

Variations in cognitive functioning in genetic generalized epilepsy: four case studies

Evangelina E. Ballini¹, Edward Helmes¹, Bruce K. Schefft²

¹ Department of Psychology, College of Healthcare Sciences, Division of Tropical Health and Medicine, James Cook University, Cairns, Australia

² University of Cincinnati, Cincinnati, OH, USA

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Correspondence

Evangelina Ballini
7 Cottonwood Close
Mount Sheridan, Australia, 4868
Phone: 61 0 7 4036 3082
E-mail: evangelina.ballini@my.jcu.edu.au

SUMMARY

Introduction. The traditional view of cognition in idiopathic or genetic generalized epilepsy (GGE) is that “one size fits all” i.e. only very mild generalized impairment might be detected, if any. This paper describes four case studies of cognitive functioning in GGE patients with photosensitivity and reflexive seizures.

Aim. The aim was to discover whether each individual’s set of cognitive deficits varied in accordance with his/her other clinical phenomena such as photosensitivity and kinds of reflexive seizures.

Method. Neurological and cognitive performance was assessed by comprehensive evaluation of each patient based on interviews, neurologist’s EEG reports and neuropsychological tests. Assessment of cognitive domains included estimated pre-morbid I.Q. based on reading ability and demographic norms, current I.Q., attention factors, verbal memory, visual memory and executive functions.

Results. Clinical signs and investigative studies indicated that two cases typically began reflexive seizure episodes with facial myoclonia which evolved into tonic-clonic convulsions or generalized myoclonic seizures. These patients had widespread attention and working memory deficits, some severe, together with lowered intelligence scores. In contrast, two other cases (with no history of myoclonus) had generalized reflexive seizures originating in the occipital lobes, very mild localized visual dysfunction and high intelligence.

Conclusions. The systematic variation in extent and nature of cognitive dysfunction illustrated in these cases with reflexive seizures (preceded by myoclonia or visual phenomena) would be explained by a more recent conceptualization of GGE as encompassing regional differences in variable hyperexcitability located at cortical levels or functional neural networks.

Key words: neurocognitive dysfunction • photosensitivity • reflexive seizures • areas of variable hyperexcitability

INTRODUCTION

Cognitive profiles for GGE sub-types

Genetic generalized epilepsy’s idiopathic origins and generalized seizures suggests a benign impact on cognitive functioning, and if this is so, any impairment would be expected to manifest as a slight lowering of abilities generally, without localized deficits (Hom-

met et al., 2006). The terms *idiopathic generalized epilepsy* (IGE) or the more recent *genetic generalized epilepsy* (GGE) are synonymous and cover a collection of sub-types, each with a particular symptomology characterized by seizure-type, age at onset of the disorder,

and a diurnal or nocturnal trigger for seizures (Wolf, 2005). The sub-types are united by the pathognomonic spike-and-wave pattern observed on EEG but differ in their genetic aetiology.

In reality, the heterogeneity of GGE sub-types would argue against one cognitive profile for all, and indeed the research literature does report localized cognitive deficits (Hommet et al., 2006). For example, juvenile myoclonic epilepsy (JME) deficits of executive function have been found to be associated with cortical dysfunction of the prefrontal cortex specifically the anterior cingulate (Devinsky et al., 1997; Hommet et al., 2006).

Reflexive seizures represent an anomaly in researchers' knowledge of the brain's mechanisms in generalized epilepsy: a localized seizure onset occurring within a generalized epilepsy disorder (Zifkin, 2010). Their findings on the mechanisms of reflexive seizures, especially the absence of uniformity in levels of excitability across such brains, might begin to explain the reported variety of cognitive dysfunctions and the presence of localized impairments associated with genetic generalized epilepsy.

Varieties of reflexive seizures

Reflexive seizures, such as absences, generalized convulsions, or bilateral myoclonic jerks, occur when the person with epilepsy has regions of cortical or sub-cortical hyperexcitability (Zifkin and Inoue, 2004). Ferlazzo et al. (2005) have described such regions of hyperexcitability as overlapping or coinciding with areas physiologically activated during sensory, cognitive or motor stimulation. Complex cognitive stimuli can activate widely distributed regions involving multiple cortical areas or alternatively, relatively localized cortical networks subserving specific functions might be activated by simple sensory stimuli (Ferlazzo et al., 2005; Wolf and Koeppe, 2012).

