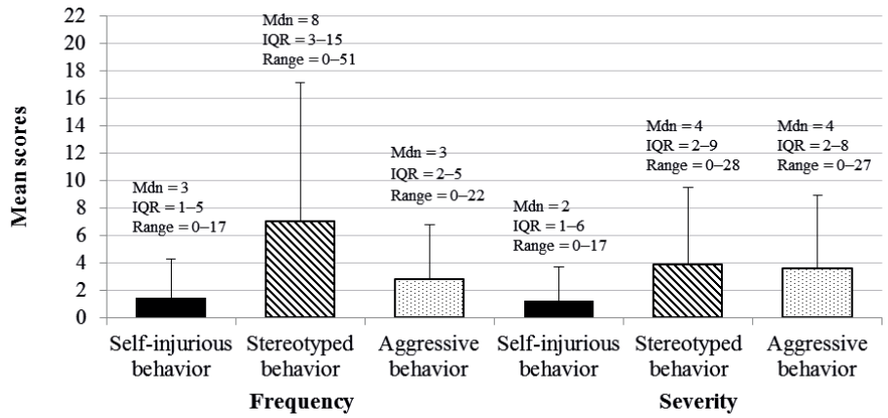
	SIB		Stereotyped behavior		Aggressive behavior	
	Frequency	**Severity**	**Frequency**	**Severity**	**Frequency**	**Severity**
SIB						
Frequency	-	.972**	.347**	.361**	.125*	.098
Severity		-	.346**	.365**	.128*	.101
Stereotyped behavior						
Frequency			-	.901**	.053	.025
Severity				-	.106	.078
Aggressive behavior						
Frequency					-	.876**
Severity						-

Note. SIB = Self-injurious behavior. * $p < .05$, ** $p < .001$.

Frequency and severity of challenging behavior

Self-injurious behavior was reported in 34.9% of subjects, stereotyped behavior in 59.8%, and aggressive/destructive behavior in 63%; 87.8% of subjects exhibited one or more of these challenging behaviors. The frequency of the behavior was clinically deviant compared with the norms for adults with ID, adjusted for gender, in 7.1%, 17.5%, and 11.6% of subjects, respectively. In total, 55 of 189 subjects (29.1%) had at least one type of clinically deviant behavior. For descriptive statistics and Kendall's tau-b correlation coefficients between BPI subscales, see Figure 6.1 and Table 6.2. The self-injurious behaviors that were reported most often were self-scratching (13.8%), self-biting (9.5%), and head-hitting (9.5%). With respect to stereotyped behavior, grimacing (29.6%), yelling/screaming (25.4%), rocking/repetitive body movements (18.0%), and gazing at hands or objects (18.0%) were reportedmost frequently. Being verbally abusive with others (32.8%), hitting others (26.9%), and pushing others (26.9%) were the aggressive/destructive behaviors which occurred most often.

Figure 6.1: Means and 1 standard deviation error bars per BPI subscale.

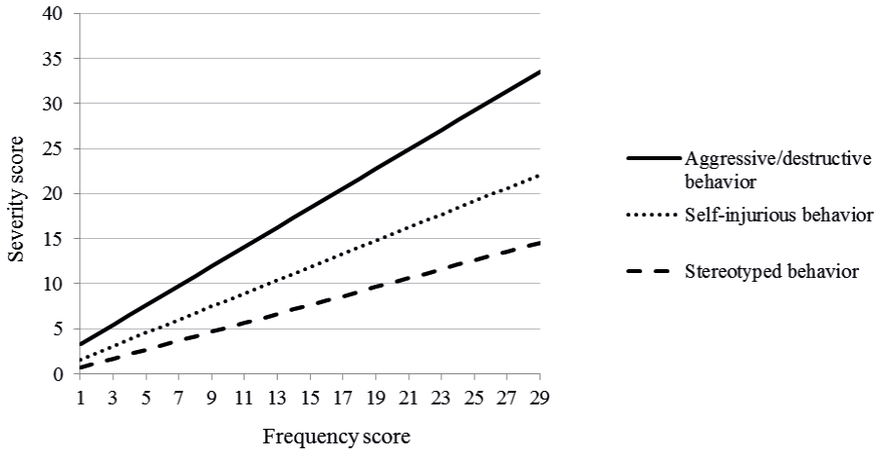


Note: Medians (Mdn) and interquartile ranges (IQR) are derived from positively scored items only.

Item-level analyses showed that self-injurious and aggressive/destructive behaviors were most often displayed on a monthly basis (in 37.8% and 52.9% of cases, respectively) whereas stereotyped behaviors occurred most often daily (in 51.3% of cases). A different trend was identified for the severity of behaviors. Self-injurious and stereotyped behaviors were most often evaluated as being a slight problem (39.5% and 37.1% of cases, respectively) whereas aggressive/destructive behaviors were mostly perceived as a moderate problem (40.3% of cases). The behavior was considered a severe problem in 27.2% of cases for self-injurious behavior, in 25.1% of cases for stereotyped behavior, and in 27.8% of cases for aggressive/destructive behavior. As some subjects showed multiple types of behavior, the total number of subjects who exhibited at least one behavior thatwas considered a severe problemwas 56 (29.6%).

Kendall's tau-b correlation analyses yielded very high positive correlation coefficients between the frequency and severity of each behavioral type (τ_b = 0.876–0.972, all p values < .001). Separate linear regression analyses with standardized scores confirmed these associations and showed that frequency scores explained 82.4% of variance in severity of self-injurious behavior, 80.0% of variance in severity of stereotyped behavior, and 62.7% of variance in severity of aggressive/destructive behavior. The regression lines are depicted in Figure 6.2. The slope value was highest for aggressive/destructive behavior (B = 1.08, SE = 0.08), compared with self-injurious behavior (B = 0.73, SE = 0.04), and lowest for stereotyped behavior (B = 0.50, SE = 0.02), indicating that aggressive/destructive behavior is perceived as problematic more quickly than self-injurious or stereotyped behavior.

Figure 6.2: Regression trend lines predicting standardized severity scores from standardized frequency scores per subscale.



Associations between epilepsy, ID, and challenging behavior

Results of the bivariate and multivariate logistic regression predicting clinically deviant challenging behavior are presented in Table 6.3. Bivariate logistic regression analyses showed that a more severe level of ID and a lower number of AEDs increased the likelihood of having clinically deviant self-injurious behavior (OR = 4.16, p = .033 and OR = 0.54, p = .018, respectively). After adjusting for level of ID, use of psychotropic medication, and the other predictors in a multivariate analysis, the effect of a lower number of AEDs remained significant (OR = 0.39, p = .004), but none of the other epilepsy or ID characteristics was significantly associated with self-injurious behavior.

With respect to stereotyped behavior, bivariate analyses indicated direct significant associations between clinically deviant stereotyped behavior and a higher number of seizure types (OR = 1.56, p < .001), a higher seizure frequency (OR = 1.02, p = .015), a lower number of AEDs (OR = 0.70, p = .048), and a more severe level of ID (OR = 14.76, p < .001). Although not statistically significant, there was also a clinically meaningful association between stereotyped behavior and epilepsy type, with the likelihood of having stereotyped behavior being twice as high when having a combined epilepsy type (OR = 2.04, p = .069). Taking the level of ID, use of psychotropic medication, and the other predictors into account, the likelihood of stereotyped behavior was significantly increased by the number of seizure types (OR = 1.44, p = .030), but significantly decreased by the number of prescribed AEDs (OR = 0.44, p < .001). The effects of seizure frequency and a combined epilepsy type were no longer present in the multivariate analysis.

Table 6.3: Logistic regression analyses predicting clinically deviant challenging behavior (frequency).

	Bivariate analyses		**Multivariate analayses**	
	B (SE)	**OR 95%-CI**	**B (SE)**	**OR**
SIB				
Age at onset	-0.09 (0.08)	0.91 (0.79–1.06)	-0.06 (0.08)	0.95 (0.81–1.10)
Generalized & focal epilepsy	0.80 (0.58)	2.23 (0.72–6.94)	0.40 (0.64)	1.45 (0.43–5.23)
Seizure frequency	0.01 (0.02)	1.01 (0.98–1.04)	-0.01 (0.02)	1.00 (0.95–1.04)
Number of seizure types	0.27 (0.15)	1.31[a] (0.98–1.75)	0.35 (0.22)	1.42 (0.92–2.18)
Number of AEDs	-0.62 (0.26)	0.54* (0.32–0.90)	-0.94 (0.32)	0.39**(0.21–0.74)
ID discrepancy	-0.62 (0.67)	0.54 (0.14–2.00)	-0.16 (0.79)	0.84 (0.18–3.99)
Severe level of ID	1.43 (0.67)	4.16* (1.12–15.42)	1.02 (0.79)	2.78 (0.59–13.02)
			χ^2 = 17.83*, Nagelkerke R^2 = 0.22	
Stereotyped behvior				
Age at onset	-0.05 (0.04)	0.95 (0.88–1.03)	0.01 (0.05)	1.01 (0.92–1.11)
Generalized & focal epilepsy	0.72 (0.39)	2.04[a] (0.95–4.41)	0.20 (0.49)	1.22 (0.47–3.15)
Seizure frequency	0.02 (0.01)	1.02* (1.01–1.04)	0.01(0.02)	1.01 (0.98–1.04)
Number of seizure types	0.45 (0.11)	1.56*** (1.25–1.95)	0.37 (0.17)	1.44* (1.04–2.00)
Number of AEDs	-0.36 (0.18)	0.70* (0.49–1.00)	-0.82 (0.24)	0.44*** (0.27–0.71)
ID discrepancy	-0.92 (0.48)	0.40[a] (0.16–1.02)	-0.29 (0.60)	0.75 (0.23–2.44)
Severe level of ID	2.69 (0.63)	14.76*** (4.32-50.46)	2.30 (0.71)	9.56** (2.47–40.20)
			χ^2 = 47.55***, Nagelkerke R^2=0.38	
Aggressive behavior				
Age at onset	-0.02 (0.04)	0.98 (0.90–1.06)	0.02 (0.05)	1.02 (0.92–1.12
Generalized & focal epilepsy	-0.03 (0.46)	0.97 (0.40–2.37)	-0.52 (0.54)	0.60 (0.21–1.71)
Seizure frequency	0.02 (0.01)	1.02 (0.99–1.04)	-0.00 (0.02)	1.00 (0.97–1.03)
Number of seizure types	0.35 (0.13)	1.42** (1.11–1.81)	0.21 (0.18)	1.23 (0.87–1.74)
Number of AEDs	0.17 (0.21)	1.18 (0.78–1.78)	0.02 (0.26)	1.02 (0.62–1.68)
ID discrepancy	0.61 (0.46)	1.84 (0.75–4.54)	1.12 (0.56)	3.08* (1.04–9.15)
Severe level of ID	1.71 (0.57)	5.52** (1.79–17.01)	2.21 (0.71)	9.13** (2.29–36.4)
			χ^2 = 22.07**, Nagelkerke R^2 = 0.22	

Note. B = beta, SE = standard error, OR = odds ratio, CI = confidence interval, AEDs = antiepileptic drugs, ID = intellectual disability. [a] p < .1, * p < .05, ** p < 0.1, *** p < .001.

Clinically deviant aggressive/destructive behavior was significantly related to a higher number of seizure types (OR = 1.42, p = .006) and a more severe level of ID (OR = 5.52, p = .003) in bivariate analyses. After adjusting for the use of psychotropicmedication and the other predictors in a multivariate analysis, none of the epilepsy characteristics was associated with aggressive/destructive behavior. However, the presence of an ID domain discrepancy did significantly increase the likelihood of having deviant aggressive/destructive behavior (OR = 3.08, p = .043) as well as a more severe level of ID (OR = 9.13, p = .002).

Post hoc exploratory analyses were performed by means of a chi-square or Fisher's exact test in order to assess the use of specific AEDs in relation to clinically deviant behavior. Because of polypharmacy and the concomitant use of, on average, three

AEDs, we could not determine the exclusive influence of each individual AED.With respect to self-injurious behavior, valproic acid was used less often in the subgroup with than in the subgroup without clinically deviant behavior (21.4% versus 52.4%, $p = .028$). In addition, none of the subjects in the subgroup with clinically deviant self-injurious behavior used topiramate or lacosamide, compared with 16.0% and 8.6% in the subgroup without (not significant). There were no significant differences in AED use between subjects with clinically deviant aggressive/destructive or stereotyped behavior and those without.

Discussion

The present study demonstrates that challenging behavior is a serious cause for concern among people with epilepsy and ID who reside at a tertiary epilepsy center. A total of 29.6% of the sample exhibited self-injurious, stereotyped, or aggressive/destructive behavior that is perceived as a severe problem by daily caregivers. Aggressive/destructive behavior was perceived as problematic more quickly compared with self-injurious or stereotyped behavior. Moreover, 29.1% of the sample exhibited clinically deviant behavior based on ID population norms of frequency scores, with (motoric) stereotyped behavior being encountered most frequently compared with ID population norms.

The results showed that some of the epilepsy and ID characteristics were related to challenging behavior. The likelihood of clinically deviant self-injurious and stereotyped behavior (but not aggressive/destructive behavior) tended to be smaller if a higher number of AEDs were prescribed on a daily basis. One might speculate that this might be due to the mood-stabilizing properties of certain AEDs;[30] for example, the use of valproic acid was significantly lower in subjects with selfinjurious behavior. Conversely, there are some AEDs that may have negative effects on behavior,[1] although this was not demonstrated in our study, probably due to polypharmacy in nearly all subjects and/or small sample size. In clinical practice, it is important to continue to evaluate efficacy and potential adverse effects regularly. Further research is necessary to determine behavioral effects of (combinations of) AEDs in people with ID, especially because the diagnosis of ID is often considered an exclusion criterion in medication trials. Another explanation for the negative association between the number of AEDs and self-injurious and stereotyped behavior might relate to the treatment effect leading to seizure improvement and hence improvements in behavior.[31] More (longitudinal) research focusing on treatment effects of AEDs on behavior in people with ID is recommended.

Furthermore, clinically deviant stereotyped behavior was present significantly more often in those with mixed seizure types, suggesting a severe form of epilepsy

that can be difficult to treat. Stereotyped behaviors are controlled behaviors which are thought to have a potential calming effect on an over-aroused nervous system.[32,33] Hence, it may be that they are (subconsciously) exhibited as a coping strategy for the burden of severe epilepsy, particularly when a person already has limited coping resources because of a more severe level of ID. It can also be hypothesized that the patients with a severe form of epilepsy have an underlying complex or brain impairment thatmight separately lead to behavioral abnormalities.

Clinically deviant aggression was not significantly associated with an aspect of epilepsy but was linked to ID characteristics. A more severe level of ID and an ID domain discrepancy (i.e., one domain of adaptive functioning being considerably more or less developed than another) significantly increased the likelihood of aggressive/destructive behavior. One could hypothesize that there is a risk the person with an ID domain discrepancy might be overestimated by others or by the person himself, resulting in an aggressive response to (over)demanding situations or internal frustration. Future research is necessary to clarify this mechanism.

