Trait Impulsivity Correlates with Active Myoclonic Seizures in Genetic Generalized Epilepsy

Marte Syvertsen,^{a,b} Jeanette Koht,^{a,b} Kaja Selmer,^{c,d} Ulla Enger,^a *Deb K. Pal,^e Anna Smith^e

^aDepartment of Neurology, Drammen Hospital, Vestre Viken Hospital Trust, Norway

^bInstitute of Clinical Medicine, University of Oslo, Oslo, Norway

^cDivision of Clinical Neuroscience, Department of Research and Innovation, Oslo University Hospital, Oslo, Norway

^dNational Center for Epilepsy, Oslo University Hospital, Sandvika, Norway

^eDepartment of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom

^eMRC Centre for Neurodevelopmental Disorders, King's College London, London, United Kingdom

^eKing's College Hospital, London, UK

^eEvelina London Children's Hospital, London UK

*Corresponding author:

Deb K Pal PhD MRCP

Department of Basic and Clinical Neuroscience

Institute of Psychiatry, Psychology and Neuroscience

Kings College London

125 Coldharbour Lane

Camberwell

London

SE5 9NU

deb.pal@kcl.ac.uk

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Abstract

Background: Juvenile myoclonic epilepsy (JME) is a common subtype of genetic generalized epilepsy (GGE) arising in adolescence and is often associated with executive function deficits. Some executive function components like response inhibition have been extensively evaluated in JME, but few studies have focused upon trait impulsivity or compared between GGE subtypes. The aim of the present study was to compare the association of trait impulsivity in JME with other GGE subtypes.

Methods: GGE patients aged between 14-40 years (n=137) were divided into JME (n=92), and other GGEs (n=45: 8 childhood absence epilepsy, 22 juvenile absence epilepsy, and 15 epilepsy with generalized tonic-clonic seizures only). The study participants were recruited through medical records of the general population of Buskerud County and the neighboring municipalities, covering 477,000 people or 9.1% of Norway's total population. All participants underwent a clinical interview including the Barratt Impulsiveness Scale (BIS), an established measure of trait impulsivity. We controlled for other potential predictors of BIS score using ANCOVA.

Results: There were no differences between JME and other types of GGE for BIS scores, but the presence of myoclonic seizures within the last year, irrespective of GGE subtype, was independently associated with significantly increased behavioral impulsivity.

Conclusions: This study demonstrates that trait impulsivity in GGE is most strongly related to the recent occurrence of myoclonic seizures rather than GGE subtype.

Key words: juvenile myoclonic epilepsy, Barratt Impulsiveness Scale, ADHD, impulsivity

1. Introduction

Juvenile Myoclonic Epilepsy (JME) was for several years considered to be a benign disorder [1], with intellectual abilities assumed to be within the normal range, normal neurological examination, normal magnetic resonance imaging of the brain and a favorable response to treatment in the majority of patients [2, 3]. However, several imaging studies confirmed abnormalities in microstructure and connectivity involving the frontal lobes in people with JME [4-7] and neuropsychological studies have revealed varying deficits of executive function (EF) [8, 9]. EF refers to a set of cognitive processes involved in planning, monitoring, and goal-directed behavior, which includes response inhibition, working memory, and mental set-shifting [10] and may also encompass attentional control and planning [11]. Our recent meta-analysis of 16 studies confirms that response inhibition, a key process in EF, measured with the Stroop task, is consistently and moderately associated with JME (Cohen's $d=0.5$) with no heterogeneity [12].

Weak executive function is reflected to some degree in the construct of impulsivity, defined as “a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or to others” [13]. Impulsivity is a multidimensional construct involving the disruption of attention, perception and coordination of motor and cognitive responses, underpinned by cortico-striatal circuitry [14]. Impulsivity can be operationally partitioned into response, choice, and trait impulsivity on the basis of cognitive tests or self-report scales, although these domains often overlap in a given disorder or individual.