Ferlazzo et al., (2005) have identified four patterns of generalized or bilateral reflexive seizures, each with its own focal cortical trigger (for a succinct summary, see table 1). Photosensitivity to specific visual stimuli such as flickering lights or patterns (e.g. light/shade contrasts in sunlight or stripes on television) originates in the visual-occipital cortex. This kind of photosensitivity manifests as elementary visual phenomena which forewarn the onset of a diffuse tonic-clonic convulsive seizure (Zifkin, 2010).

Although photosensitivity is often found to be a component of juvenile myoclonic epilepsy (e.g. reflex myo-

clonic epilepsy in infancy), these seizures are not signalled by the visual phenomena accompanying seizure onset in the occipital cortex (Mayer et al., 2006). Bright uninterrupted or flashing lights and other sensory phenomena (sudden touch or noise) might stimulate repeated eyelid myoclonia if there is a heightened tendency to motor dyscontrol originating in the sensorimotor cortex (Ferlazzo et al., 2005). Repeated facial myoclonia can signal the onset of bilateral absence status terminating in convulsive seizures (Zifkin and Inoue, 2004; Mayer et al., 2006).

In contrast to the specific territories activated by visual stimuli, complex stimuli activate widespread regions of hyperexcitability (rather than single cortical territories). Cognitive tasks accessing verbal (reading, writing) or non-verbal (some motor sequences, mental rotations) functions can physiologically stimulate systems of complex functional networks. Such systems subserving cognitive triggers usually extend across both hemispheres of the frontotemporal lobes (Ferlazzo et al., 2005).

A patient's reported sensitivity to certain stimuli acting as triggers for reflexive seizures can be taken by the clinician as an indicator of which functional networks or systems might be involved during such seizures, and thus which associated cognitive functions might need to be examined for possible impairment.

The four cases described in this paper belonged to differing GGE sub-types, three of which produced a variety of cognitive impairments. The question was whether each individual's group of cognitive dysfunctions could be shown to be theoretically congruent with his/her other clinical phenomena such as sensitivity to specific stimuli, the cortical regions activated in either widespread diffusion or strictly limited fashion, and the type of reflexive seizures precipitated.

METHOD

The study was approved by the Research Ethics Committee of James Cook University, Townsville and also by the Medical Research Ethics Committee of the Cairns Base Hospital in Far North Queensland, Australia.

Design

Neuropsychological assessment of cognitive domains included estimated pre-morbid I.Q. based on demographic norms, current estimated I.Q., attention, verbal memory, visual memory and executive functions. A neurologically healthy control group to test for indi-

vidual cognitive deficits was not included, but population norms were used to convert participants' raw data to z-scores for comparison across tasks.

Cognitive performance dysfunction was assessed by a comprehensive evaluation of each patient based on interviews, EEG, MRI and/or CT reports, letters from the patient's physician, and neuropsychological test results. The intake interview and neuropsychological assessments were conducted over four sessions for each patient. Two hours were allocated for each session, depending on the patient's convenience and degree of fatigue. Most of the first session was devoted to an intake interview with the patient and any family member invited by the patient. The second and third sessions involved administration of the neuropsychological assessment tasks. The final session was devoted to completion of an emotional-social assessment (not reported here), and any outstanding cognitive tasks. An informal follow-up review of patients' medical records and ER admission notes was conducted some 12 months after completion of the initial project.

Participants

The cases described in this paper were four individuals with GGE with reflexive seizures (2 females, 2 males) with an age range of 21 to 43 years, and 9 to 13 years of formal education. They were part of a larger study (number = 24 patients) on cognition and mental disorders of adults with epilepsy with a focus on cases involving status epilepticus seizures of unknown aetiology. The larger study included brief-duration seizure cases (asymptomatic temporal lobe epilepsy or idiopathic generalized epilepsy) as comparison groups on cognitive functioning. All participants were administered the same tasks and testing.

Participants were recruited from the Emergency Department and an outpatient Epilepsy Clinic of the Cairns Base Hospital (CBH) Queensland by the hospital neurologist and epileptologist, running its Diagnostic Unit and Epilepsy Clinic at CBH. Potential participants for the larger study were selected by the neurologist from a pool of some 600 patients, the majority involving cases with status epilepticus or temporal lobe epilepsy. Any medical records of patients with symptomatic aetiologies were automatically excluded. Exclusion criteria comprised brain injury or diseases (e.g. stroke or tumour) detected on MRI or CAT scans, anxiety, psychopathology (e.g. bipolar or schizophrenia), any drug dependence within the 24 months previous to

testing, intellectual impairment or related developmental delay. Other exclusion criteria included age (participants had to be over 18 years of age) and the presence of psychogenic seizures or syncope.