We were able to take into account multiple epilepsy characteristics that make up the phenotype of epilepsy and indicate its severity. The etiology of epilepsy (and/or ID) and specific epilepsy syndromes were, however, not included in our study. It might have been that, for some patients, behavioral abnormalities resulted from the same underlying cause that is involved in the epilepsy itself, for example, a severe brain impairment.[34] Information regarding etiology was missing for a large percentage of the subjects; in those with a known cause of epilepsy, the etiologies were heterogeneous and sometimes rare and therefore resulted in small subsample sizes with insufficient statistical power. The representativeness of our sample is limited to patients with often severe epilepsy, majority of whom live in a residential care setting. Results should therefore be validated in other samples. A review of studies on deinstitutionalization and post-deinstitutionalization of adults with ID concluded that studies show no association with emotional well-being, including challenging behavior.[35]

To conclude, both epilepsy and ID characteristics may contribute independently to certain types of challenging behavior although the effects of epilepsy-related characteristics are modest when compared with ID. This study does not confirm the hypothesis that severe epilepsy strongly contributes to challenging behavior, somethingwhich has been repeatedly suggested in previous research and clinical practice. We did not find evidence for effects of seizure frequency, age at epilepsy onset, or epilepsy type on challenging behavior. The results of this study can help to anticipate challenging behavior and contribute to the search for targeted behavioral or other interventions for people with epilepsy and ID.

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7

Mood, anxiety, and perceived quality of life in adults with epilepsy and ID

Based on:

F.M. Snoeijen-Schouwenaars[a], J.S. van Ool[a], I.Y. Tan, A.P. Aldenkamp, H.J. Schelhaas[b], J.G.M. Hendriksen[b] (Submitted). Mood, anxiety, and perceived quality of life in adults with epilepsy and intellectual disability.

[a] Both authors contributed equally

[b] Joint senior authors

Abstract

Background: Depression and anxiety disorders are common among patients with epilepsy, but are relatively under-researched in patients with both epilepsy and intellectual disability (ID).

Aims: To investigate whether epilepsy and ID characteristics are associated with mood, anxiety and quality of life.

Methods and procedures: Adult patients with epilepsy and ID living at a tertiary epilepsy care facility were included (N=189). Mood, anxiety, and quality of life were assessed by standardized questionnaires. Epilepsy and ID characteristics were retrieved from patient charts or determined by psychometric instruments.

Outcomes and results: Elevated levels of depressive and anxiety symptoms were present in 21.7% and 12.7%, respectively. Anxiety was significantly associated with a focal epilepsy type and ID domain discrepancy (substantial difference between two domains of adaptive behavior), but was negatively related to seizure frequency and drug load of mood-stabilizing antiepileptic drugs. Depressive symptoms were not significantly related to epilepsy characteristics, but a severe ID and ID domain discrepancy was associated with more depressive symptoms. Quality of life was significantly worse in those with multiple seizure types and ID domain discrepancy.

Conclusions and implications: Whereas anxiety and quality of life are associated with individual epilepsy characteristics, this could not be confirmed for depressive symptoms in patients with epilepsy and ID, despite its high prevalence.

Introduction

Both depression and anxiety disorders are relatively common in patients with epilepsy. Pooled prevalence rates in this population are estimated at 22.9% and 20.2%,[1] which is much higher compared to the prevalence of depression and anxiety disorders worldwide (4.4% and 3.6%).[2] Although epilepsy relatively often co-occurs with intellectual disability (ID),[3] literature on the presence of mood disorders among patients with both epilepsy and ID is scarce, which might hamper the quality of care.

Depressive and anxiety symptoms can be associated with epilepsy for multiple reasons. They may have the same underlying neurobiological mechanism,[4] or result from epilepsy due to seizure-related or psychosocial factors, such as increased dependence, experienced stigma, restrained activity, and poor seizure control.[5,6] Results from a systematic review indicate that having an epilepsy diagnosis is associated with an increase of depressive symptoms in adults with ID, and that a severe form of epilepsy might be a risk factor for psychiatric disorders.[7] More specifically, Espie et al.[8] concluded that psychiatric symptoms were most strongly related to epilepsy characteristics, such as seizure frequency and severity. Studies comparing patients with ID and epilepsy to those without epilepsy might oversimplify the association between epilepsy and challenging behavior. This is because epilepsy is considered a very heterogeneous disorder with variability in localization, syndromes, etiology, seizure types and frequency, and treatment strategies often including polypharmacy in patients with ID.

Both depressive and anxiety symptoms can have a negative influence on daily functioning and quality of life in the population of people with epilepsy and ID, which is already known for their complex needs.[9] For example, in a study among adults with epilepsy and mild ID, it was found that psychological distress and seizure frequency were predictors of (health-related) quality of life.[10] The primary aim of this present study is to investigate whether epilepsy and ID characteristics are associated with depressive symptoms, anxiety, and social withdrawal, in adults with both epilepsy and ID. Our secondary aim is to describe associations between epilepsy and quality of life in a subset of adults with mild ID.

Method

Study design and participants

This study had a cross-sectional design and was part of the TRIANGLE study (The Relation between epilepsy, ID, And Neuropsychiatric comorbidities in a Group of patients in Long-term care for Epilepsy), which was conducted within the tertiary care

facility of Kempenhaeghe, The Netherlands. TRIANGLE is approved by the medical-ethical committee of Kempenhaeghe (No. 15.01) and the medical-ethical committee of Erasmus University medical center concluded that the rules laid down in the Medical Research Involving Human Subjects Act do not apply to this study (MEC-2016-408). The study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, October 2013). The inclusion criteria were: 1) age ≥ 18 years, 2) diagnosis of epilepsy according to the clinical definition by the ILAE,[11] 3) diagnosis of ID or current adaptive functioning at level of ID as evaluated by the individual's psychologist.

Instruments and procedure

Data with respect to mood and anxiety, quality of life, epilepsy characteristics, and ID were collected using various methods, which are specified below.

Mood and anxiety

Mood, anxiety, and social withdrawal were assessed using the Dutch version of the Anxiety, Depression and Mood Scale (ADAMS),[12,13] a by proxy measure that is specifically developed for people with ID. The ADAMS consists of 28 items which had to be rated by professional caregivers on a 4-point scale, ranging from never/no problem to often/severe problem. Whereas the original ADAMS includes five subscales (Depressive mood, Manic/hyperactive behavior, General anxiety, Social avoidance, and Obsessive/compulsive behavior), research on the Dutch translation of the ADAMS resulted in a four-factor structure as a more appropriate fit: Depressive mood, Anxiety, Social avoidance, and Other problems. The validity and reliability of this structure was investigated in two Dutch samples, one sample ≥ 50 years of age[12] and one adult sample below 50 years of age,[14] and was found to be fair to good. Higher scores on (sub)scales are indicative of more anxiety, social avoidance, or negative mood. The subscale 'Other problems' was excluded from the analyses, because of the substantial variability within the subscale.

In addition, information regarding the daily use of psychotropic medication and the history of psychiatric disorders were retrieved from the medical records.

Quality of life

The self-reported quality of life was assessed by using the Intellectual Disability Quality of Life questionnaire (IDQOL-16).[15] The IDQOL is a 16-item self-report questionnaire developed for people with a mild ID. Each (written) item is illustrated by pictograms and smileys in order to further clarify the question and response categories, which are based on a 5-point Likert scale varying from very unpleasant to very pleasant. The

items correspond to three domains of quality of life: psychological function, social functioning, and satisfaction about daily living. The IDQOL-16 was only administered among subjects with a mild level of ID, if administration of the test seemed feasible by the subject's psychologist (i.e., if the subject was likely to have sufficient verbal comprehension). During administration, the subjects were assisted by a psychologist who read the questions out loud or provided additional information (based on a document provided by the authors of the IDQOL-16) if needed. In previous studies, the IDQOL-16 domains were found to have fair to good internal consistency.[16,17]

Epilepsy characteristics

Epilepsy characteristics were retrieved from the subject's medical records and included the age at onset, epilepsy type, number of seizure types, number of seizures in the past year, the use and types of anti-epileptic drugs, and the etiology of epilepsy. The diagnosis of epilepsy was classified by a neurologist/epileptologist. Seizures were recorded by the nursing staff. Non-epileptic events, such as psychogenic non-epileptic seizures, were excluded. The epilepsy type and etiology was classified according to the most recent classification system by the International League Against Epilepsy (ILAE).[18] As a measure for drug load of AEDs with mood stabilizing properties, i.e. carbamazepine, valproic acid, and lamotrigine, the prescribed daily dose versus defined daily dose (PDD/DDD) ratio was calculated.[19] This was also calculated for benzodiazepines that were prescribed as AED, i.e., clobazam, clonazepam, diazepam, and dipotassium clorazepate. The DDDs were retrieved from the database of the WHO Collaborating Centre for Drug Statistics Methodology.[20]

Intellectual Disability

Regarding the ID, we examined the overall level of ID and the presence of an ID domain discrepancy. The level of ID was based on the three domains of adaptive deficits as described in DSM-5: the conceptual, social, and practical domain.[21] Each domain was assessed separately using standardized instruments and the results were converted into a classification of mild, moderate, severe or profound deficits. An ID profile was considered discrepant when there was a substantial intra-individual difference between two DSM-5 domains, indicating that one domain is considerably more or less deficient than the other(s). For more information regarding the assessment of level of ID and domain discrepancy, see Van Ool et al.[22]

Analyses

Descriptive statistics were calculated for the subscales of the ADAMS as well as Pearson correlation coefficients between subscales. Also, the most reported items and the

number of subjects having a score above the clinical cut-off for depressive symptoms (≥ 14) or anxiety (≥ 10) were calculated.[23]

Separate linear regression analyses were performed to examine direct associations between each epilepsy and ID characteristic and ADAMS subscale scores. Subsequently, multiple hierarchical regression analyses were performed in which predictors were added to the model in three steps. In the first step, demographic variables (age and sex) and the use of psychotropic drugs were entered, in the second step, level of ID and the presence of an ID discrepancy was added, and in the final model, the epilepsy characteristics were added. Model statistics as well as predictor statistics were examined. Associations between predictors and quality of life were assessed using Pearson correlation analyses and independent samples t-tests (or non-parametric alternatives if the variables do not meet the normality assumption). Results were considered significant if $p < .05$. All analyses were conducted in IBM SPSS Statistics version 24.

Results

Sample characteristics

A total of 240 patients were invited for the study, of whom 189 provided consent for the study (inclusion rate: 78.8%). The consent was provided by individuals and/or their legal guardian when appropriate. Participants were significantly younger than non-participants (mean difference = 6.04 years, $p = .015$) and were using psychotropic medication more often (41.8% versus 14.0% respectively, $p < .001$). Participants did not differ from non-participants with respect to level of ID or gender. Twenty-four subjects with a mild ID had completed the quality of life questionnaire.

The sample comprised 58.7% males and had a mean age of 47.9 years (SD = 15.6; range 18.3 - 85.9 years). The level of ID was mild in 20.1%, moderate in 30.7%, severe in 29.1%, and profound in 20.1%, and an ID domain discrepancy was present in 32.8%. Clinical characteristics are depicted in Table 7.1. The descriptive statistics of the ADAMS subscales are presented in Table 7.2. Elevated levels of depressive and anxiety symptoms were present in 21.7% and 12.7%, respectively. The subscales were moderately to highly correlated (Pearson r varying from .426 to .571, all *p*-values < .001). The ADAMS items that were reported most frequently, were: tense (74.1%), does not relax (70.9%), fatigued (64.6%), distracted (63.4%), and lacks energy (63.4%).

Table 7.1: Clinical characteristics of the study sample (N = 198).

Characteristics	Values
Age at onset of epilepsy (years)	Mdn = 2.0, IQR = 0–5.5, range 0–53
Infancy (< 1 yr)	32.8%
Childhood (1 - 12 yr)	54.0%
Adolesence (12 - 18 yr)	10.1%.
Adulthood (18+ yr)	3.2%
Epilepsy type[a]	
Generalized	10.6%
Focal	41.3%
Both generalized and focal	44.4%
Unknown	3.7%
Number of seizure types (semiology)[a]	Mean = 3.0, IQR = 1-4, range 0-8
Seizure frequency (last year)	Mdn = 70.0, IQR = 11.5–153.0, range 0–1206
Seizure-free	12.7%
Yearly	12.2%
Monthly	19.6%
Weekly	43.9%
Daily	11.6%
Etiology of epilepsy[a]	
Structural	28.6%
Generic	20.1%
Infectious	6.3%
Metabolic	1.1%
Unknown	43.9%
Daily use of anti-epileptic drugs	Mdn = 3.0, IQR = 2.5-4.0, range 0 – 6
Daily use of psychotropic drugs	41.8%
Psychiatric classification (DSM-IV)	20.6%

Note. [a] Based on ILAE 2017 criteria, Mdn = median, IQR = interquartile range.

Reliability analyses on the ADAMS subscales showed fair to good internal consistency (Cronbach's α = .757 to .850). Regarding the IDQOL, the psychological domain had a good internal consistency (α = .83). The domains about social functioning and satisfaction about daily living had, however, insufficient internal consistency (α = .50 and α = .58, respectively), and were therefore excluded from the analyses.

Table 7.2: Descriptive statistics of the ADAMS subscales.