The study of impulsivity is important because it is associated with psychosocial outcomes like smoking [15], binge-eating [16], excessive use of alcohol [17], drug abuse [18-20], and criminal behavior [20, 21]. A meta-analysis of 16 response inhibition studies shows moderate and homogeneous association in JME [12], and two studies have concluded that people with JME are prone to impulsive decision making (choice impulsivity) when performing a gambling task [27, 28]. However, research regarding trait impulsivity has been limited, and the methods of measurement and samples vary [22-26]. Instruments used for evaluation of trait impulsivity in JME are the Dysexecutive Questionnaire (DEX) [22, 23], the Temperament and Character Inventory-impulsivity subscale [24], the Behavior Rating Inventory of Executive Function (BRIEF) [25], and the Barratt Impulsiveness Scale (BIS)-11 [26]. People with JME demonstrate elevated trait impulsivity in all of these studies, but effect sizes differ widely. Although EF deficits are acknowledged in up to 30% of epilepsy overall [29, 30], it is difficult to tell whether impulsive behavior is specific to JME and linked with prefrontal lobe network dysfunction and fronto-striatal connectivity, part of the

pathophysiology of JME [5, 8]. Thus, the aim of this study was to compare impulsivity in JME with other types of genetic generalized epilepsy (GGE). We hypothesized that patients with JME would report increased trait impulsivity in comparison with other GGE patients.

2. Material and methods

2.1 Study population

Patients with GGE were identified through a search of medical records containing an International Classification of Diseases, 10th Revision (ICD-10) code of epilepsy (G40) at Drammen Hospital for the time period 1999-2013 [33]. Drammen Hospital serves the general population of Buskerud County and four neighboring municipalities, i.e. a population of 477,000 people or 9.1% of Norway's total population. The hospital holds no tertiary or otherwise specialized function in epilepsy care, but will normally see all patients with newly diagnosed epilepsy in the region, as a part of the recommended procedure for follow-up of epilepsy in Norway [31, 32].

2.2 Participant recruitment

Patients aged 14-40 years with GGE according to medical charts were contacted and invited to participate in the study. Parents were contacted when patients were younger than 18 years. Patients with childhood absence epilepsy (CAE) who did not use antiepileptic drugs and were seizure free for more than one year, were not contacted. After finishing the search of medical records, patients with GGE aged 14-40 years were consecutively recruited from the EEG-laboratory at Drammen Hospital. Additionally, information about the study and an invitation to participate was published in the magazine of The Norwegian Epilepsy Association. Those who declined a visit at the hospital were offered a home visit.

2.3 Definitions

Based on EEG-recordings and clinical information from the interview and medical charts, participants were classified as JME, CAE, juvenile absence epilepsy (JAE) or epilepsy with generalized tonic-clonic seizures only (EGTCS). CAE, JAE and EGTCS were defined according to the classification of the International League Against Epilepsy (ILAE) [33]. The definition of JME was based on the criteria of the consensus on management and diagnosis of JME, class II [34]. It is stated in the ILAE classification that occasional myoclonic seizures may occur in JAE [33], and absences may occur in JME [34]. Hence, we put emphasis on the dominating seizure type when classifying the different subtypes of

GGE. If absences dominated, the epilepsy was classified as absence epilepsy. If myoclonic seizures dominated, the epilepsy was classified as JME [35]. Patients with intellectual disability ($IQ < 70$) and patients with dysmorphic features were excluded, as were patients who no longer had active epilepsy (no antiepileptic drug treatment and/or no seizures within the last five years) [36]. Intentional non-compliance was defined as quitting antiepileptic drug treatment against medical advice. Active myoclonic seizures/GTCS/absences were defined as occurrence of such seizures at least once within the last year. Exposure to lamotrigine, levetiracetam, or valproate was defined as previous or present use of one of these drugs.

2.4 Clinical interview and Barratt Impulsiveness Scale

All participants underwent a clinical interview by the first author, according to a semi-structured questionnaire designed for this study, details of which are shown in Table 1. The interview included the question “Have you ever discontinued antiepileptic medication against medical advice?” Answering “yes” to this question was defined as intentional non-compliance. Consequently, the definition of intentional non-compliance was based on self-report.