FOUR CASE STUDIES

To protect the anonymity and confidentiality of the participants, the case names used here are pseudonyms.

Photosensitivity

Three of the four cases described here showed a photo-paroxysmal response (PPR) on their EEG recordings. One patient did not respond to intermittent photic stimulation (IPS), but reported seizures precipitated by strobe lights during adolescence and early youth i.e. age-dependent photosensitivity (Wolf and Koepp, 2012).

Photosensitivity has been defined as "an abnormal visual sensitivity of the brain in reaction to flickering light sources or patterns expressed in the EEG as generalized spike-and-wave discharge or photo-paroxysmal response (PPR)" (Covanis, 2005). Photosensitivity can occur in several family members suggesting a genetic origin (Zifkin and Trenite, 2000; Taylor et al., 2003), and is most prevalent in idiopathic epilepsies such as IGE, JME and less commonly in localization-related occipital epilepsies (Taylor et al., 2004; Covanis, 2005).

Covanis (2005) has described two types: *purely photosensitive epilepsy* where all an individual's seizures are triggered only by lights or by intermittent photic stimulation (IPS) in the laboratory; and *epilepsy with photosensitivity* where an individual's disorder has a photosensitive component which might sometimes trigger reflexive generalized seizures but the patient may have other kinds of seizures also.

A variety of triggers include television, video and computer games, natural light (sunlight reflection), and environmental light (fluorescent, disco strobes) (Destina Yalçin et al., 2000; Covanis, 2005; Szabo, 2010).

SHER: Eyelid myoclonia in JME

History

Sher was a 21 years old single female, from an indigenous background, with a family history of epilepsy including rapid blinking. First seizure onset was at 18 years of age, with a history of 8 major seizures at time of testing. Sher described seizure onset as fast eyelid fluttering and blinking which warned her to lie down. "I lie down, my eyes and head start to jerk back, the big fit comes. I'm really tired afterwards". She described sei-

zure episodes demonstrating sensitivity to both flickering lights (television) and bright lights (mechanized fair-ground rides at night).

Investigations and diagnosis

An EEG at 21 years reported a posterior dominant rhythm of 10 Hz alpha which was symmetric and responsive to eye opening. Throughout the resting record there were runs of generalised polymorphic theta and delta slowing, and moderately frequent 1–2 second bursts of generalised sharp and slow wave activity at 3–5 Hz frontocentrally. Photic stimulation at 7 Hz was associated with a train of generalised discharges, resulting in a diagnosis of JME with photosensitivity

Neuropsychological assessment

Neuropsychological assessment found mild to moderately impaired functions of attention and working memory, executive dyscontrol of attention. Her Verbal I.Q. was significantly lower than might be expected when compared to someone of the same age, demographic profile, and average reading level. Mildly impaired vocabulary and naming scores most likely reflected poor school attendance due to cultural factors. Impaired inhibition of attention responses matched the EEG report of a frontocentral focus for abnormal activity.

Diagnostic Considerations

Uncontrollable rapid blinking and head jerking back might fit a diagnosis of eyelid myoclonia with absences (EMA) followed by a convulsive seizure (Panayiotopoulos, 2005a). In addition, people with EMA are all photosensitive not only to the flickering lights which might evoke reflex seizures in other epilepsies, but also to bright uninterrupted light (Covanis, 2005). However, Sher denied having brief absences, epilepsy onset was relatively late for EMA (18 years) and her EEG did not match a typical EMA pattern (Destina Yalçin et al., 2006; Capovilla et al., 2009).

BELA: Perioral myoclonia and absence status

Perioral myoclonia with absences (PMA) have been described as short, sometimes repetitive, abrupt myoclonia around the mouth, involving contractions of the facial and mastication muscles, twitching at corners of the mouth, or more rarely, widespread chewing and jaw jerking. Most of these jerks appear strongly localized but they can occur bilaterally (Mayer et al., 2006).

Impaired awareness ranges from mild to severe, average duration is about 4 seconds (Mayer et al., 2006).