	M	SD	Range	Above clinical cut-off[a]
Depressive symptoms	9.99	7.04	0–34	21.7%
Anxiety	4.73	3.73	0–15	12.7%
Social withdrawal	4.94	4.02	0–17	Not available

Note. [a] Based on cut-off values determined by Hermans & Evenhuis[23]

Table 7.3: Linear regression analyses predicting affective outcomes

	Unadjusted analyses			Adjustud analyses		
	B (SE)	**β**	***p***	**B (SE)**	**β**	***p***
Depressive symptoms						
Number of seizure types	0.14 (0.27)	.04	.596	-0.42 (0.38)	-.11	.270
Seizure frequency	0.19 (0.03)	.05	.531	0.03 (0.04)	.08	.884
Focal epilepsy	0.22 (1.67)	.10	.198	2.23 (1.58)	-.10	.160
Drug load mood-stabilizing AED	-0.91 (0.71)	-.09	.205	-0.59 (0.70)	-.06	.399
Drug load benzodiazepine AED	0.42 (0.81)	.04	.607	0.44 (0.80)	.04	.552
Use of rescue medication	-0.05 (0.05)	-.06	.379	-0.08 (0.06)	-.10	.183
ID discrepancy	2.79 (1.07)	.19	.010*	3.25 (1.13)	.22	.004**
Level of ID (severe/profound)	0.43 (1.03)	.03	.673	3.05 (1.22)	.22	.013*
Anxiety						
Number of seizure types	-0.04 (0.14)	-.02	.803	0.09 (0.19)	.04	.653
Seizure frequency	-0.03 (0.02)	-.15	.035*	-0.05 (0.02)	-.23	.006**
Focal epilepsy	1.74 (0.88)	.15	.050*	1.67 (0.78)	.14	.034
Drug load mood-stabilizing AED	-0.73 (0.38)	-.14	.053	-0.91 (0.35)	-.17	.009**
Drug load benzodiazepine AED	-0.06 (0.43)	-.01	.898	0.22 (0.40)	.04	.546
Use of rescue medication	-0.03 (0.03)	-.08	.254	-0.01 (0.3)	-.02	.788
ID discrepancy	1.82 (0.56)	.23	.001**	1.45 (0.56)	.18	.010**
Level of ID (severe/profound)	-0.72 (0.54)	-.10	.187	0.47 (0.60)	.06	.435
Social avoidnce						
Number of seizure types	-0.04 (0.15)	-.02	.790	-0.10 (0.22)	-.05	.669
Seizure frequency	-0.02 (0.02)	-.08	.269	-0.03 (0.02)	-.11	.260
Focal epilepsy	1.58 (0.94)	.12	.095	1.45 (0.93)	.11	.120
Drug load mood-stabilizing AED	-0.19 (0.41)	.03	.651	-0.00 (0.41)	.00	.998
Drug load benzodiazepine AED	-0.68 (0.46)	-.11	.138	-0.59 (0.47)	-.09	.212
Use of rescue medication	-0.01 (0.03)	-.02	.814	-0.00 (0.03)	.00	.998
ID discrepancy	1.48 (0.62)	.17	.017*	1.24 (0.66)	.15	.062
Level of ID (severe/profound)	-0.22 (0.59)	-.03	.702	0.76 (0.72)	.10	.289

Note. B=beta, SE=standard error, OR=odds ratio, CI=confidence interval, AEDs=antiepileptic drugs, ID=intellectual disability. [a] p < .1, * p < .05, ** p < 0.1, *** p < .001.

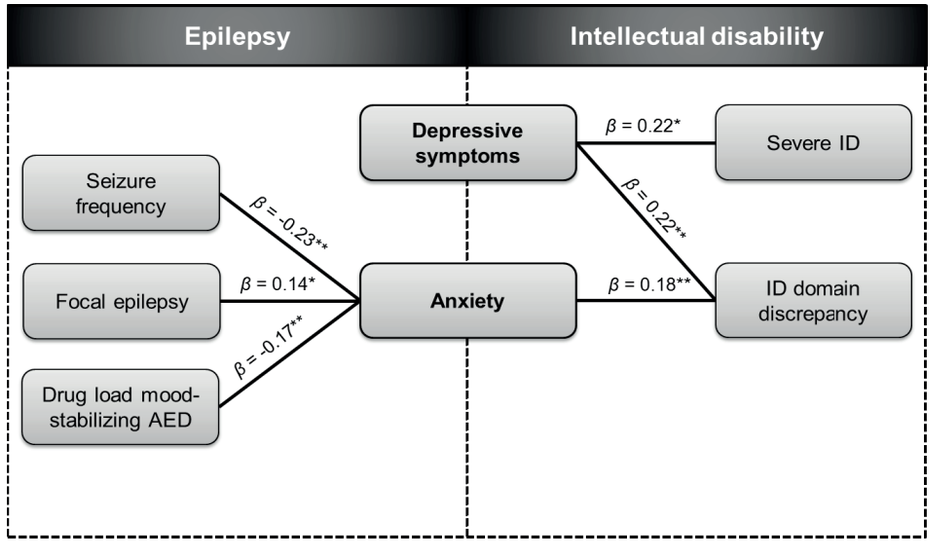
Associatons between epilepsy, ID, and mood and anxiety

Results of the linear regression analyses predicting depressive symptoms, anxiety, and social avoidance are presented in Table 7.3. The models yielded different results per outcome measure. For both depressive symptoms and anxiety, adding ID characteristics (level of ID and presence of ID domain discrepancy) resulted in a significant increase in explained variance (R^2 change = .053, p = .004 and R^2 = .033, p = .026, respectively). The introduction of epilepsy characteristics in the final model did not yield a significant increase in explained variance of depressive symptoms, but did for anxiety (R^2 change = .034, p = .301 and R^2 change = .087, p = .002, respectively). Hence, the final models

explained 20.0% of the variance in depressive symptoms (F = 3.86, p < .001) and 31.0% of the variance in anxiety scores (F = 6.95, p < .001). Regarding social avoidance, none of the epilepsy or ID characteristics in the final model were significantly associated with social avoidance, and adding these variables in the second and third step did not result in a significantly increase in explained variance (after entering ID variables: R^2 change = .014, p = .248; after entering epilepsy variables: R^2 = .037, p = .300).

Essentially, none of the epilepsy characteristics were related to depressive symptoms. However, having a more severe level of ID and the presence of an ID domain discrepancy were significantly associated with more depressive symptoms (p = .013 and p = .004, respectively). Anxiety levels were also significantly associated with the presence of an ID domain discrepancy (p = .010), but not with the level of ID. Regarding epilepsy characteristics, anxiety levels were significantly higher in subjects with focal epilepsy (p = .034). Lower levels of anxiety were significantly associated with a high drug load of mood stabilizing AEDs (carbamazepine, valproic acid, and lamotrigine) and a high seizure frequency (p = .009 and p = .006, respectively). See Figure 7.1 for an overview of statistically significant predictors.

Figure 7.1: Overview of significant associations between variables.



Note. β = standardized regression coefficient indicating the (small) effect size.

Post-hoc regression analyses were performed to investigate which ID domains were particularly poor in case of high levels of depressive symptoms and anxiety. Results of these analyses indicated that depressive symptoms were significantly higher when having a discrepancy at the expense of the practical domain (B = 3.42, SE = 1.54, p = .028), anxiety levels were mostly linked to a discrepancy at the expense of the social domain (B = 1.18, SE = 0.68, p = .086), and there was significantly more social avoidance when having a discrepancy at the expense of the social domain (B = 1.57, SE = 0.74, p = .035).

Self-reported quality of life

Spearman Rank correlation analyses were performed to investigate the associations between the IDQOL's subscale psychological functioning and number of seizure types, seizure frequency, and the PDD/DDD ratio of mood stabilizing AEDs (see Table 7.4). There was a strong, negative association between the number of seizure types and the reported quality of life with respect to psychological functioning (rho = -.551, p = .005). Although not statistically significant, there was a medium association between quality of life and seizure frequency (rho = -.349) and PDD/DDD ratio of mood stabilizing AEDs (rho = .312), with a higher frequency related to a poorer quality of life and a higher drug load of mood stabilizing AEDs related to a greater quality of life. In addition, subjects who had an ID domain discrepancy reported a significant poorer quality of life than subjects without a discrepancy (difference in medians = 3.0, p = .020). There was no association between seizure type and quality of life. Also, correlation analyses between ADAMS subscales and IDQOL psychological functioning yielded no significant associations (Spearman's rho varying from -.224 to - .016, all p values < .05).

Table 7.4: Associations between epilepsy characteristics and quality of life.

	Quality Of Life - psychological functioning	***p***
Number of seizure types	Spearman r = -.551	.005**
Seizure frequency	Spearman r = -.349	.094
Drug load mood AEDs	Spearman r =.312	.138
Both focal and generalized epilepsy		.423
Yes	Mdn = 20.5, IQR = 19.0 – 24.3	
No (only focal)	Mdn = 20.0, IQR = 18.0 – 22.0	
ID discrepancy		.020*
Yes	Mdn = 22.0, IQR = 19.0 – 23.0	
No	Mdn = 19.0, IQR = 11.5 – 20.0	

Note: AEDs = antiepileptic drugs, ID = intellectual disability, Mdn = median, IQR = interquartile range.

Discussion

Depressive and anxiety symptoms are a relevant and important issue among patients with epilepsy and ID, as 21.7% and 12.7% of them show evidence for a mood or anxiety disorder. This rate of depressive symptoms is in line with the pooled prevalence of depression estimated at 22.9% for patients with epilepsy in general.[1] However, the results of our study suggests that the prevalence of anxiety is less pronounced in patients with both epilepsy and ID as compared to the pooled prevalence of anxiety disorders (20.2%) in the general population of patients with epilepsy.[1]

The associations between epilepsy and ID characteristics in relation to mood and anxiety were different per affective outcome. Epilepsy was significantly associated with anxiety in both positive as well as negative directions. After adjusting for demographics and other predictors, higher levels of anxiety were associated with having a focal epilepsy type, whereas lower levels of anxiety were associated with a high drug load of mood stabilizing AEDs and, surprisingly, a high seizure frequency. Although we did not have information about the localization of the epilepsies in our sample, the link between focal epilepsy and anxiety has also been described in previous studies[24,25] and might be explained by the involvement of temporal brain structures in many patients with epilepsy and anxiety.[26,27] In addition, focal epilepsies (in other structures) may include focal seizures without impaired awareness of which the conscious experience might be more frightening for someone or lead to a fear of injury.

Remarkably, anxiety appeared to be inversely related to a higher seizure frequency, even when the use of benzodiazepines as AED (daily or as rescue medication) was taken in to account. This is in contrast with recent findings by Dehn et al.,[28] who demonstrated that a higher seizure frequency was significantly correlated with anxiety in patients with difficult-to-treat epilepsy (but without cognitive impairments) admitted to an epilepsy center. This difference might be explained by the fact that all our patients are living at a tertiary epilepsy center and that their seizure frequency is higher than in the study by Dehn et al.[28] It could be hypothesized that the patients are therefore more habituated to having seizures and to its consequences in daily life. Also, professional caregivers who are specialized in epilepsy are always in close proximity, and provide patients with seizures with care and attention. Such environmental factors were beyond the scope of this study, but should be included in future research.

Despite a relative high number of patients having elevated levels of depressive symptoms, none of the epilepsy characteristics were found to be significantly associated with depressive symptoms or social withdrawal. This seems to conflict with some studies on epilepsy and depression in patients without ID, suggesting that depression is associated with epilepsy-related characteristics.[28,29] However, a review study by Hoppe and Elger[30] concluded that the overall evidence is weak if stress-

related epilepsy factors, such as social stigma, are taken into account. A social stigma might be less prominent in this sample, as they all live together with other patients with epilepsy and are therefore less "distinguished" from other members of the society. Furthermore, knowledge about the pathogenic mechanisms in the relationships between epilepsy, depression, and anxiety has been increasing.[31] Future research is necessary to determine to what extent the underlying pathophysiology of epilepsy, depression, and anxiety applies to people with ID.

Irrespective of the epilepsy, this study demonstrated that ID characteristics were significantly associated with depressive and anxiety symptoms. With respect to the association between a more severe level of ID and depressive symptoms, it should be considered that the corresponding ADAMS subscale consists of several somatic symptoms. People with a more severe ID and epilepsy often are part of a frail population with multiple health problems,[32] which might imply an increased vulnerability in this subgroup. Individuals who had an ID domain discrepancy, indicating that one domain of adaptive functioning is considerably more or less deficient than the other(s), had significantly higher depressive and anxiety levels than those without. Especially the practical and social abilities were more impaired in those with more depressive symptoms and anxiety, respectively. Although this concept of discrepancy requires further investigation, one could hypothesize that people with an ID domain discrepancy might be confronted with their (physical) limitations or are at risk of being overestimated by others, which may lead to feelings of frustration or stress.

Finally, despite the small subsample size, our findings confirm that a more severe epilepsy is associated with poorer quality of life regarding the domain of psychological functioning, which seems to emphasize the burden of epilepsy in their daily life. The quality of life was also significantly poorer in those with an ID domain discrepancy. There was, however, no direct association between the self-reported quality of life and the depressive and anxiety levels. This might be due to measurement techniques, such as the difference in information source (self-report versus report by proxy) and the time span (current situation versus past six months). Although the representativity of our sample is limited to patients with primarily severe epilepsy who lived in a residential care setting, this study emphasizes the relevance of depressive and anxiety symptoms in patients with epilepsy and ID. Whereas anxiety and perceived quality of life are associated with individual epilepsy characteristics, this could not be confirmed for depressive symptoms in patients with epilepsy and ID, despite its high prevalence. The epilepsy and ID characteristics identified as predictors of depressive symptoms and anxiety can help professionals working with this vulnerable population in the anticipation of such comorbidities and may contribute to good clinical care.

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8

Psychogenic nonepileptic seizures in adults with epilepsy and ID

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Abstract

Purpose: To describe the main characteristics of psychogenic nonepileptic seizures (PNES) in adults with epilepsy and intellectual disability (ID), and to analyse the differences regarding psychosocial functioning, epilepsy severity and ID between patients with PNES and a control group without PNES.

Methods: Medical records of adults with ID and epilepsy living at an epilepsy care facility (N = 240) were screened for PNES and evaluated by a neurologist. A control group consisting of patients with epilepsy and ID, without PNES, was matched according to age, sex and level of ID. Characteristics of PNES and epilepsy were provided by the subject's nursing staff or retrieved from patient charts, psychosocial data were collected by standardised questionnaires and level of ID was individually assessed using psychometric instruments.

Results: The point prevalence of PNES was 7.1%. The patients with PNES (n = 15) were most often female and had a mild or moderate level of ID. Compared to controls, they showed more depressive symptoms, experienced more negative life events and had more often an ID discrepancy (ID profile with one domain particularly more impaired than another). Stress-related triggers were recognised in a large majority by the nursing staff.

Conclusion: PNES appears to be a relatively rare diagnostic entity among inpatients with both epilepsy and ID. However, the complexity of diagnosing PNES in this population, and the similarities in stressrelated triggers for PNES in patients with and without ID, suggest that PNES may be underdiagnosed in the ID population. Diagnostic challenges of PNES and, as subcategory, reinforced behavioural patterns are discussed.

Introduction

Psychogenic non-epileptic seizures (PNES) are defined as sudden and involuntary paroxysmal events that resemble epileptic seizures, but are not induced by an organic cause. In addition, there is positive evidence or it is strongly suspected that the events are related to a psychogenic cause. These events can involve changes in behaviour, motor activity, sensation, cognitive processing, or autonomic function.[1,2] The term PNES can be misleading, as one not only needs to exclude epilepsy, but also other organic causes that can lead to a similar semiology.

The diagnosis of PNES consists of a two-phase process, of which the patient needs to be informed as soon as possible. First, organic causes, including especially epilepsy, have to be excluded as a cause of the seizures. Epilepsy may coincide with PNES, however, and it is necessary to determine whether or not the paroxysmal event can be attributed to epilepsy. The gold standard for excluding epilepsy is video-EEG monitoring of a characteristic seizure that does not show the electrographic discharges seen during an epileptic seizure.[2,3] In the second phase, psychological aetiologies that cause the paroxysmal events must be assessed. The highest level of certainty, "documented PNES", is reached when a non-epileptic seizure with semiology typical to PNES is captured on video-EEG, along with a patient history of psychosocial characteristics consistent with PNES.[2] As this certainty level cannot always be reached, for example because of limited access to video EEG, the recognition of PNES with a lower level of certainty (i.e., "possible", "probable", or "clinically established") also becomes relevant.