The BIS questionnaire, version 11 was administered to all participants. The BIS consists of 30 items scored on a four-point scale with total score ranging from 30 to 120, higher scores indicating more impulsive behavior. We selected the BIS to assess behavioral impulsivity as it has excellent psychometric properties, it is a well-established and validated tool for investigating impulsive behavioral traits, and it has been used by researchers for more than fifty years [20, 37]. A large population dataset ($n=23,677$) of the BIS-11 was recently published, including European participants from the customer base of 23andme, a consumer genetics company [38].

A Norwegian version of the BIS-11 was available, based on the work of three independent translators at the Faculty of Psychology, University of Bergen. The three independent translations were compared and discussed until consensus on wording was reached. A fourth translator back-translated the final version into English [39]. The Norwegian version of BIS-11 was considered a reliable tool in a sample of patients with Parkinson’s disease ($n=43$) and patients with chronic headache ($n=20$) and healthy controls ($n=47$) [39], but it has not previously been used in Norwegian epilepsy patients.

2.5 Statistical methods

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 25 [40]. A one-way between-groups analysis of covariance (ANCOVA) was conducted to test differences between groups, and to estimate the variance associated with other

potential predictors. The independent variable was type of epilepsy (JME versus other type of GGE), and the dependent variable was total BIS score. Other potential predictors used as covariates were: age, gender, exposure to lamotrigine, exposure to levetiracetam, exposure to valproate, previous examination for attention deficit hyperactivity disorder (ADHD), intentional non-compliance, active GTCS, active myoclonic seizures, and active absences. Exposure to lamotrigine, levetiracetam and/or valproate was included as these drugs are the most common in treatment of GGE, and all have relevant cognitive and behavioral adverse effects. Lamotrigine and valproate may be used as mood stabilizers, and levetiracetam may cause irritability and psychosis [41].

Previous examination for ADHD was chosen above being diagnosed with ADHD, as the total number of participants diagnosed with ADHD was low ($n=9$), and several others had stated that they fulfilled the criteria of ADHD when examined, but were not diagnosed as the symptoms were considered to be related to their epilepsy. We explored only main effects since the study was not adequately powered to detect multiple interactions (Table 2). Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and correlations among the covariates.

A post hoc two-way between-groups analysis of variance (ANOVA) was performed in order to explore the impact of active myoclonic seizures and a diagnosis of JME on the total BIS score. t-tests were performed for comparison of BIS scores between groups. p -values ≤ 0.05 were considered statistically significant.

2.6 Ethics

The study was approved by the Regional Committee for Medical Research Ethics, South East Norway (ethical agreement no. 2013/1027) and by the data protection officer of Drammen Hospital. Written informed consent was obtained from all study participants.

3. Results

3.1 Participants

205 patients were contacted and invited to participate in the study, of which 141 (69%) agreed to be included (Table 1). The mean age of nonparticipants was 25.8 years, and 35 (55%) were female. Five additional patients were recruited from The Norwegian Epilepsy Association. Nine patients were excluded due to intellectual disability (3), suspected monogenic disorder (1), other epilepsy than GGE (3) or epilepsy which was no longer active (2). Finally, 137 patients were included; 92 with JME, 8

with CAE, 22 with JAE and 15 with EGTCS. Of the patients classified as JME, 32 (35%) did not report an obvious morning predominance of seizures. However, seizure types, EEG findings, and age at seizure onset of these patients were typical of JME: thirteen of them had absences, but myoclonic jerks was the dominant seizure type; nineteen had never had absences. These 32 patients were kept in the JME group, as that was the type of GGE best matching their clinical picture.

3.2 Impulsivity in JME versus other types of GGE

The total variance in BIS score explained by the ANCOVA model was 19%, and the model was statistically significant ($F=2.60$, $df=11$, $p=0.005$). Epilepsy syndrome (JME versus other type of GGE) had no significant impact on impulsivity measured by BIS (Table 2). Mean total BIS score was 65.1 ± 10.4 (range 46-92) in participants with JME and 62.0 ± 9.1 (range 39-79) in participants with other types of GGE ($p=0.094$). There was a significant difference when comparing total BIS score of people with JME to the 23andme cohort (mean BIS score 55.9, mean age 53.8 years, 55% female), and healthy Norwegian controls (mean BIS score 58.1, mean age 37.6 years, 80% female) [38, 39].