Absence status epilepticus is more common in PMA than in any other IGE sub-syndrome (57%), and frequently ends with generalized tonic-clonic seizures (Bilgiç et al., 2001; Panayiotopoulos, 2005b). PMA are rare in the complex partial seizures of TLE, but are more likely to occur during secondarily generalized tonic-clonic seizures (Shorvon and Walker, 2005).

Brain scans are normal but interictal EEG shows generalized discharges of spikes or multiple (3–4) spikes, and slow waves (4–7) Hz, usually asymmetrical, giving impression of a localized focus (Panayiotopoulos, 2005a, 2005b).

History

Bela was a 35 year old female, married, with a family history of epilepsy. Seizure onset was at 7 years of age with brief tonic-clonic seizures sometimes triggered by flashing lights. Later seizures with loss of consciousness lasted 20 minutes, with tongue-biting and occasional incontinence, followed by lethargy and sleep for up to six hours. Bela's husband described her as being "dazed and twitching all day before an attack".

Investigations and diagnosis

Neuroimaging was normal. An EEG at 35 years of age recorded facial twitching episodes associated with discharges of generalized 3 Hz spike-and-wave activity, without a photo-paroxysmal response. Bela did report having to avoid nightspots in her youth, after several occurrences of convulsive seizures triggered by the strobe lights, suggesting age-dependent photosensitivity. Bela was diagnosed as having GGE and perioral myoclonia with absences. Yet, if her husband's comment about her being "dazed all day" is accepted, then her repeated absences were a form of absence status epilepticus, which after several hours often ended in a tonic-clonic seizure.

Neuropsychological assessment

Cognitive assessment found widespread attention dysfunction, including moderate to severely impaired inhibition of attention responses associated with the anterior cingulate gyrus and mildly impaired visual selective attention and flexibility, both functions associated with the right pre-frontal cortex. Estimated I.Q. was significantly lower than might be expected when compared to someone of the same age, demographic profile, and average reading level.

Diagnostic Considerations

Some features of Bela's case suggest the possibility of secondary reading epilepsy i.e. the twitches of orofacial muscles which sometimes accompany the act of reading (Wolf and Koeppe, 2012). She mentioned reading as a pass-time but said she could no longer focus on the words, often having to re-read a page or stop reading altogether. She did not draw a causal connection between reading difficulties and any major seizures. Complex language-related triggers (reading or talking) require time to build-up, perhaps several minutes, before precipitating a seizure (Wolf and Koeppe, 2012).

Idiopathic Occipital Lobe Epilepsy?

Taylor et al. (2003) wrote that occipital lobe epilepsies can be misdiagnosed as they often present as other seizure syndromes. The following two cases were diagnosed with GGE, but the neurologist also suggested idiopathic occipital lobe epilepsy (IOLE) as an alternative possibility. The two disorders have been differentiated on their levels of cognitive functioning: IOLE has been found to negatively affect not only visual functions, but also attention, memory, verbal abilities (Gülgönen et al., 2000).

JOSH: GGE with bilateral occipital lobe onset

History

Josh was 41 years old when he attended the epilepsy clinic for assessment and diagnosis. He had had four convulsive seizures in the past six years, and there was a family history of epilepsy. Josh reported suffering from migraines since about 25 years of age, several of which had been triggered by a sensitivity to artificial lighting. His first convulsive seizure occurred at 35 years of age, late at night after seeing a movie. On-lookers described him falling backward and tongue-biting. He reported subsequent seizures occurring at night when he was over-tired after more than twelve hours at work. The strobe lighting in his work-place had not triggered convulsive seizures to date.

Investigations and diagnosis

An EEG recorded at 41 years of age detected bilateral abnormalities predominant in the occipital region during intermittent photic stimulation (IPS). A CT scan taken at the time of assessment and after the most recent seizure was unremarkable. Josh's neurologist diagnosed GGE, with occipital epilepsy as a possible alternative. The clinical history supported a GGE diagnosis since clinical signs for idiopathic occipital lobe

epilepsy (IOLE) were absent: no preceding visual aura or the colourful hallucinations characteristic of OLE.

Neuropsychological assessment

While neuropsychological assessment did not detect any generalized impairments, localized visual deficits included mildly impaired retrieval from visual memory ($z = -1.89$), contrasting with an estimated Verbal I.Q. of 132 (very superior). Visual fluency ($z = -0.33$) was much reduced compared to verbal fluency ($z = 2.83$). Other functions were remarkably intact and well preserved.