PNES is considered to be a multifactorial biopsychosocial disorder;[4] many psychosocial and biological factors have been described that contribute to its development or prolongation.[1,5] Studies have shown that the majority of patients with PNES are female (75%) and report previous trauma (up to 70%); also, a history of co-morbid psychiatric or psychosocial problems is common.[2]

PNES are also recognised among patients with ID.[4,6,7] A below average intelligence quotient (i.e. IQ < 85) might be a risk factor for PNES,[8] although it remains unclear whether this study also included patients with ID (IQ < 70). There is limited evidence regarding the presentation and incidence of PNES in this subpopulation, as patients with ID are often excluded from studies. Duncan and Oto[9] compared patients with PNES with and without ID and concluded that a diagnosis of epilepsy, the use of anti-epileptic drugs, episodes of psychogenic nonepileptic status, and situational or emotional triggers were more prevalent among those with ID. Sexual abuse seemed to be more frequent among those without ID. Another theory suggested that PNES in people with ID manifests less profoundly as an emotional conflict, but more as a reinforced behavioural pattern, which can be considered a subcategory of PNES. By

exhibiting this reinforced behavioural pattern a secondary gain is reached, such as receiving attention or avoiding demands or unpleasant situations.[10] By producing seizure-like events that are paradoxically reinforced by caregivers, these patients may have unconsciously and unintentionally learned how to control the environment. This idea was elaborated upon in a study by Magudda et al.,[11] who described characteristics of a patient group with mild ID. Remarkably, this subgroup developed PNES after a decrease in epileptic seizure frequency. All of these patients had early-onset epilepsy, for which caregivers probably provided much attention. The authors hypothesise that the decrease in epileptic seizure frequency or cessation of epilepsy might have led to a loss of this advantage, after which the epileptic seizures had been substituted by PNES. Baslet et al.[6] identified a subgroup of PNES patients who presented with neurological impairments and ID, but showed less severe psychiatric impairment. Psychopathology, including depression, anxiety and somatic distress, was often present, however.

The aims of the present study are twofold: (1) to describe (clinical) characteristics of PNES in adults with ID and epilepsy, and (2) to compare epilepsy severity and psychological and behavioural characteristics between those with PNES and a matched control group without PNES, all with epilepsy and ID.

Methods

Participants

Electronic charts of adult patients living at the residential care facility of Kempenhaeghe, a tertiary epilepsy centre in The Netherlands, were screened for evidence of non-epileptic events between January 2014 and December 2016. Only those who met the following criteria were included: impaired intellectual functioning (IQ < 70), age ≥ 18 years, and diagnosis of PNES following evaluation by a neurologist and, when necessary, other medical specialists. Those with PNES must have had more than one seizure-like event in the past two years, which had to include a hypothesised behavioural or psychosocial component. Seizures with an organic cause were excluded. In this article we consider the reinforced behavioural pattern as a subcategory of PNES. Our screening of 240 eligible patients yielded 17 patients with PNES (7.1%). As two patients did not provide consent for the study, a total of 15 subjects with PNES were included in the final analyses.

A control group consisting of 15 patients with epilepsy and ID, without PNES, was matched according to age, sex, and level of ID. For each PNES subject, all matching patients were identified and one of the possible matched was randomly automated selected.

Instruments and procedure

This cross-sectional, observational study is part of the TRIANGLE study (The Relation between epilepsy, ID, And Neuropsychiatric comorbidities in a Group of patients in Long-term care for Epilepsy). TRIANGLE is approved by the local ethical committee of Kempenhaeghe (No. 15.01). All subjects or legal representatives (if appropriate) provided consent for the study.

All information regarding PNES was collected through a questionnaire completed by the subject's nursing staff (see Appendix 1). This questionnaire was created by a research team including a health care psychologist, psychotherapist and neurologist. Both objective (e.g., frequency, time and location, and injuries as a result of PNES) as well as subjective characteristics (e.g., suspected triggers and impact on daily life) were addressed.

The level of ID was diagnosed according to DSM-5 in terms of mild, moderate, severe or profound.[12] Each ID domain, i.e., conceptual, social and practical, was assessed separately using an abbreviated version of the Wechsler Adult Intelligence Scale – fourth edition[26] and the Vineland-II subscales Socialization and Daily Living Skills.[14] A significant difference between domains was considered to be an ID domain discrepancy (for more information regarding this method, see Van Ool et al.[13]

The severity of epilepsy was determined using the Epilepsy Impact Scale Kempenhaeghe (EPIEK),[15] which is based on five aspects: seizure frequency, number of anti-epileptic drugs, use of emergency anti-epileptic drugs, use of protective measures for epilepsy, and adjustments in the subject's daily schedule after a seizure. The relevant information was retrieved from the subject's medical records. The EPIEK yields an epilepsy severity score ranging from 0-10, a higher score indicating a more severe form of epilepsy.

For the assessment of depressive symptoms, anxiety symptoms, aggressive/destructive behaviour, and life events, three standardised questionnaires were administered among the subject's nursing staff. Depressive and anxiety symptoms were assessed using the Anxiety, Depression, And Mood Scale (ADAMS)[16,17] and aggressive/destructive behaviour was assessed using the Behavior Problems Inventory (BPI),[18,19] higher scores reflecting more severe symptoms or behaviour. Both the ADAMS and BPI have been validated among people with ID.[17,18] The number of life events in the past year was calculated using the Checklist Life Events (CLE).[20,21]

Analyses

First, clinical characteristics of PNES are described. The correlation between frequency of PNES and epileptic seizures in the past year was examined using Spearman's rank

correlation analysis. As neither variable met the criteria for a normal distribution, a log-transformation was performed prior to the analysis. Second, differences between subjects with PNES and the control group are analysed with statistical analyses appropriate for case-control studies, i.e., paired T-test or Wilcoxon signed rank test for continuous variables and McNemar's test for dichotomous variables. All analyses were conducted two-tailed, with *p* values <.05 considered statistically significant.

Results

The age of PNES subjects ranged from 19.3 to 70.6 years (mean = 46.6 years, SD = 15.6) and did not differ from the controls (mean = 45.9, SD = 15.2, *p* = .588). The majority were of female gender (66.7%) and had a mild or moderate level of ID (33.3% and 40.0%, respectively). All subjects had had at least one seizure in the past year and were prescribed daily anti-epileptic drugs.

PNES characteristics

The PNES diagnosis was based on video-EEG in 53.3%, on video evaluation by a neurologist in 13.3%, and on history-taking in the remaining cases. In 80% of subjects, the semiology of PNES showed similarities with an epileptic seizure type which the subject also regularly presented. Most common were tonic-like, tonic-clonic-like and absence-like seizures. PNES started during adulthood in two-thirds of cases; in the majority (80.0%), PNES occurred at various times of day and at various locations. There were, however, subjects who showed PNES only in the morning (n=1), only at night (n=1), or only in the evening (n=1). In only three cases did the PNES occur at the subject's residence. The frequency of PNES was mostly weekly (40.0%) or monthly (40.0%); the remaining three subjects exhibited PNES (almost) daily. Patient files showed that epileptic seizures were recorded more frequently than PNES in 73.3% cases. There was a tendency towards a negative association between the frequency of PNES and epileptic seizures (Spearman's r = -.453, p = .090).

A psychiatrist was involved in the clinical care of over half the subjects (53.3%); 26.7% had an comorbid psychiatric diagnosis. Also, daily use of psychotropic medication for treatment of psychiatric, psychological or behavioural problems was common (53.3%). According to the nursing staff, triggers for PNES were identified in the majority (86.7%). These triggers involved stress, negative mood, unexpected events, (over)demanding situations and overstimulation. The nursing staff responded to PNES by ignoring the seizure or distracting the patient in 53.3%. In other cases they soothed the patient, tried to start a conversation or responded as they would to an epileptic seizure. Small injuries as a result of PNES were reported in 26.7%; the PNES had an impact on daily life in 60.0% of subjects. Clinical characteristics of the PNES group are described in Appendix 8.2.

Table 8.1: Differences between PNES and control group.

Characteristics	PNES		Control group		*P* value
Epilepsy severity	M = 6.93	SD = 1.33	M = 5.80	SD = 3.00	n.s.[a]
Depressive symptoms	M = 12.87	SD = 8.33	M = 6.53	SD = 4.60	< .05[a]
Anxiety symptoms	M = 5.53	SD = 4.41	M = 3.87	SD = 2.97	n.s.[a]
Negative life events	Mdn = 4	IQR = 2–7	Mdn = 2	IQR = 1–2	< .01[b]
Aggressive behaviour	Mdn = 2	IQR = 0–7	Mdn = 1	IQR = 1–4	n.s.[b]
Daily use psychotropic drugs	53.33%		26.67%		n.s.[c]
Comorbid psychiatric diagnosis	26.67%		13.33%		n.s.[c]
Psychiatrist involved	53.33%		13.33%		< .10[c]
ID domain discrepancy[d]	66.67%		13.33%		< .05[c]

Note. [a]Paired T-test; [b]Wilcoxon signed rank test; [c]McNemar's Test. [d]A discrepancy indicated a significant intra-individual difference between two out of three domains of adaptive functioning (conceptual, social, or practical domain). PNES = (Psychogenic) nonepileptic seizures; ID = Intellectual disability; M = Mean; SD = Standard deviation; Mdn = Median; IQR = Interquartile range; n.s. = not significant.

PNES subjects versus controls

Associations with respect to epilepsy severity and psychological characteristics between the PNES and control group are presented in Table 8.1. Of the continuous variables, the number of negative life events and the severity of aggressive/destructive behaviour did not meet the normality assumption. Therefore, Wilcoxon signed rank tests were performed as non-parametric alternative of paired T-tests.

Both the PNES and control group had had at least one epileptic seizures in the past year and were using anti-epileptic drugs on a daily basis. The epilepsy in both groups was severe, with a median severity score of nearly 7 in the PNES group and 6 in the control group using a scale from 0 to 10 (not statistically significant). The PNES group differed from the control group with respect to psychological characteristics. Paired T-tests indicated that PNES subjects had significantly more depressive symptoms than controls (mean difference = 6.3, $t(14)$ = 2.39, p = .031). Although they also had a higher mean score on anxiety symptoms and a higher median score on aggressive behaviour, these differences were too small to reach statistical significance (p = .212 and p = .529, respectively). Furthermore, PNES subjects had experienced significantly more negative life events in the past year (Z = -2.61, p = .009), such as major injuries, decline

in mobility and severe illness or death of a friend or family member. The history of critical life events at an earlier age was unknown for most subjects, as well as possible traumas. There was a trend indicating that a psychiatrist was more frequently involved in the care of PNES subjects compared to the control group (p = .070). PNES subjects also had an ID domain discrepancy (p = .013) more often than controls, which was usually at the expense of social or practical adaptive skills (50% and 40%, respectively). A higher percentage of PNES subjects used psychotropic drugs (53.3% versus 26.7%) and had a comorbid psychiatric diagnosis (26.7% versus 13.3%; e.g., autism spectrum disorder, depression), although these differences did not reach statistical significance (p = .289 and p = .625, respectively).

Discussion

In this study on PNES in patients with epilepsy and ID, we found that two-thirds of our PNES sample was female, which is in line with the general findings on PNES in people without ID.[2] The semiology of PNES was heterogeneous and included mostly tonic-clonic-like, tonic-like, or absence-like seizures. Often, the semiology showed similarities with one of the epileptic seizure types of the patient. As this research took place in a tertiary epilepsy centre, all subjects had active epilepsy (all had had at least one seizure in the past year).

In line with the literature on PNES in people without ID, the patients in our sample showed psychosocial vulnerabilities as well. The triggers for PNES that were identified by the nursing staff (in 87% of cases) included mostly stress-related situations, such as unexpected events, (over)demanding situations, and overstimulation. Another risk factor was a depressive mood. The relevance of psychosocial aspects, possibly in the development of PNES, is confirmed by the findings of our case-control study: patients with PNES had higher levels of depressive symptoms and had experienced more negative life events (medians 4 versus 2), which could relate to trauma (recollections). Patients with PNES also had significantly more often an ID domain discrepancy (67% versus 13%), in which the person had relatively poorer skills on one domain of adaptive functioning compared to another domain. This indicates that professionals should be aware of the risk of overestimating the person in order to avoid (over)demanding situations. Furthermore, the PNES group also had higher rates of comorbid psychiatric diagnoses, involvement of a psychiatrist in their clinical care (because of psychological or behavioural problems), and daily use of psychotropic medication than the control group, although statistical significance was not reached.

There seemed to be a tendency towards a negative association between the frequency of PNES and epilepsy, although only inter-individually. This might be in accordance with results from Magudda et al.,[11] who described that patients with a

mild ID developed PNES after a decrease in epileptic seizure frequency. They suggest that this decrease might have led to a reduction in attention received from caregivers, and in order to compensate for this loss of advantage, patients subconsciously learned to display PNES instead. When the epilepsy severity between those with and without PNES was compared, the difference was not statistically significant in our study. There were some patients who only showed PNES at a particular location or time of day, which might indicate that there was a situational trigger. Such situational triggers were found to be more prevalent among patients with ID in previous research.[9] PNES in this patient group may be characterised by a behavioural pattern that is reinforced by the environment in some patients, especially in those with a situational trigger or low epileptic seizure frequency. This reinforced behavioural pattern should not be confused with intentional simulation, however. To further investigate this theory, more extensive longitudinal research is necessary, including clinical observations of antecedents and consequences of PNES and an assessment of coping style. Although the subjects came from one tertiary care facility, which increases homogeneity and reliability of data sampling, they constituted a small sample size and hence poor statistical power.

In our study sample, the PNES diagnosis was confirmed by video-EEG in about half of the patients and by video evaluation by a neurologist in 13%, which means that a substantial number of subjects had an "unconfirmed" diagnosis of PNES. The level of certainty of PNES according to LaFrance et al.[12] was difficult to assess in this sample. In some cases, the non-epileptic event was captured on video EEG, but the history of psychosocial factors consistent with PNES was questionable, for example because valid and reliable instruments to assess psychological aspects in people with ID are limited and people with ID themselves are less capable of reliably noticing or explaining psychosocial aspects. In other cases, the PNES semiology was positively evaluated by a neurologist and psychosocial triggers were identified, but a video EEG assessment was not considered feasible by the multidisciplinary team, because of the relatively low frequency of PNES and potential burden for the – often vulnerable – patient. As all of our subjects also had active epilepsy, results on (video-)EEG showed epileptiform activity in most cases which complicated the differential diagnosis. Although clinical decisions on the care for people with ID should always take into account the potential burden for the patient, a comprehensive assessment of suspected PNES is important to prevent over- or undertreatment, especially given the reported impact on daily life in the majority of patients in our study.