3.3 Factors influencing impulsivity in GGE

Factors significantly influencing total BIS score were previous examination for ADHD ($F=15.02$, $df=1$, $p<0.001$), and active myoclonic seizures ($F=5.59$, $df=1$, $p=0.034$, Table 3). A post hoc two-way between-groups ANOVA examining the interaction between active myoclonic seizures and JME on total BIS score revealed that there was no statistically significant interaction effect ($F<0.001$, $df=1$, $p=0.987$), meaning that active myoclonic seizures influenced total BIS score regardless of GGE subtype .

Post hoc analyses demonstrated that patients with active myoclonic seizures had significantly higher BIS scores (mean 66.5 ± 9.5 , range 46-94) than those without active myoclonic seizures (mean 61.5 ± 10.0 , range 39-92, $t=3.0$, $df=135$, $p=0.004$, Figure 1). Patients previously examined for ADHD had significantly higher BIS scores (mean 70.5 ± 11.4 , range 51-94), compared with those not examined for ADHD (mean 62.3 ± 8.9 , range 39-91, $t=4.2$, $df=135$, $p<0.001$).

4. Discussion

The present study did not reveal a significant difference in trait impulsivity between JME and other types of GGE. However, the presence of myoclonic seizures, the cardinal symptom of JME, was associated with increased trait impulsivity, regardless of epilepsy type. To the best of our knowledge, this has not been demonstrated earlier.

Even though the exact pathogenesis of JME and other GGEs is still unknown, it has been postulated that the seizure-generating mechanisms of JME involve decreased thalamic inhibition of the supplementary motor cortex and premotor cortex [7], and that this network abnormality also involves areas of the frontal lobes important to executive function. This hypothesis offers an explanation as to why cognitive efforts may trigger myoclonic seizures in people with JME [5, 6] and is relevant to the phenomenon of praxis induction, which is particularly common in JME [42]. A region of focus within this network is the dorsolateral prefrontal cortex, which is involved in behavioral inhibition, regulation of attention, and cognitive control in social situations [43-45]. Intriguingly, impulsive decision-making by JME patients during a gambling task was shown to be associated with increased activation of the dorsolateral prefrontal cortex [27], and patients with active seizures made more risky choices. Patients with JME who were free of any kind of seizures, including myoclonic seizures, performed similarly to controls, electing cautious responses with small gains and losses [27, 28]. Moreover, connectivity studies have shown that degree of abnormal connectivity was related to disease severity [6, 7]. These results are consistent with our finding of increased trait impulsivity in patients with active myoclonic seizures.

Even though there was an association between trait impulsivity and active myoclonic seizures, no difference in trait impulsivity was demonstrated when comparing JME to other types of GGE. Correct classification and diagnosis of epilepsy syndrome was a key factor in our study design and sometimes represents a considerable clinical challenge. According to the ILAE and the international consensus on diagnosis of JME, people with JME often have absences, and people with JAE may have myoclonic seizures [33, 34]. Differentiating between the two syndromes is not necessarily easy when all three seizure types are present (GTCS, absences, and myoclonic seizures). We chose to emphasize the dominating seizure type: myoclonic jerks for JME, and absences for JAE. However, if there is an association between trait impulsivity and active myoclonic jerks, more weight should perhaps be added to this symptom, bearing the potentially problematic consequences of impulsivity in mind [15-21]. It could be that people with absence epilepsy experiencing occasional myoclonic seizures represent a different type of epilepsy with different seizure-generating mechanisms than absence epilepsy without myoclonic seizures. Perhaps this group of patients has more in common with JME and should be classified as such.

A control group of non-GGE epilepsy was not included in the present study. We identified one other study using the BIS-11 in JME, comparing the scores of patients with JME (n=20) to a control group of temporal lobe epilepsy (n=20), and healthy controls (n=26). In addition to higher BIS scores than healthy controls, patients with JME also had significantly higher BIS scores than those with temporal

lobe epilepsy, in support of trait impulsivity as a JME-related feature. Other types of GGE were not included, however, and seizure activity was not taken into consideration [26].