JON: GGE with right occipital lobe onset

History and diagnosis

Jon was 43 years old, married with children, and worked in a senior position in a machinery workshop. He attended the clinic for a review of his condition, after a generalized convulsive seizure which was probably due to abruptly discontinuing his medication (phenytoin). Family history and the sole trigger suggest a purely photosensitive base for Jon's seizures (Guerrini et al., 1995; Zifkin and Inoue, 2004)

Jon's first seizure was at 7 years of age and occurred in the school playground. It began with visual scintillations in the left upper visual field. On the left side of his vision he was able to see only the lower half of images whilst vision on the right remained normal (left superior quadrantanopia). He then lost consciousness. Similar events occurred at least twice a year and were diagnosed as migraines until his teens, when a diagnosis of epilepsy and phenytoin treatment reduced the frequency of convulsive seizures.

His wife described the more recent seizures which have all occurred whilst watching television. They begin with sustained head and eye deviation to the left with no vocalisation or response to questioning, lasting 15–20 seconds after which he begins to shake and quiver with all four limbs for another 30 seconds. He then becomes obtunded for 10–15 minutes. His wife has not noticed any absence seizures, but Jon described very brief "turns" (10 seconds) which occur 2–3 times monthly. They are preceded by sensations of spatial disorientation in usually familiar settings (e.g. "where's the door to my house?").

Investigations

At 37 years, an EEG recorded paroxysms of high voltage slow activity bilaterally indicating genetic generalised epilepsy. A more recent EEG at the clinic showed right

occipital abnormalities, together with a PPR response. A CT detected no structural abnormalities.

Neuropsychological assessment

Performance of cognitive tasks was in the average to above average range, with estimated Verbal I.Q. = 138 (very superior) and Performance I.Q. = 117 (high average). Compared to his overall superior level of performance, a few nonverbal tasks assessing the right hemisphere's visual and/or spatial functions revealed reduced performance which did not reach impairment levels. These included recall of abstract visual figures ($z = -1.40$) and visual scanning for a specific location in space. The temporal and occipital lobes might be very mildly affected by focal activity as recorded in the EEG. These minor dysfunctions should be taken in context, since his overall performance was at a consistently superior level across most cognitive domains.

In conclusion, all four cases had EEG reports of generalized spike-and-wave activity, and they had either PPR in their most recent EEG laboratory results or a history of photosensitive seizures. In addition, all four cas-

es had evidence of reflexive seizures being precipitated by visual stimuli. Even though they all had genetic generalized epilepsy unified by the presence of photosensitivity, their neuropsychological assessments found individual variations in the nature and level of cognitive dysfunction.

RESULTS

Table 1 details the diagnostic criteria for each participant's epilepsy disorder, the presence of any reflexive components in the seizure semiology, seizure properties and reserve capacity (years of education). Information about medications and abnormal EEG results is included. No abnormalities were detected by CT or MRI scans carried out for each patient. To protect anonymity, case names are pseudonyms.

The disorder characteristics and EEG findings in table 1 subdivide the four GGE participants into two pairs of cases: Josh and Jon both had an occipital onset to their abnormal EEG activity, while Bela and Sher were observed to have facial myoclonia, sometimes associated with seizure activity. Their cognitive dysfunc-

Table 1. Disorder characteristics, medications and EEG results for GGE cases

Case Name	Josh	Jon	Sher	Bela
Gender	M	M	F	F
Age	41	43	21	35
Mode of Onset				
Generalized	√	√	√	√
Localized		√		
Aetiology				
Idiopathic/Genetic	√	√	√	√
Reflex Components				
Absences				√
Photosensitivity	√	√	√	√
Eyelid Myoclonia			√	
Perioral Myoclonia				√
Seizure Properties				
Seizure Type	T-C	T-C	JME	T-C
Age at onset	35	7	18	7
No. years burden	6	36	3	28
GGE Seizure burden	4	6	8	56
Reserve Capacity				
Years Schooling	10	13	11	9

EEG results and medications

Josh – abnormal. Bi-occipital onset and PPR (nil medications)

Jon – abnormal. Right occipital onset and PPR (Phenytoin)

Sher – generalized abnormal activity. PPR (Sodium Valproate & Carbamazepine)

Bela – generalized abnormal activity (Carbamazepine & Topamax)

Note: T-C – tonic-clonic; JME – juvenile myoclonic; PPR – photo-paroxysmal response

tion reflects the same separation into two patterns of deficit scores as reported in tables 2 and 3, and as represented in figures 1 to 5.