The point prevalence of 7.1% we found is clearly below reported diagnostic rates of PNES in the general population, varying from 12% to 30% for patients referred to a tertiary epilepsy centre.[22,25] Nor does it match the evidence from Reuber et al.,[8] suggesting that an IQ below average is a risk factor for PNES. Perhaps this risk factor

does not apply to our patient population who predominantly had a more severe level of ID. Other explanations rather than a very low IQ for the low prevalence might be the diagnostic challenges with respect to non-epileptic events, the retrospective nature of this study, or difficulties in the differentiation between PNES and epilepsy in individuals with ID, which have been observed in previous studies.[23,24] As a more severe level of ID is associated with a more severe epilepsy,[13] PNES may have been "overshadowed" by epilepsy. To address these issues, future research should use a prospective study design and include outpatients with ID. Considering the very low number of subjects and incomplete diagnostic processes in our study, the significant differences between patients with and without PNES are remarkable and emphasize that our PNES sample is a distinct subgroup.

Conclusion

This clinical study describes the main characteristics of PNES among inpatients with ID and epilepsy, a neglected and vulnerable subpopulation. An important diagnostic challenge includes the difficult differentiation between PNES and somatic or behavioural comorbidities, overshadowing by severe epilepsy (and therefore PNES may not be recognised or misinterpreted by caregivers), and the limited tools available to assess psychogenic factors as psychological aetiologies for non-epileptic seizures that are appropriate for people with ID. This emphasizes the importance of a multidisciplinary approach, involving health professionals who are experienced in working with people with epilepsy and ID. Professionals should be aware of the possibility of PNES in people with ID and the similarities with the adult PNES population without ID, including a female predisposition, psychological or psychiatric comorbidities and (traumatic) life events. Cases with PNES usually had a mild or moderate ID and an ID domain discrepancy. Especially in those with a more severe level of ID and/or impaired social-emotional functioning, a reinforced behavioural pattern might also be considered as a subcategory of PNES. Enhanced diagnostics of PNES in patients with ID is important for the development of a systematic approach to detect PNES and to provide evidence-based treatment.

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Appendices

Appendix 8.1: Questionnaire on (suspected) psychogenic non-epileptic seizures (PNES).

1. Are PNES suspected in the patient? If so, how is PNES presented?

_____

2. How is the PNES diagnosed?
☐ Diagnosis based on video-EEG
☐ Diagnosis based on video evaluation by neurologist
☐ Probable diagnosis by neurologist (based on secondary observations and history taking)
☐ PNES is only suspected

3. At what age did PNES occur for the first time?
☐ During childhood (age 0-11)
☐ During adolescence (age 12-17)
☐ During adulthood (age 18+)

4. What is the suspected aetiology of PNES?

_____

5. At what time of day do PNES occur?
☐ Especially in the morning
☐ Especially in the afternoon
☐ Especially in the evening
☐ Especially at night
☐ At a specific time of day: _____
☐ At variable times of day

6. In what situations do PNES occur?
☐ At home/in the residence
☐ Outside
☐ During daytime activities
☐ In public spaces
☐ Elsewhere: _____
☐ At variable locations

7. How often do PNES occur?
☐ Daily
☐ Weekly
☐ Monthly
☐ Yearly

8. Has there been a time period at which PNES occurred more or less frequently than usual? If so, have there been any special/unusual circumstances during that time period?

_____

9. Are there any triggers for PNES identified? If so, what are these triggers?

_____

10. What is the semiology of PNES?

_____

11. Do PNES cause injuries?
☐ No
☐ Yes, occasionally there are minor injuries (at least 1)
☐ Yes, regularly there are minor injuries
☐ Yes, occasionally there are severe injuries (severe = treatment by doctor was necessary
☐ Yes, regularly there are severe injuries

12. In what way does the nursing staff respond to PNES?

_____

13. What is the impact of PNES for the patient's daily life?
☐ No impact
☐ Minor impact
☐ Severe impact

14. Is there a treatment plan for PNES?

_____

Appendix 8.2: Clinical characteristics of subjects with PNES.

	Gender	Level ID	PNES onset	PNES frequency	Epilepsy seizure frequency (last year)	PNES semiology	Psychiatric diagnosis	> clinical cut-off for anxiety or depression	Negative life events
1	Female	Moderate	Adulthood	Weekly	56	Shaking arms and legs, raised arms, yelling, falling	None (but psychiatrist involved)	Depression	Minor and major injury
2	Male	Severe	Adulthood	Monthly	341	Stretching arms, one at the time, while making eye contact	None (but psychiatrist involved)	None	None
3	Female	Moderate	Adulthood	Weekly	25	Falling close to another person, cramped upper body while making eye contact	None (but psychiatrist involved)	Depression and anxiety	New housemate, menopause, decline in vision/hearing, decline in mobility, conflict with housemate, change in daytime activities, loss of daytime activities
4	Female	Moderate	Adolescence	Daily	5	Falling, moving around in circles on floor, foetus position, abnormal swallowing, making noises	None (but psychiatrist involved)	None	Structural change in staff, new housemate, conflict with housemate
5	Female	Mild	Adulthood	Daily	2	Shaking body movements, asymmetric arm movements	Multiple Complex Developmental Disorder	Depression	Structural change in staff, new housemate, minor injury, loss of valuable things, conflict with housemate
6	Female	Severe	Adulthood	Monthly	154	Blinking eyes, eyes turn away	None	None	Structural change in staff, severe illness of friend or family, death of friend or family, change in visits from friends or family, sexual problems, conflict with housemate, conflict with family or staff member
7	Male	Mild	Adolescence	Daily	204	Making noises, waving head, falling, shaking arms	Autism, ADHD	None	Structural change in staff, new housemate, minor injury, decline in mobility, sexual problems
8	Female	Moderate	Childhood	Weekly	29	Shaking arms, trembling, yelling, falling	Depression	None	Structural change in staff, conflict with housemate, conflict with family or staff member, sexual problems
9	Female	Mild	Unknown	Monthly	85	Yelling, major movements	None	Depression and anxiety	Structural change in staff, new housemate, minor and major injury, decline in mobility, decline in vision/hearing, conflict with housemate, conflict with family or staff member
10	Female	Moderate	Adulthood	Weekly	247	Decreased consciousness, along with automatisms	None	Depression and anxiety	Decline in mobility, conflict with housemate, conflict with family or staff member, sexual problems
11	Female	Severe	Unknown	Monthly	234	Staring, sometimes along with falling	None	None	None
12	Male	Severe	Adulthood	Monthly	86	Stretching arms and legs, after staring into lights. (Note: photosensitive epilepsy is excluded)	None	None	Structural change in staff, minor and major injury, decline in mobility
13	Male	Moderate	Adulthood	Monthly	86	Disorganised consciousness, sometimes along with movements in arms	None (but psychiatrist involved)	None	Major injury, conflict with housemate
14	Female	Mild	Adulthood	Weekly	52	Tapping with hand, shaking arm	None	None	Minor injury, financial problems, severe illness of friend or family, death of friend or family, conflict with family or staff member
15	Male	Mild	Adulthood	Weekly	14	Fidgeting, blinking eyes, trembling 1 leg, shaking arm	Depression	None	Minor and major injury, decline in mobility, severe illness of friend or family, death of friend or family, conflict with housemate, conflict with family or staff member

9

General discussion

The overall aims of the studies presented in this dissertation were to:

1. contribute to a better understanding of neuropsychiatric comorbidities in adults with epilepsy and ID by investigating associations between neuropsychiatry and epilepsy and ID characteristics;
2. contribute to multiple aspects of the diagnostic processes in people with epilepsy and intellectual disability (ID).

This chapter provides an overview of the main findings, evaluates the methodology of the studies and discusses the implications for clinical practice as well as for future research.

Diagnostic processes: filling the gaps

Diagnostics are an important aspect within the care for people with epilepsy and ID. The comprehensive diagnostics of epilepsy and ID (including differential diagnosis) are essential for an accurate diagnosis and adequate treatment plan. Not only epilepsy and ID require thorough examination, also the frequently noted comorbidities in this population deserve proper attention, including medical, physical, cognitive, and behavioral comorbidities.[1,2] Accurate diagnoses regarding the different aspects of ID, epilepsy and comorbidities are a prerequisite for adequate care and treatment of these patients.

Diagnosis of ID

Worldwide, ID is often diagnosed using classification systems such as DSM[3] or ICD.[4] In both classification systems, the diagnosis of ID is accompanied by a severity classification based on impairments in adaptive functioning: mild, moderate, severe or profound. The diagnostic criteria of ID as described in the DSM are revised in 2013[3] and formally implemented in the Dutch care system in 2017. These revisions include a severity classification on three specific domains of adaptive functioning: conceptual, practical and social. Each of these domains should be assessed using standardized tests along with clinical information.

Assessment of each ID domain

In chapter 2, we measured each domain of adaptive functioning in a Dutch sample of adults with epilepsy and ID. The practical and social domains were addressed with the Dutch version of the Vineland-II subscales Daily living skills and Socialization, respectively. With conceptual intelligence ("IQ") being considered a measure of

conceptual skills,[5] the conceptual domain was determined preferably by results of intelligence tests, with alternatives for individuals with a more severely impaired intellectual functioning. Combining the three domains, our results showed that most adults with epilepsy had moderate or severe deficits in adaptive functioning, and that the severity of deficits was significantly associated with a more severe and refractory epilepsy, including a higher seizure frequency, mixed seizure types, having both generalized and focal epilepsy, and an earlier age at epilepsy onset. Whereas it is well known that the prevalence of epilepsy increases with the severity of ID,[6] the increase in epilepsy severity among people with severe ID is less well documented. This subgroup might reflect a large number of patients with epileptic encephalopathy, which is often accompanied by developmental slowing or regression.[7] Causal inferences cannot be made, as both severe epilepsy and ID are usually caused by a severely affected brain or brain networks, or have the same underlying cause, such as genetically determined syndromes.[8] Longitudinal research of epilepsy characteristics is needed to clarify the long-term impact on aspects of cognitive and adaptive functioning, while taking into account the etiology of epilepsy.

The downside of comprehensive diagnostics is that the individual assessments can be intensive, time-consuming, and a burden for patients and their family. In people with ID and/or epilepsy, the individual intelligence assessment might lead to frustration or fatigue, or might be affected by seizure activity and medication side-effects, which can affect the validity and reliability of the test outcome. Briefer methods for estimating global intelligence might be desirable in some situations, in particular when reassessing patients for screening or rehabilitation purposes or in research settings. The most commonly used intelligence tests available in the Dutch language are the Wechsler Intelligence Scale for Children-Third Edition (WISC-III)[9] and the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV),[10] each consisting of ten core subtests. In chapter 3, multiple short forms (including three to five subtests) of the WISC-III and WAIS-IV were created and the psychometric properties between the versions were compared in large samples of children and adults with neurological disorders. Several short forms appeared to have good reliability and met the minimal criteria set for acceptability.[11] Additional analyses were performed on subsamples of children and adults who were either in the low to borderline category (full scale IQ < 80) or in the average to high category (full scale IQ ≥ 80), which is especially relevant when re-evaluating a patient of whom previous results are already known, as it can guide the choice for the most optimal short form in individual cases.

Interestingly, the WAIS-IV short forms with the greatest psychometric properties were the ones that maintained the four-factor structure (i.e., one subtest per factor), providing more clinically relevant information and increasing the construct validity of the short form. The composition of these short forms deviates from the published

Wechsler Abbreviated Scale of Intelligence (WASI), which is only available in certain languages and includes four subtests corresponding to two factors only.

- Assessment of the level of ID on three domains separately (conceptual, social and practical domains) provides a more accurate representation of the adaptive functioning of the individual.
- The selection of instruments should be based on the context, availability in own language and psychometric quality.

ID domain discrepancy

The assessment of ID in terms of three domains of adaptive functioning gives the opportunity to define a concept of ID between-domain discrepancy, in which one domain is particularly more deficient than another. Using the introduced set of standardized criteria for identifying an ID discrepancy as outlined in chapter 2, nearly one-third of all subjects had a discrepancy in their ID profile. Among those with moderate ID, more than half met the discrepancy criteria, which was a significantly larger proportion compared to those with a profound ID (5.3%). This might be related to the broader spectrum of self-care skills and (social) activities in which individuals with a moderate ID are regularly engaged; hence personal specific strengths and needs become more visible. In addition, a lower rate of ID discrepancies could be explained by a floor effect in those with a profound level of ID, as this is the lowest level.

Impairment in the social domain was most often the reason for the discrepancy, indicating that the social skills were more impaired than practical and/or conceptual adaptive behavior. This ID profile might be associated with the high prevalence of autism and autistic-like features among people with ID and/or epilepsy,[12] which is characterized by deficiencies in social communication and social interactions.[3] In addition, social impairments may also relate to the lack of opportunity to develop such skills, due to the combination of having an ID as well as living in the more protective and less demanding environment of the residential setting when compared to living in the community.

Regardless of the level of ID, the likelihood of having an ID discrepancy was significantly higher in those with a focal epilepsy type and, regarding types of seizures, with a mixed seizure type. It could be hypothesized that these associations are explained by focal lesions causing both the epilepsy and (specific) impairments in adaptive functioning. To further clarify the working mechanisms, future research should focus on associations between adaptive functioning and specific brain areas that are regularly affected by epilepsy, such as the temporal lobe, for example using neuroimaging.

As, to the best of our knowledge, no other studies have been published regarding ID discrepancies in terms of differences between the three domains of adaptive functioning, it is worth considering whether our reported discrepancy rate is actually deviant from the general ID population. Nevertheless, this proportion seems clinically relevant, and should therefore be validated in other ID populations, including patients with ID and epilepsy living in community settings. Addressing an ID domain discrepancy in daily clinical practice could have important implications for the treatment strategies to meet both the strengths and needs of the individual, in order to minimize the risk of overestimating or underestimating an individual and prevent from challenging behavior.

» ID domain discrepancy is common among people with epilepsy and a moderate level of ID.
» Impairment in the social domain was most often the reason for the ID discrepancy, indicating that social skills are particularly more impaired than conceptual and practical skills.

Screening for depression and anxiety

Depression and anxiety disorders are the most common psychiatric disorders in people with epilepsy, with pooled prevalence rates of 22.9% and 20.2%,[13] respectively. Affective disorders are also regularly encountered in adults with ID.[14] Depressive and anxiety symptoms can be difficult to recognize in people with ID, however, due to their limited cognitive and verbal abilities, or may be overshadowed by severe epilepsy. Regularly screening of patients with both epilepsy and ID using valid instruments can be helpful to (early) detect depressive and anxiety symptoms. There was, however, no validated Dutch screening instrument for adults with ID was available.