In addition to not including a non-GGE epilepsy control group, it is a considerable limitation that a concurrent healthy control group was not included in the present study. Even though our main focus of interest was to compare trait impulsivity across the subtypes of GGE, a healthy control group would have added important information.

Still, the sample size of the present study was considerably larger than that of previous studies of trait impulsivity in JME [22-26], and consequently provided the possibility to estimate variance associated with a number of potential predictors, including antiepileptic drug use and intentional non-compliance. Including non-compliance was particularly important, as it might be expected that non-compliant patients discontinuing medication against medical advice would be more impulsive. The variance associated with this variable was negligible, however. Nevertheless, an objective measure of non-compliance, like monitoring plasma concentrations of antiepileptic drugs, was not included, and intentional non-compliance was based on self-report. Thus, non-intentional non-compliance (non-adherence), i.e. non-compliance due to forgetfulness and distraction could not be assessed. This may well have explained some of the variance associated with behavioral impulsivity and in fact may share some of the variance associated with active myoclonic seizures: impulsive individuals may be more likely to struggle with adherence to medical prescription and lifestyle modification due to distraction and difficulties with planning and maintaining healthy behavior. However, these traits may lead to breakthrough GTCS and absences, not just myoclonic seizures. The fact that we found no statistical association between behavioral impulsivity and active GTCS or absences suggests that the association between BIS score and compliance is less important. We cannot entirely rule out active myoclonic seizures as a marker of seizure frequency however, as these seizures are more common than GTCS, and absence seizures may be subtle and sometimes not noticed. Although 19% of the total variance in the BIS score was explained by our statistical model, it is clear that several unidentified factors contribute significantly to trait impulsivity in this patient group and remain to be recognized.

In addition to active myoclonic seizures, we found that being examined for ADHD was a strong moderator of BIS score, with significantly higher scores in the group examined for ADHD. This is not surprising, as impulsivity is included in the definition of ADHD [47], and executive dysfunction in ADHD is well described [48]. Interestingly, microstructural changes involving the dorsolateral prefrontal cortex are demonstrated both in ADHD and in JME [4, 49]. Increased prevalence of ADHD

in the epilepsy population is well documented [50, 51], but the link between ADHD, JME and frontal lobe dysfunction has to the best of our knowledge not been explored.

Even though we present a large study sample, participation rate was not optimal (69%) and may introduce selection-bias. It is not unlikely that the individuals most affected by trait impulsivity were among the non-participants. Highly impulsive individuals are probably challenging to recruit for clinical studies involving a physical appointment, like ours. We know from our review of medical records that some of the non-participants had considerably disorganized lifestyles, sometimes involving drug abuse and criminal records. Hence, a sub-optimal participation rate could bias the findings towards less pronounced impulsivity.

In previous research regarding JME, neither the structural and functional connectivity studies [5-7], nor the choice impulsivity studies [27, 28] included patients with other types of GGE. If there is an association between the hallmark *symptom* of JME, namely the myoclonic seizures, rather than the diagnosis of JME per se, and we know myoclonic seizures can be present in patients with other types of epilepsy such as absence epilepsy, future studies should focus on the myoclonic seizure type across syndromes. This could also be of aid in the search for genetic causes of GGE, indicating for example the need for multiphenotype analysis across subtypes. An association between active myoclonic seizures and impulsivity has not been demonstrated earlier, however, and needs replication in future studies.