Severity and spread of cognitive impairment

Table 2 summarizes the relative severity and spread of cognitive deficits in each of the four cases, and two pairs of deficit profiles have emerged. Josh and Jon, both with an occipital seizure onset and photo-paroxysmal response, produced Visual Memory scores which were well below their overall performance on cognitive tasks. Bela and Sher produced similar deficit profiles involving impaired attention control and working memory dysfunction. Bela produced impaired episodic memory scores. Table 2 contains single task z-scores, while the z-scores in figures 2–5 each represent mean performance on several tasks.

Pre-morbid intellectual functioning

Table 3 compares predicted pre-morbid I.Q., based on

the Wechsler Test of Adult Reading (WTAR) demographic scales, and estimated current intelligence for Bela and Sher. In contrast, Josh and Jon produced significantly *higher* current intelligence scores than might be expected, based on the WTAR scales. Josh had higher current I.Q and Verbal I.Q. while Jon had higher than predicted I.Q., Verbal I.Q. and Performance I.Q.

Cognitive Domains

Figure 1 depicts Verbal and Performance score indices, which together constitute the current I.Q. The two pairs of cases (Josh and Jon versus Bela and Sher) also show opposite trends in intellectual abilities (see figure 2).

Figure 2 shows that a sole pattern of strengths and weaknesses was absent for cognitive tasks which constituted the four indices of intellectual abilities. What did emerge was a contrast between the two pairs of cases in overall level of task performance, which became most evident in the Working Memory scores.

Figure 3 depicts an average level of performance in

Table 2. Severity and spread of cognitive deficits for the four GGE participants

Cognitive Domains	Josh *	Jon *	Sher * +	Bela * &	% Cases
Attention					50%
Response Inhibition			-1.96	-3.00	
Response Switch			-2.23	-2.86	
Selective Attention				-1.83	
Flexibility Attention			-1.64	-1.64	
Language					25%
Vocabulary			-1.92		
Naming			-2.00		
Episodic Memory					25%
Learning				-1.88	
Delayed Recall				-1.54	
Visual Memory					50%
Learning		<i>R</i>			
Retrieval	-1.89	<i>R</i>			
Working Memory					50%
Digit Span			-1.67	-1.59	
Digit-Symbol				-1.79	
¹ Total spread over cognitive domains	1	0	3	3	

Notes:

- ¹ – spread of impairment i.e. number of cognitive domains found to be impaired
- * – photosensitivity is present
- * + – photosensitivity and eyelid myoclonia
- * & – photosensitivity and perioral myoclonia with absences
- R – reduced, compared to own performance scores in Verbal Memory domain

Levels of impairment (z-scores in bold): **borderline** –1.51; **very mild impairment** –1.64; **mild impairment** –1.96; **moderate** –2.33; **severe** –3.09

Table 3. Comparisons of pre-morbid and current intelligence for the GGE participants

Case Name	I.Q	VIQ	PIQ
Name BELA (IGE)			
Current estimated I.Q.	90	92	92
WTAR-demographic predicted I.Q.1.	99	98	100
Current versus predicted I.Q. discrepancy	-9	-6	-8
Significantly lowered intelligence (p < .05)?	Yes	No	No
(10–24% cumulative percentage)			
Name SHER (IGE)			
Current estimated I.Q.	80	72	92
WTAR-demographic predicted I.Q.1	84	85	86
Current versus predicted I.Q. discrepancy	-4	-13	+6
Significantly lowered intelligence (p < .05)?	No	Yes	No
(25–49% cumulative percentage)			

Note: 1 – prediction interval for WTAR-demographic predicted I.Q. is 95%.