In chapter 4, the reliability and validity of the Anxiety, Depression, and Mood Scale (ADAMS) was investigated. This informant-based screening instrument developed for people with ID was translated into Dutch in 2012 and has already been validated among people with ID aged 50 years or older.[15] We showed that the ADAMS is also a valid and reliable screening tool for people with ID aged 18 to 50. Therefore, we recommend the ADAMS to be implemented as an (early) screening instrument for anxiety and depressive symptoms in clinical practice.

» The Anxiety, Depression, and Mood Scale (ADAMS) is a useful screening tool for depression and anxiety in adults with ID.

Epilepsy and ID in relation to neuropsychiatry: what's to blame?

Previous studies have shown that epilepsy and ID have each been linked to a variety of behavioral, affective, and psychiatric comorbidities.[16-18] After conducting a systematic review of the literature on both epilepsy and ID in relation to neuropsychiatric comorbidities (chapter 5), it can be concluded that there is a paucity of in-depth and good-quality studies on this topic and prevalence studies are not available. There were only fifteen studies of sufficient quality (regarding the risk of bias) and they mostly focused on either the presence of epilepsy or presence of the ID in relation to neuropsychiatry. The studies included different types of neuropsychiatric outcomes and studied heterogeneous study populations with respect to epilepsy and ID. Despite the low level of evidence, there were a few tendencies noted:

- the presence of epilepsy showed a slight association with negative mood symptoms in those with ID, but not with other types of psychiatry or behavior;
- the presence of ID was linked to psychiatric disorders in people with epilepsy and a more severe level of ID to types of challenging behavior;
- epilepsy-related factors indicating a more severe form of epilepsy seemed to be associated with more neuropsychiatric comorbidity in people with both epilepsy and ID.

In order to further examine the associations between epilepsy- and ID-related characteristics and neuropsychiatric comorbidities, the TRIANGLE study was conducted among 189 patients living at the tertiary care facility of Kempenhaeghe. In this dissertation, we focused on depressive and anxiety symptoms, challenging behavior and psychogenic non-epileptic seizures (PNES) as forms of neuropsychiatry.

Point prevalence of neuropsychiatric comordities

With pooled prevalence rates of 22.9% and 20.2%, depression and anxiety disorders are among the most prevalent psychiatric disorders in people with epilepsy.[13] In the population of people with ID, the prevalence rates of affective disorders (including depression) vary from 3.6 – 6.6%[14] and for general anxiety disorder from <2%- 17.4%,[19] depending on the method or classification system used. In the TRIANGLE study (chapter 7), 21.7% and 12.7% of the patients showed elevated levels of depressive and anxiety symptoms, respectively, possibly indicating a disorder. The rate of depressive symptoms is comparable to the prevalence of depression in people with epilepsy but much higher compared with people with ID. Regarding anxiety a different pattern seems to be the case: we found rates that are comparable to the population of people with ID, but smaller compared to people with epilepsy.

Regarding challenging behavior, we only took into account some common types of challenging behavior in people with ID: self-injurious behavior, stereotyped behavior and aggressive/destructive behavior. The prevalence of challenging behavior among people with ID was studied in multiple large ID population studies, which resulted in point prevalence rates between 10 and 22.5%.[20-22] In people with epilepsy, the prevalence has not been systematically studied previously. Results from the TRIANGLE study (chapter 6) indicated that 29.6% of the sample exhibited self-injurious, stereotyped, or aggressive/destructive behavior that is perceived as a severe problem by daily caregivers and 29.1% of the sample exhibited clinically deviant behavior based on ID population norms of frequency scores. More specifically, the frequency of the behavior was clinically deviant in 7.1% for self-injurious behavior, in 17.5% for stereotyped behavior and in 11.6% for aggressive/destructive behavior.

PNES are defined as sudden and involuntary paroxysmal events that resemble epileptic seizures, although not induced by an organic cause, and are related to a psychogenic cause.[23] Whereas diagnostic rates vary from 12% - 30% for patients referred to a tertiary epilepsy center,[24,25] the point prevalence in the TRIANGLE study was 7.1% (chapter 8). This rate also includes a reinforced behavioral pattern as subcategory of PNES, which may be particularly applicable to people with ID as a large majority of caregivers reported stress-related triggers. By exhibiting seizure-like events a secondary gain is reached (such as avoiding an unpleasant situation) and the events are therefore paradoxically reinforced by caregivers. As the diagnosis of PNES may be particularly challenging in patients who also have epilepsy and ID, PNES may be underdiagnosed in this population.

The point prevalence rates of depressive and anxiety symptoms and challenging behavior are possibly biased since a large proportion of patients was using psychotropic medication (41.8%). It can be concluded, however, that these are serious issues among people with both epilepsy and ID, and they should be anticipated on and considered in individual (treatment) plans. The results emphasize the importance of regularly screening for anxiety and depressive symptoms in people with epilepsy and ID in clinical practice, for example by administering the ADAMS every two years plus whenever in doubt. This may lead to early detection and allows for a quick and adequate treatment or intervention.

- » Depressive symptoms, anxiety and challenging behaviors are relatively prevalent among people with epilepsy and ID.
- » PNES seems relatively rare among people with epilepsy and ID, although diagnostic barriers may have led to underdiagnosis.

Epilepsy and ID characteristics in relation to neuropsychiatric comorbidities: what's to blame?

We assessed the individual contribution of epilepsy and ID characteristics on depressive symptoms and anxiety and on aggressive/destructive, stereotyped and self-injurious behavior. The associations that are significant are summarized in Figure 1. Interestingly, although some epilepsy factors were related to specific neuropsychiatric outcomes, in general no epilepsy factor was prominently associated with neuropsychiatric comorbidity in general.

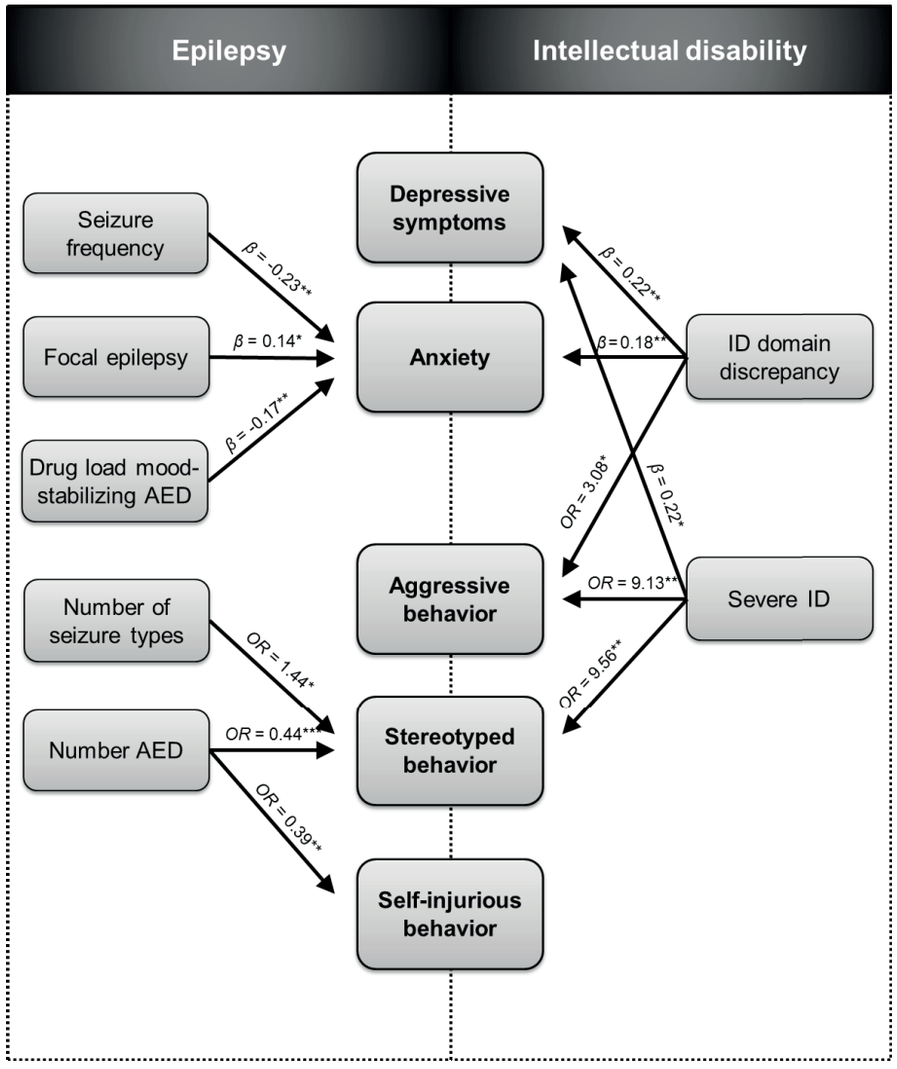
Remarkably, the two ID-related characteristics, a more severe level of ID and the presence of an ID domain discrepancy, were related to most neuropsychiatric outcomes: depressive symptoms, anxiety, aggressive/destructive behavior and stereotyped behavior. On the other side, most epilepsy-related characteristics were not significantly related to neuropsychiatric comorbidity or only to a certain type. For some epilepsy factors, particularly those related to medication, even a negative association was found. As some of the anti-epileptic drugs can have mood-stabilizing effects,[26] a high drug load or polypharmacy may suppress negative affective states and (perhaps consequently) challenging behavior, although more extensive research is needed to further clarify this finding. Furthermore, anxiety appeared to be inversely related to a higher seizure frequency, even when the use of benzodiazepines as antiepileptic drugs (daily or as rescue medication) was taken in to account. This is in contrast with previous results from Dehn et al.,[27] which might be due to the extremely high seizure frequency in our study sample or the residential setting where professional caregivers are often in close proximity to provide patients with seizures with care and attention.

The association between a focal epilepsy type and anxiety might be due to epileptic activity in temporal brain structures related to anxiety[29,29] and/or the intact awareness in focal seizures of which the conscious experience might be frightening for someone. Stereotyped behavior was present significantly more often in those with mixed seizure types, suggesting a severe form of epilepsy that can be difficult to treat. Stereotyped behaviors are controlled behaviors which are thought to have a potential calming effect on an over-aroused nervous system.[30,31] Hence, it may be that they are (subconsciously) exhibited as coping strategy for the burden of severe epilepsy, particularly when a person already has limited coping resources due to a more severe level of ID.

Associations between epilepsy, ID and PNES were assessed using a matched case-control design, due to the small sample size of patient with PNES. Especially women with mild to moderate ID and psychosocial difficulties seem vulnerable for PNES, the latter being also the case for patients with PNES but without ID32,33. In a large majority, (situational) triggers for PNES were identified by the nursing staff. This is in line with

the hypothesis that PNES in this patient group may be characterized by a behavioral pattern that is reinforced by the environment in at least some of the patients.

Figure 9.1: Overview of significant associations between epilepsy or ID characteristics and depressive symptoms, anxiety, aggressive behavior, stereotyped behavior and self-injurious behavior.



Note. * $p < .05$, ** $p < .01$, *** $p < .001$. β = standardized regression coefficient, OR = odds ratio. A negative β or OR smaller than 1.0 indicates an inverse association.

The overall conclusion is that epilepsy and ID characteristics considered in this dissertation may contribute independently to certain types of neuropsychiatric comorbidities, although the effects of epilepsy-related characteristics are modest compared to ID regarding depressive symptoms and challenging behavior. These findings emphasize the complexity of the associations between epilepsy, ID and neuropsychiatric comorbidities. Therefore, a multidisciplinary approach that takes into account all relevant aspects should be the mainstream clinical care for this population. The multifactorial base of epilepsy and ID should be embedded in education for professionals working with people with epilepsy and ID, especially the nursing staff. The findings can help to anticipate on neuropsychiatric comorbidities in people with epilepsy and ID (and hence provide informative prognostic counseling) and to contribute to the search for targeted (behavioral) interventions.

- With respect to depressive symptoms and challenging behavior: ID seems to have a more prominent effect than epilepsy-related characteristics.
- Women with mild/moderate ID and psychosocial difficulties seem vulnerable for PNES.

Methodological evaluation of the TRIANGLE study

The methodology regarding the assessment of the conceptual domain of ID consisted of various instruments, depending on the level of functioning. This has led to difficulties in comparing the outcome of the conceptual domain with the social and practical domains, although we have tried to be conservative in this regard. Anticipating on advances in current knowledge, the Vineland-II subscale Communication appears to show a great overlap with conceptual intelligence,[34] and could therefore also be used as a close approximation of the conceptual domain in future research. This would enhance making (standardized) comparisons between domains and improves the content validity. Other solutions would be to use instruments to assess the domains of adaptive behavior which are available in other languages. For example, the Adaptive Behavior Assessment System–Third Edition (ABAS-III)[35] and the Diagnostic Adaptive Behavior Scale (DABS)[36] are promising instruments that align with the tripartite structure of adaptive behavior in DSM-5. They are, however, not yet available in the Dutch language and the use of the DABS is limited to individuals from 4–21 years of age.

The TRIANGLE study included only patients from one of the two tertiary care facilities in the Netherlands. On one hand, this increases homogeneity and reliability of data sampling. On the other hand and despite the high inclusion rate,

the representativity of this sample is limited to a specialized group of adults with mostly severe epilepsy and ID, of which the majority lived in a residential care setting. Results should therefore be validated in other samples. A review of studies on deinstitutionalization and post-deinstitutionalization of adults with ID concluded that there is no association with emotional well-being, including challenging behavior.[37]

We were able to take into account multiple epilepsy characteristics that make up the phenotype of epilepsy and indicate its severity. There were, however, a few factors not included, such as the etiology of epilepsy and/or ID and the exact localization of epilepsy in the brain. It might have been that, for some patients, behavioral or affective abnormalities resulted from the same underlying cause that is involved in the epilepsy itself, for example a severe brain impairment.[38] Also, contextual factors that might relate to neuropsychiatry were beyond the scope of this research, for example type of living setting, interactions with co-residents and the way the staff treats the person during the day. The instruments were selected based on their psychometric quality, feasibility and international availability, yet they are mostly by proxy instruments that rely on (secondary) observations and sometimes interpretations by informants. This relates to the lack of reliable measures that can be used among people with ID directly. In clinical practice, results from secondary measures should be validated by direct observations and be placed in the person's perspective and setting before making clinical inferences.

Future directions

The multidisciplinary TRIANGLE study will be continued in Kempenhaeghe, also to gain more insights on the medical perspectives in people with epilepsy and ID, including psychiatric disorders, etiology and therapeutic considerations including AED effects. As the TRIANGLE study has a cross-sectional design, no firm conclusions about causality can be drawn.