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Declaration of interests

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References

- [1] Asconape J, Penry JK. Some clinical and EEG aspects of benign juvenile myoclonic epilepsy. *Epilepsia* 1984;25: 108-14.
- [2] Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile myoclonic epilepsy: a 5-year prospective study. *Epilepsia* 1994;35: 285-96.
- [3] Canevini MP, Mai R, Di Marco C, Bertin C, Minotti L, Pontrelli V, et al. Juvenile myoclonic epilepsy of Janz: clinical observations in 60 patients. *Seizure* 1992;1: 291-8.
- [4] Kim JH. Grey and white matter alterations in juvenile myoclonic epilepsy: a comprehensive review. *J Epilepsy Res* 2017;7: 77-88.
- [5] Vollmar C, O'Muircheartaigh J, Symms MR, Barker GJ, Thompson P, Kumari V, et al. Altered microstructural connectivity in juvenile myoclonic epilepsy: the missing link. *Neurology* 2012;78: 1555-9.
- [6] Vollmar C, O'Muircheartaigh J, Barker GJ, Symms MR, Thompson P, Kumari V, et al. Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study. *Brain* 2011;134: 1710-9.
- [7] O'Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, et al. Abnormal thalamocortical structural and functional connectivity in juvenile myoclonic epilepsy. *Brain* 2012;135: 3635-44.
- [8] Wolf P, Yacubian EM, Avanzini G, Sander T, Schmitz B, Wandschneider B, et al. Juvenile myoclonic epilepsy: A system disorder of the brain. *Epilepsy Res* 2015;114: 2-12.
- [9] Wandschneider B, Thompson PJ, Vollmar C, Koepp MJ. Frontal lobe function and structure in juvenile myoclonic epilepsy: a comprehensive review of neuropsychological and imaging data. *Epilepsia* 2012;53: 2091-8.

- [10] Miyake A, Friedman NP. The nature and organization of individual differences in executive functions: four general conclusions. *Curr Dir Psychol Sci* 2012;21: 8-14.
- [11] Jurado MB, Rosselli M. The elusive nature of executive functions: a review of our current understanding. *Neuropsychol Rev* 2007;17: 213-33.
- [12] Smith A, Syvertsen M, Pal DK. Meta-analysis of response inhibition in juvenile myoclonic epilepsy. *Epilepsy Behav* 2020; in press.
- [13] Chamberlain SR, Sahakian BJ. The neuropsychiatry of impulsivity. *Curr Opin Psychiatry* 2007;20: 255-61.
- [14] Robbins TW. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philos Trans R Soc Lond B Biol Sci* 2007;362: 917-32.
- [15] Audrain-McGovern J, Rodriguez D, Epstein LH, Cuevas J, Rodgers K, Wileyto EP. Does delay discounting play an etiological role in smoking or is it a consequence of smoking? *Drug Alcohol Depend* 2009;103: 99-106.
- [16] Ziauddeen H, Farooqi IS, Fletcher PC. Obesity and the brain: how convincing is the addiction model? *Nat Rev Neurosci* 2012;13: 279-86.
- [17] Nigg JT, Wong MM, Martel MM, Jester JM, Puttler LI, Glass JM, et al. Poor response inhibition as a predictor of problem drinking and illicit drug use in adolescents at risk for alcoholism and other substance use disorders. *J Am Acad Child Adolesc Psychiatry* 2006;45: 468-75.
- [18] Moallem NR, Courtney KE, Ray LA. The relationship between impulsivity and methamphetamine use severity in a community sample. *Drug Alcohol Depend* 2018;187: 1-7.
- [19] Garcia-Marchena N, Ladron de Guevara-Miranda D, Pedraz M, Araos PF, Rubio G, Ruiz JJ, et al. Higher impulsivity as a distinctive trait of severe cocaine addiction among individuals treated for cocaine or alcohol use disorders. *Front Psychiatry* 2018;9: 26.
- [20] Patton J, Stanford M, Barratt E. Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology* 1995;51: 768-74.
- [21] Foroozandeh E. Impulsivity and impairment in cognitive functions in criminals. *Forensic Res Criminol Int J* 2017;5: 00144.

- [22] Iqbal N, Caswell H, Muir R, Cadden A, Ferguson S, Mackenzie H, et al. Neuropsychological profiles of patients with juvenile myoclonic epilepsy and their siblings: an extended study. *Epilepsia* 2015;56: 1301-8.
- [23] Iqbal N, Caswell HL, Hare DJ, Pilkington O, Mercer S, Duncan S. Neuropsychological profiles of patients with juvenile myoclonic epilepsy and their siblings: a preliminary controlled experimental video-EEG case series. *Epilepsy Behav* 2009;14: 516-21.
- [24] Moschetta S, Fiore LA, Fuentes D, Gois J, Valente KD. Personality traits in patients with juvenile myoclonic epilepsy. *Epilepsy Behav* 2011;21: 473-7.
- [25] Pulsipher DT, Seidenberg M, Guidotti L, Tuchscherer VN, Morton J, Sheth RD, et al. Thalamofrontal circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy. *Epilepsia* 2009;50: 1210-9.
- [26] Rzezak P, Moschetta SP, Lima E, Castro CX, Vincentiis S, Coan AC, et al. Distinct domains of impulsivity are impaired in juvenile myoclonic epilepsy but not in temporal lobe epilepsy. *Epilepsy Behav* 2015;45: 44-8.
- [27] Wandschneider B, Centeno M, Vollmar C, Stretton J, O'muircheartaigh J, Thompson PJ, et al. Risk-taking behavior in juvenile myoclonic epilepsy. *Epilepsia* 2013;54: 2158-2165.
- [28] Zamarian L, Hofler J, Kuchukhidze G, Delazer M, Bonatti E, Kemmler G, et al. Decision making in juvenile myoclonic epilepsy. *J Neurol* 2013;260: 839-46.
- [29] Hoie B, Sommerfelt K, Waaler PE, Alsaker FD, Skeidsvoll H, Mykletun A. The combined burden of cognitive, executive function, and psychosocial problems in children with epilepsy: a population-based study. *Dev Med Child Neurol* 2008;50: 530-6.
- [30] Jackson DC, Dabbs K, Walker NM, Jones JE, Hsu DA, Stafstrom CE, et al. The neuropsychological and academic substrate of new/recent-onset epilepsies. *J Pediatr* 2013;162: 1047-53 e1.
- [31] Syvertsen M, Nakken KO, Edland A, Hansen G, Hellum MK, Koht J. Prevalence and etiology of epilepsy in a Norwegian county: a population based study. *Epilepsia* 2015;56: 699-706.
- [32] Nakken KO, Kjendbakke ES, Aaberg KM. Ny kunnskapsbasert retningslinje om epilepsi [New evidence based guideline on epilepsy]. *Tidsskr Nor Laegeforen* 2017;137: 16-17.

- [33] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30: 389-99.
- [34] Kasteleijn-Nolst Trenite DG, Schmitz B, Janz D, Delgado-Escueta AV, Thomas P, Hirsch E, et al. Consensus on diagnosis and management of JME: from founder's observations to current trends. *Epilepsy Behav* 2013;28 (Suppl 1): S87-90.
- [35] Syvertsen M, Hellum MK, Hansen G, Edland A, Nakken KO, Selmer KK, et al. Prevalence of juvenile myoclonic epilepsy in people <30 years of age: a population-based study in Norway. *Epilepsia* 2017;58: 105-112.
- [36] Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, et al. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia* 2011;52 (Suppl 7): 2-26.
- [37] Stanford M, Mathias C, Dougherty D, Lake S, Anderson N, Patton J. Fifty years of the Barratt impulsiveness scale: an update and review. *Personality and Individual Differences* 2009;47: 385-95.
- [38] Sanchez-Roige S, Fontanillas P, Elson SL, Gray JC, de Wit H, MacKillop J, et al. Genome-Wide Association Studies of impulsive personality traits (BIS-11 and UPPS-P) and drug experimentation in up to 22,861 adult research participants identify loci in the *CACNA1I* and *CADM2* genes. *J Neurosci* 2019;39: 2562-2572.
- [39] Lindstrom JC, Wyller NG, Halvorsen MM, Hartberg S, Lundqvist C. Psychometric properties of a Norwegian adaption of the Barratt Impulsiveness Scale-11 in a sample of Parkinson patients, headache patients, and controls. *Brain Behav* 2016;7:e00605.
- [40] IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp; 2017.
- [41] Beydoun A, D'Souza J. Treatment of idiopathic generalized epilepsy: a review of the evidence. *Expert Opin Pharmacother* 2012;13: 1283-98.
- [42] Yacubian EM, Wolf P. Praxis induction. Definition, relation to epilepsy syndromes, nsological and prognostic significance. A focused review. *Seizure* 2014;23:247-51.
- [43] Weissman DH, Perkins AS, Woldorff MG. Cognitive control in social situations: a role for the dorsolateral prefrontal cortex. *Neuroimage* 2008;40: 955-962.
- [44] Lebedev MA, Messinger A, Kralik JD, Wise SP. Representation of attended versus remembered locations in prefrontal cortex. *PLoS Biol* 2004;2: e365.