To further unravel the impact of epilepsy and ID on neuropsychiatric comorbidities, longitudinal research is recommended. Longitudinal studies can help to understand the course of neuropsychiatric comorbidities in this population and the long-term impact of epilepsy and specific epilepsy characteristics, for example by following-up the study population for at least 10 years. Incorporating imaging techniques to detect seizure localization might provide insights into brain structures both involved in epilepsy and neuropsychiatry. The etiology of epilepsy and/or ID should be included as well, especially since knowledge on syndromic and genetic phenotypes is rapidly increasing these days. In addition, the study population should be extended to a larger proportion of people with epilepsy and ID who live in community settings, in order to validate the current findings and to clarify the role of environmental factors such as

social stigma and the experience of different opportunities and demands. A control group without epilepsy is needed to further investigate the concept of ID domain discrepancy and its occurrence in the ID population.

As the neuropsychiatric outcomes were averaged over a certain period in the TRIANGLE study, potential pre-, peri- and postictal behavioral changes are not taken into account. Shorter-term longitudinal observational research could be conducted to examine such effects, for example by observing patients multiple times a day for a period of several weeks. With respect to PNES, the hypothesis of underdiagnosis of this phenomenon advocates for epidemiological research within the general ID population and to promote awareness. In addition, prospective research could help to gain more insights about explanatory factors for PNES in ID compared to those without ID. The hypothesized subcategory of PNES, a reinforced behavioral pattern, deserves more attention as this subcategory might require a different approach regarding the intervention.

Future clinical research can contribute appropriate intervention or treatment methods regarding challenging behavior, PNES and psychiatric symptoms or disorders.

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Summary

Epilepsy is conceptually defined as a brain disease characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. Epileptic seizures imply the transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain1. Epilepsy is relatively common in people with intellectual disability (ID), with a pooled prevalence rate of 22.2% which increases with the severity of ID. Compared to people without ID, the epilepsy among those with ID is often more severe, chronic, and refractory to treatment, which has a pervasive impact on their quality of life. Epilepsy and ID have each been linked to a variety of behavioral, affective, and psychiatric comorbidities. For the full spectrum of challenging behavior, affective symptoms and psychiatric disorders, we have used the term "neuropsychiatric comorbidities" in this thesis. The nature and extent of these comorbidities becomes more complicated in the population with both epilepsy and ID. Especially when considering the many factors that are involved in epilepsy, such as etiology, epilepsy syndromes, seizure types and frequency, increased epilepsy severity in those with ID, and the more frequent use of antiepileptic drugs (AEDs). In this thesis, several studies were conducted to get a better understanding of neuropsychiatric comorbidities in people with epilepsy and ID.

Part 1: Diagnostic processes: filling the gaps

In the first part, the studies focused on methodological aspects of the diagnostic processes within the fields of ID and assessment of mood and anxiety. The diagnostic criteria of ID have been revised in the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5), which is legally implemented in the Dutch mental health care system since January 2017. Regarding the classification of ID, the severity in terms of adaptive functioning is now to be addressed on three domains: the conceptual, social and practical domain. The assessment of the level of ID on three domains separately provides a more accurate representation of the adaptive functioning of the individual. Moreover, this new classification gives the opportunity to define a concept of ID domain discrepancy, in which one domain is particularly more deficient than another, in a standardized way.

In **chapter 2**, methods are described to assess each of the three domains of adaptive functioning separately, as well as the criteria to identify an ID domain discrepancy. The associations between epilepsy characteristics and level of ID, and between epilepsy characteristics and the presence of an ID domain discrepancy are explored among

189 adults with epilepsy and ID, living at the residential facilities of Kempenhaeghe. An ID domain discrepancy seems present in about one-third, particularly in those with moderate ID (53%), and is related to a focal (localized) epilepsy type and a mixed seizure type. A more severe and refractory epilepsy, including various seizure types, a high seizure frequency, a combined epilepsy type (both focal and generalized epilepsy) and an early age at onset, is significantly related to more severe impairments in conceptual, social and practical adaptive behavior. As the proportion of subjects with an ID discrepancy is substantial, professionals should be aware of this and take all domains of ID into account when studying or working with this vulnerable population.

As the conceptual domain was assessed by using an intelligence test, **chapter 3** has built on this by studying the accuracy of abbreviated versions of the two most commonly used intelligence tests in The Netherlands: the Wechsler Intelligence Scale for Children – Third edition (WISC-III) and the Wechsler Adult Intelligence Scale – Fourth edition (WAIS-IV). Multiple abbreviated versions are created and their psychometric properties are examined in 986 children and 324 adults with neurological disorders, including epilepsy. Psychometric properties of the short forms are discussed for the subgroups with an extremely low to borderline full scale IQ and the subgroup with average to high full scale IQ. Short forms may be useful in research settings to obtain a global estimate of intelligence, and in clinical settings to screen periodically for possible intellectual deterioration.

In **chapter 4**, the reliability and validity of the Dutch version of the Anxiety, Depression And Mood Scale (ADAMS) is investigated among 198 adults with ID from multiple centers, including a subsample of adults with epilepsy. Since the psychometric properties of the ADAMS were already examined in a Dutch population of older people with ID (aged 50 years or older), this study focused particularly on adults with ID aged between 18 and 50. The Dutch ADAMS appeared to be a reliable and valid instrument and can be used in research and clinical practice in adults with ID.

Part 2. Epilepsy and ID characteristics in relation to neuropsychiatric comorbidities: what's to blame?

In the second part, associations between epilepsy, ID and neuropsychiatric comorbidities in adults with epilepsy and ID are investigated. In **chapter 5**, the literature of the past 20 years is reviewed. Fifteen studies of sufficient quality are identified, with sometimes inconsistent results. We conclude that the presence of epilepsy only is not a clear determinant of neuropsychiatric comorbidity in people with ID, although a few studies noted a link between the presence of epilepsy and negative mood symptoms in those with ID. Despite the low level of evidence, the presence of ID seems linked to psychiatric disorders in people with epilepsy, a more severe level of ID to types of

challenging behavior and epilepsy-related factors indicating a more severe form of epilepsy seems associated with more neuropsychiatric comorbidity in people with both epilepsy and ID.

In **chapter 6** and **chapter 7**, the effects of multiple epilepsy and ID characteristics on challenging behavior (self-injurious, stereotyped and aggressive behavior) and affective symptoms (depressive symptoms and anxiety) are investigated among 189 adults with epilepsy and ID, living at the residential facilities of Kempenhaeghe. In addition, self-reported quality of life of a subgroup of 24 patients with mild to moderate ID and epilepsy is studied. Challenging behavior and affective symptoms are assessed using questionnaires filled out by professional caregivers. Self-injurious behavior is present in 35% of subjects, stereotyped behavior in 60%, and aggressive/destructive behavior in 63%, and the behaviors exceed clinical norms in 7%, 18% and 12%, respectively. Elevated levels of depressive and anxiety symptoms are present in 21.7% and 12.7%, respectively. The links between epilepsy and ID characteristics and these neuropsychiatric comorbidities seem to differ per outcome and there are positive as well as negative associations detected. Regarding challenging behavior, the effects of epilepsy-related characteristics are modest when compared to ID. Clinically deviant self-injurious behavior is associated with a lower number of daily used AEDs, stereotyped behavior is associated with a higher number of seizure types and a lower number of daily used antiepileptic drugs and aggression is associated with the presence of an ID domain discrepancy. For affective symptoms, only anxiety appears to be associated with epilepsy characteristics, although both anxiety and depressive symptoms are associated with ID characteristics. Anxiety is associated with a focal epilepsy type and ID domain discrepancy, but is negatively related to seizure frequency and drug load of mood-stabilizing AEDs. Depressive symptoms are not related to epilepsy characteristics, but a severe ID and ID domain discrepancy is associated with more depressive symptoms. Quality of life is significantly worse in those with multiple seizure types and ID domain discrepancy. Although the representativity of this sample is limited to adults with primarily severe epilepsy who lived in a residential care setting, the studies emphasize the relevance of both challenging behavior and affective symptoms as serious issues among adults with epilepsy and ID. The findings may help professionals working with this vulnerable population in the anticipation of such comorbidities and may contribute to good clinical care. Yet, the link between epilepsy, ID and neuropsychiatry appears to be complex and involves many individual factors to take into account. A multidisciplinary approach is therefore highly recommended.

Chapter 8 focused on psychogenic nonepileptic seizures (PNES) in adults with epilepsy and ID, living at the residential facilities of Kempenhaeghe, a phenomenon that is defined as sudden and involuntary paroxysmal events that resemble epileptic seizures, but are not induced by an organic cause. In addition, there is positive

evidence or it is strongly suspected that the events are related to a psychogenic cause. In this study, the main characteristics of 15 adults with PNES are described and the differences between those with PNES and a matched control group without PNES are analyzed. The point prevalence of PNES was 7.1% and comprised mostly females and persons with a mild or moderate level of ID. Compared to controls, they showed more depressive symptoms, experienced more negative life events and had more often an ID domain discrepancy. Stress-related triggers were recognized in a large majority by the nursing staff, which may indicate that there is a subcategory of PNES characterized by a reinforced behavioral pattern. The complexity of diagnosing PNES in this population suggests that it may be underdiagnosed in the ID population.

Finally, **chapter 9** provides a general discussion of the results of the studies. Implications for clinical practice and recommendations for future research are discussed as well.

Nederlandse samenvatting

Epilepsie is een neurologische aandoening die gekenmerkt wordt door het optreden van epileptische aanvallen, waarbij tijdelijk abnormale en verhoogde activiteit plaatsvind in (delen van) het brein. Epilepsie komt relatief vaak voor bij mensen met een verstandelijke beperking (VB). De prevalentie van epilepsie bij de totale VB-populatie is 22.2%, maar neemt toe naarmate de VB ernstiger is. Bij mensen met een VB is de epilepsie vaak ernstiger, chronisch en moeilijker te behandelen dan bij mensen zonder een VB, wat een grote invloed heeft op hun kwaliteit van leven. Vanuit de huidige literatuur is bekend dat zowel epilepsie als VB samenhangt met een verscheidenheid aan gedrags-, emotionele- en psychiatrische problematiek. In dit proefschrift gebruiken we de term “neuropsychiatrische comorbiditeit” om te verwijzen naar het hele spectrum aan gedragsproblematiek en psychische klachten en stoornissen. De omvang en aard van deze comorbiditeiten zijn complex in de populatie van mensen met zowel epilepsie als een VB en hierover is vooralsnog weinig bekend. De heterogeniteit van epilepsie maakt het extra ingewikkeld, met factoren zoals de etiologie, epilepsiesyndromen, aanvalstypen en – frequentie, de ernstigere epilepsie bij mensen met VB en het hogere gebruik van anti-epileptica. In dit proefschrift worden verschillende studies beschreven die pogen meer inzicht te geven omtrent neuropsychiatrische comorbiditeit bij mensen met epilepsie en een VB.

Deel 1. Diagnostische processen: opvullen van lacunes

Het eerste deel van dit proefschrift is gericht op methodologische aspecten van diagnostiek binnen de vakgebieden van VB, stemming en angst. De classificiatiecriteria van VB zijn herzien in de Diagnostic and Statistical Manual of Mental Disorders – 5e editie (DSM-5), welke is geïmplementeerd in de Nederlandse gezondheidszorg sinds januari 2017. In de classificatie van VB, de ernst op gebied van adaptief functioneren dient nu te worden beschreven op basis van drie domeinen: het conceptuele, sociale en het praktische domein. Het afzonderlijk in kaart brengen van deze drie domeinen wordt een meer representatief beeld gegeven van het adaptief functioneren van de persoon. Daarnaast geeft deze manier van classificeren de mogelijkheid om een VB domein discrepantie, waarbij het ene domein beduidend meer beperkt is dan een ander domein, op een gestandaardiseerde manier vast te stellen.

In **hoofdstuk 2** zijn methodes beschreven om ieder domein van adaptief functioneren afzonderlijk vast te stellen en worden criteria beschreven wanneer mogelijk sprake is van een VB domein discrepantie. De samenhang tussen epilepsiekenmerken en het niveau van de VB, en tussen epilepsiekenmerken en het

hebben van een VB domein discrepantie is onderzocht bij 189 volwassenen met epilepsie en een VB die wonen binnen Kempenhaeghe. Een VB domein discrepantie leek bij bijna een derde voor te komen, met name bij mensen met een matige VB (53%), en bleek samen te hangen met een focale (gelokaliseerde) vorm van epilepsie en met een hoger aantal verschillende aanvalstypen. Een ernstigere vorm van epilepsie met betrekking tot meer aanvalstypes, een hogere aanvalsfrequentie, een vroeger debuut en een gecombineerd epilepsietype met zowel focale als gegeneraliseerde epilepsie blijkt gerelateerd te zijn aan meer ernstigere beperkingen in conceptueel, sociaal en praktisch adaptief functioneren. Gezien het vele voorkomen van een VB domein discrepantie is het belangrijk dat professionals zich hiervan bewust zijn en met alle domeinen rekening houden in de zorg voor deze kwetsbare doelgroep en op gebied van wetenschappelijk onderzoek.

In **hoofdstuk 3** wordt nader ingegaan op de nauwkeurigheid van de verkorte intelligentietest, die tevens gebruikt is in hoofdstuk 2. De ontwikkeling en betrouwbaarheid van verkorte versies van twee van de meest gebruikte intelligentietesten in Nederland, namelijk de Wechsler Intelligence Scale for Children – Third edition (WISC-III) and the Wechsler Adult Intelligence Scale – Fourth edition (WAIS-IV), wordt beschreven. Meerdere verkorte versies zijn ontwikkeld en hun psychometrische waarden zijn getoetst bij 986 kinderen en 324 volwassenen met neurologische aandoeningen, waaronder epilepsie. De nauwkeurigheid is onderzocht bij subgroepen met een extreem laag tot (laag)gemiddelde intelligentie (totaal IQ < 80) en bij subgroepen met gemiddelde tot hoge intelligentie. Verkorte intelligentietesten kunnen met name geschikt zijn voor onderzoeksdoeleinden om een globale schatting te krijgen van het intellectuele functioneren en in de klinische praktijk om (regelmatig) te screenen voor eventuele intellectuele achteruitgang.

De betrouwbaarheid en validiteit van de Nederlandse versie van de Anxiety, Depression And Mood Scale (ADAMS) is onderzocht in **hoofdstuk 4**. Aangezien de psychometrische waarden van de ADAMS al zijn onderzocht bij mensen van 50+ met een VB, heeft deze multicentrische studie zich gericht op volwassenen onder de 50 jaar. De ADAMS is afgenomen bij vaste begeleiders van 198 volwassenen met een VB, waarvan een deel ook epilepsie heeft. Het blijkt dat de Nederlandse ADAMS een voldoende valide en betrouwbaar instrument is dat kan worden gebruikt om angst- en stemmingsklachten in kaart te brengen in de klinische praktijk en voor onderzoeksdoeleinden.

Deel 2. Epilepsie- en VB-kenmerken in relatie tot neuropsychiatrische comorbiditeit.

Het tweede deel van dit proefschrift richt zich op de samenhang tussen epilepsie, VB en neuropsychiatrische comorbiditeit bij volwassenen. In hoofdstuk 5 wordt de literatuur van de afgelopen 20 jaar samengevat en geanalyseerd. Er blijken enkel vijftien studies van voldoende kwaliteit over deze combinatie van onderwerpen te zijn gepubliceerd, met soms inconsistente resultaten. Er kan geconcludeerd worden dat alleen het hebben van epilepsie geen duidelijk samenhang heeft met neuropsychiatrische comorbiditeit, hoewel enkele studies een link vonden tussen epilepsie en stemmingsklachten bij mensen met een VB. Ondanks dat het bewijs gering is, lijken er nog enkele andere tendensen te zijn:

- het hebben van een VB lijkt gerelateerd te zijn aan psychische stoornissen bij mensen met epilepsie en een ernstige niveau van VB met gedragsproblemen;
- epilepsiefactoren die duiden op een ernstigere vorm van epilepsie lijken gerelateerd te zijn aan neuropsychiatrische comorbiditeit bij mensen met een VB.

In **hoofdstuk 6** en **hoofdstuk 7** worden de effecten van verschillende epilepsie- en VB-kenmerken op gedragsproblemen (zelfverwondend, stereotiep en agressief/destructief gedrag) en affectieve symptomen (depressieve kenmerken en angst) onderzocht bij 189 volwassenen met epilepsie en VB, die 24-uurs zorg ontvangen vanuit Kempenhaeghe. Daarnaast is gekeken naar zelf-gerapporteerde kwaliteit van leven bij een subgroep van 24 volwassenen met licht tot matige VB en epilepsie. Gedragsproblemen en affectieve symptomen zijn in kaart gebracht door middel van vragenlijsten die ingevuld zijn door vaste (veelal persoonlijk) begeleiders.

Zelfverwondend gedrag komt voor in 35% van de volwassenen, stereotiep gedrag in 60% en agressief/destructief gedrag in 63%. Deze gedragingen overschreden klinische normen in 7%, 18% en 12%, respectievelijk. Daarnaast heeft 22% een verhoogde scores op depressieve kenmerken en 13% een verhoogde score op angst. De samenhang tussen epilepsie- en VB-kenmerken and deze neuropsychiatrische comorbiditeiten blijken te verschillen per uitkomstmaat en er zijn zowel positieve als negatieve relaties gevonden. De invloed van epilepsie blijkt beperkt te zijn in vergelijking met de VB. Het hebben van klinisch afwijkend zelfverwondend of stereotiep gedrag blijkt minder vaak voor te komen bij mensen die dagelijks meerdere typen anti-epileptica gebruiken; stereotiep gedrag komt daarentegen vaker voor bij degenen met meer verschillende aanvalstypen en mensen met een ernstiger niveau van VB. Agressie blijkt niet samen te hangen met epilepsiekenmerken, maar komt wel vaker voor in geval van een ernstiger niveau van VB en een VB domein discrepantie. Met betrekking tot depressieve kenmerken en angst valt op dat alleen angst gerelateerd

lijkt te zijn aan epilepsiekenmerken, terwijl beide samenhangen met ID-kenmerken. Er worden meer angstklachten gevonden in geval van een focale epilepsie en een VB domein discrepantie, maar juist minder bij mensen met een hogere aanvalsfrequentie en bij een hogere dagelijkse dosis stemmings-stabiliserende anti-epileptica. Hoewel er geen samenhang is gevonden tussen depressieve kenmerken en epilepsiekenmerken, komen er meer depressieve kenmerken voor in geval van een ernstiger niveau van VB en een VD domein discrepantie. Kwaliteit van leven wordt ervaren als lager wanneer iemand meerdere aanvalstypen heeft en bij degenen met een VB domein discrepantie.

Ondanks dat de representativiteit van dit onderzoek beperkt is tot volwassenen met veelal ernstige epilepsie die in een residentiële woonvorm wonen, benadrukken de studies de relevantie van zowel gedragsproblemen als affectieve kenmerken als aandachtspunten in deze doelgroep. De bevindingen kunnen professionals en betrokkenen die te maken hebben met deze doelgroep helpen in het anticiperen op dergelijke comorbiditeit, wat ten goede kan komen aan de kwaliteit van zorg. Echter blijft de samenhang tussen epilepsie, VB en neuropsychiatrie complex en dienen vele individuele factoren in acht te worden genomen. Een multidisciplinaire aanpak wordt daarom sterk aanbevolen.

Hoofdstuk 8 is gericht op psychogene niet-epileptische aanvallen (PNEA) bij volwassenen met epilepsie en een VB, wonende bij Kempenhaeghe. PNEA is gedefinieerd als een plotselinge en paroxysmale verandering in gedrag of bewustzijn, die lijkt op een epileptische aanval, maar zonder de voor epilepsie typische elektrofysiologische veranderingen. Daarnaast is er bewijs of een sterk vermoeden dat de aanval samenhangt met psychogene factoren. In deze studie worden de voornaamste kenmerken van 15 volwassenen met PNEA beschreven en worden verschillen tussen de groep met PNEA en een (gematchte) controlegroep zonder PNEA geanalyseerd. Er blijkt sprake van PNEA bij 7% van de mensen met epilepsie en een VB die 24-uurs zorg ontvangen vanuit Kempenhaeghe, waarvan de meeste vrouw zijn en een lichte of matige VB hebben. In vergelijking met de controlegroep laten de mensen met PNEA meer depressieve symptomen zien, hebben zij meer negatieve gebeurtenissen meegemaakt en komt een VB discrepantie vaker voor. Stress-gerelateerde triggers voor PNEA waren aangedragen door een meerderheid van de begeleiders, wat mogelijk duidt op een vorm van een geconditioneerd gedragspatroon als subcategorie binnen PNEA. De complexiteit van diagnostiek naar PNEA bij mensen met een VB geeft een risico op onderdiagnostiek in de VB-populatie.

Tot slot, in **hoofdstuk 9** wordt alle resultaten samengevat en worden de implicaties voor de klinische praktijk en aanbevelingen voor vervolgonderzoek besproken.

Valorization

Epilepsy and intellectual disability (ID) relatively often co-occur.[1] The epilepsy among those with ID is often more severe, chronic, and refractory to treatment, which can have a pervasive impact on their quality of life.[2,3] Moreover, epilepsy and ID have each been linked to a variety of behavioral, affective, and psychiatric comorbidities.[4-6] A better understanding of the complex associations between neuropsychiatric comorbidities and epilepsy and ID has important implications for good clinical practice and treatment of these individuals.

Relevance of findings

Diagnostics are an important aspect within the care for people with epilepsy and ID. The comprehensive diagnostic processes can be time-consuming, intensive, and a burden for patients. Reliable screening instruments can be helpful if comprehensive diagnostics are too demanding or time-consuming for patients or caregivers. In this dissertation, the reliability and validity of multiple screening instruments are investigated (see chapter 3 and 4). Chapter 3 showed that abbreviated versions of two intelligence tests (WISC-III and WAIS-IV) provide an accurate estimation of global intellectual functioning. These short forms take significantly less time than a full examination, which can reduce the burden for patients and the psychologist assessing the patient. In chapter 4, the Anxiety, Depression And Mood Scale (ADAMS) appeared to be a reliable screening instrument for detection of early signs of depressed mood or anxiety disorder for adults aged below 50 years. The instrument was already validated among adults aged 50+ years,[7] but evidence for younger adults was lacking. Early detection of such symptoms is relevant for all age groups, as it can help to guide individual treatment plans and therefore prevent from developing a severe affective disorder.

With respect to the classification of ID, a methodology to assess three domains of adaptive functioning is described in this dissertation. This was based on DSM-5 criteria of ID,[8] which is legally implemented in the Dutch mental health care system since January 2017. Chapter 2 focusses particularly on the concept and assessment of an ID domain discrepancy, in which one domain is significantly more deficient than another. As the studies described in chapter 6, 7 and 8, this ID domain discrepancy appeared to be associated with aggression, anxiety, depressive symptoms and psychogenic nonepileptic seizures. These findings emphasize the relevance of this concept and should, therefore, be implemented in the care for people with ID. Addressing an ID domain discrepancy in daily clinical practice could, for example, have implications for the treatment strategies to meet both the strengths and needs of the individual,

which might minimize the risk of overestimating or underestimating an individual. The instruments and methodology can be applied to adults with all levels of ID and can be adapted to children with ID. Other instruments to assess domains of adaptive functioning that are available might be suitable as well.

The second part of this dissertation provides information on the associations between neuropsychiatric outcomes and (independent) epilepsy and ID characteristics. The findings illustrate the wide variety of neuropsychiatric comorbidities among patients with epilepsy and ID and the complexity of associations between many factors. It is important for health care professionals working with patients with both epilepsy and ID to be aware of the prevalence of neuropsychiatric comorbidities (especially depressive symptoms), by being sensitive to early signs. Also, the complex interplay with associated factors, with positive and negative directions, should be taken into account.

The role of epilepsy (characteristics) in general on neuropsychiatry among people with ID seems to be modest compared to ID characteristics, which indicates that other factors beyond epilepsy should be considered at all times. Therefore, a multidisciplinary approach is highly recommended.

Target groups

The findings described in this dissertation are relevant for multiple target groups. The main target group consists of patients with epilepsy and ID and their relatives. Some of the findings are relevant to other patient populations as well, for example the ID population in general or to patients with neurological disorders. Another important target group includes health care professionals, such as psychologists and behavioral scientists, physicians (specialized in the care for people with ID), neurologists, nurses and direct support staff working in the field of ID and/or epilepsy. Finally, the results are very relevant for scientists, as the findings require validation in other study populations and multiple recommendations for future research are described.

Activities for innovation and implementation of knowledge

The studies described in this dissertation are also published or submitted as scientific articles in peer-reviewed journals. In order to expand the readership to as many target populations as possible, several findings have been published in Dutch journals as well. In addition, many of the findings were presented and discussed during oral and poster presentations at national and international symposia and congresses in the fields of epilepsy or ID, and the aim is to continue this in the (near) future. Another aim is to include the findings in educational materials on this topic and to embed these in the

Study Center of Epilepsy (in Dutch: Leerhuis Epilepsie), which is an initiative of the two main epilepsy centers in The Netherlands: Kempenhaeghe and SEIN. This Study Center of Epilepsy provides teaching courses (tailor-made if required) on epilepsy to health care professionals in all regions of The Netherlands. In this way, multiple attempts are made to reach health care professionals and scientists of various fields.

Future plans also include a special effort to reach patients and their relatives and non-academic health care professionals. By using a standardized format, a series of short videos will be created in the form of a co-production by Kempenhaeghe and CCE ("Centrum voor Consultatie en Expertise"). Each video will focus on a specific element of epilepsy, ID and neuropsychiatry and will be supported by documented experiences of a patient and his/her (professional) caregivers. By using simple language, subtitles and visual elements, the video will be made suitable for a wide audience. Funding for this project is being requested. If this succeeds, the video series will be made available for free on the Internet, and may be used for educational purposes as well.

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Jans van Ool

About the author

Jans Sophie van Ool werd op 22 september 1990 geboren in Budel. In 2008 behaalde zij haar VWO-diploma aan het Pleincollege 't Joris in Eindhoven. Aansluitend begon zij de opleiding Pedagogische Wetenschappen en Onderwijskunde aan de Radboud Universiteit Nijmegen, waarin zij in 2011 haar bachelor diploma behaalde. Tijdens het tweede studiejaar werd Jans toegelaten tot het extra-curriculaire programma van de Radboud Honours Academy, waardoor zij de kans kreeg zichzelf meer te ontwikkelen en een onderzoeksstage in binnen- en buitenland (Bureau Jeugdzorg, Jeugdbescherming en Keck School of Medicine, Los Angeles) te doen. Hierdoor ontstond (ook) een grote interesse in het doen van wetenschappelijk onderzoek, waardoor Jans ervoor heeft gekozen om twee masteropleidingen te doen. Zij behaalde haar diploma van de onderzoeksmaster Gedragswetenschappen bene meritum in 2013 en het masterdiploma Orthopedagogiek in 2014. Haar klinische- en onderzoekstage heeft Jans gedaan bij Karakter Kind- en Jeugdpsychiatrie in Oosterbeek, een locatie die gespecialiseerd is in diagnostiek en behandeling bij jongeren met een lichte verstandelijke beperking. Vanaf de laatste drie studiejaren was Jans werkzaam als woonbegeleider bij Kempenhaeghe, voornamelijk in de weekenden en vakanties. Haar affiniteit met de doelgroep volwassenen met epilepsie en verstandelijke beperking groeide in deze tijd enorm. Een promotieonderzoek binnen Kempenhaeghe, waarmee ze startte in november 2014, sloot dan ook perfect aan. Vanaf augustus 2018 werkt Jans ook als orthopedagoog binnen het Centrum voor Epilepsiewoonzorg van Kempenhaeghe, waar ze klinisch werk combineert met wetenschappelijk onderzoek.

Jans Sophie was born on September 22nd 1990 in Budel. In 2008, she graduated her secondary school education at the Pleincollege 't Joris in Eindhoven. Next, she started the bachelor study Pedagogical Sciences at Radboud University Nijmegen and received her bachelor's degree in 2011. In the second year, she participated in the extra-curricular study program of the Radboud Honors Academy, during which she attended several courses and did research internships in both The Netherlands ("Bureau

Jeugdzorg", department of youth protection) and abroad (Keck School of Medicine, Los Angeles). During these research internships, her interest in research increased greatly. Therefore, Jans decided to follow both the research master Behavioral Sciences as well as the clinical master of Pedagogical Sciences, both at Radboud University Nijmegen, which she finished in 2013 and 2014 respectively. The clinical and research internship took place at Karakter Child Psychiatry in Oosterbeek, an institution specialized in diagnostics and treatment for children and adolescents with a mild intellectual disability. During the last 3 years of college, Jans was employed as a direct support staff member at Kempenhaeghe. While providing care for adults with epilepsy and intellectual disability, her affinity with this population grew significantly. Starting as a PhD candidate at Kempenhaeghe in 2014, with a focus on mood and behavior among people with epilepsy and intellectual disability, fitted perfectly. Since August 2018, Jans is employed as a behavioral scientist at Kempenhaeghe, department of residential care, and works as a both a scientist and practioner.

List of publications

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- **Van Ool, J.S.,** Snoeijen-Schouwenaars, F.M., Aldenkamp, A.P., Hendriksen, J.G.M. (2016). A systematic review of neuropsychiatric comorbidities in patients with both epilepsy and intellectual disability. *Epilepsy & Behavior, 60,* 130-137.
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