- [45] Rowe JB, Passingham RE. Working memory for location and time: activity in prefrontal area 46 relates to selection rather than maintenance in memory. *Neuroimage* 2001;14: 77-86.
- [46] Syvertsen MR, Thuve S, Stordrange BS, Brodtkorb E. Clinical heterogeneity of juvenile myoclonic epilepsy: follow-up after an interval of more than 20 years. *Seizure* 2014;23:344-8.
- [47] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington DC: American Psychiatric Association; 2013.
- [48] Rubia K. Cognitive neuroscience of attention deficit hyperactivity disorder (ADHD) and its clinical translation. *Front Hum Neurosci* 2018;12: 100.
- [49] Rubia K, Alegria A, Brinson H. Imaging the ADHD brain: disorder-specificity, medication effects and clinical translation. *Expert Rev Neurother* 2014;14: 519-38.
- [50] Alfstad KA, Clench-Aas J, Van Roy B, Mowinckel P, Gjerstad L, Lossius MI. Psychiatric symptoms in Norwegian children with epilepsy aged 8-13 years: effects of age and gender? *Epilepsia* 2011;52: 1231-8.
- [51] Davies S, Heyman I, Goodman R. A population survey of mental health problems in children with epilepsy. *Dev Med Child Neurol* 2003;45: 292-5.

Tables

	JME N=92	Other GGE N=45
Female	55 (60%)	26 (58%)
Age at inclusion (years)	25.8 ± 6.9	23.5 ± 6.7
Epilepsy duration (years)	11.1 ± 6.5	11.3 ± 8.1
Active GTCS	20 (22%)	8 (18%)
Active myoclonic seizures	63 (68%)	7 (16%)
Active absence seizures	9 (10%)	9 (20%)
Exposure to lamotrigine	61 (66%)	29 (64%)
Exposure to valproate	56 (61%)	27 (60%)
Exposure to levetiracetam	42 (46%)	11 (24%)
Previous examination for ADHD	23 (25%)	6 (13%)
Intentional non-compliance	26 (28%)	10 (22%)

Table 1: Clinical characteristics of the study-participants. JME = juvenile myoclonic epilepsy, GGE = genetic generalized epilepsy, GTCS = generalized tonic-clonic seizures, ADHD = attention deficit hyperactivity disorder.

Variables	F value	p value
JME versus GGE	0.04	0.844
Age	0.71	0.402
Gender	0.02	0.885
Active GTCS	0.85	0.359
Active myoclonic seizures	4.59	0.034
Active absence seizures	1.51	0.222
Exposure to lamotrigine	0.01	0.916
Exposure to levetiracetam	0.79	0.377
Exposure to valproate	<0.01	0.981
Previous examination for ADHD	15.02	<0.001
Intentional non-compliance	1.10	0.296

Table 2: Associations of BIS score in multivariate ANCOVA analysis. JME = juvenile myoclonic epilepsy, GGE = genetic generalized epilepsy, GTCS = generalized tonic-clonic seizures.

Figures

Figure 1: Bar graph showing mean Barratt Impulsiveness Scale (BIS) scores for patients with juvenile myoclonic epilepsy (JME) versus other type of genetic generalized epilepsy (GGE) with and without active myoclonic seizures. *Mean BIS score active myoclonic seizures = 66.5, mean BIS score inactive myoclonic seizures 61.5, $p=0.004$.

Figure to appear in color online only.