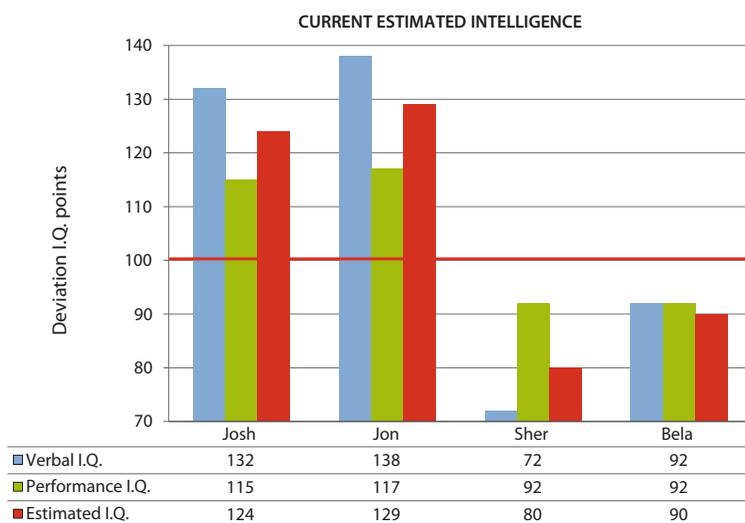


Figure 1. Individual performances in current estimated intelligence for the GGE participants.

Note: Red line of normality – current estimated I.Q. of 100

Attention factors as measured by the *Test of Everyday Attention*. The only consistent pattern seems to be one of opposing trends in level of performance between the two pairs of cases. Each z-score represents mean performance on several tasks. Table 2 z-scores are for single tasks, and indicate that Sher and Bela were mildly to moderately impaired for tasks of selective attention or flexibility in switching attention.

Figure 4 reflects mean scores for four kinds of executive functions. Sher and Bela show moderate to severe

deficits in control of attention responses, an executive function associated with the anterior cingulate area of the medial frontal lobes. Similar results are given in table 2 which lists z-score performance on individual attention tasks. Another point of interest is Josh’s significant difference in mean z-scores between Verbal Fluency and Visual Fluency measures.

Figure 5 depicts learning and recall processes from episodic, verbal and visual memory. The contrast found in Josh’s scores between Verbal and Visual Fluency is

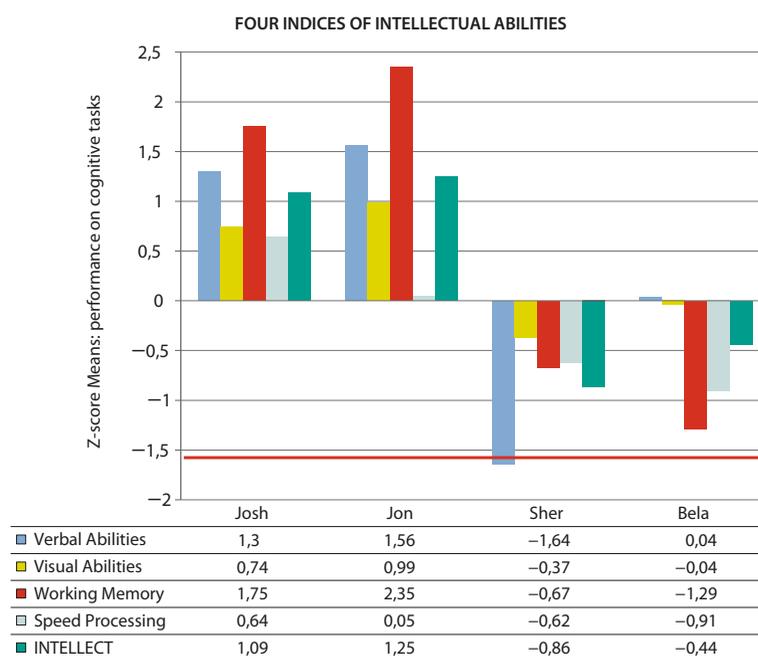


Figure 2. Individual performances in Intellectual Abilities for the GGE participants.

Note: Red line of abnormality = -1.64

repeated here, between his Verbal and Visual Memory processes. Jon's level of performance in memory tasks was average, which contrasts with his superior levels in tasks assessing intelligence. In contrast to Josh's impaired Visual Learning, Bela's impairments involved Verbal Memory.

Summary of results

Bela and Sher's assessment indicated a generalized lowering of current I.Q. based on their word-reading ability and what might be expected given their demographic status. Both participants showed lowered performance in the four factors of attention (sustained, selective, divided, switching/flexibility). They were both most impaired on tasks accessing control of attention responses which suggests some executive dysfunction in central areas of the prefrontal region, including the anterior cingulate. Both were also mildly impaired in tasks accessing working memory functions, and this is also consistent with prefrontal involvement.

In contrast to Bela and Sher, Josh and Jon produced above average and superior performance levels in current I.Q. Also in contrast, their highest scores were gained during Working Memory tasks. For Jon, Visual Memory was an area of weakness (rather than actual

impairment) insofar as his performance levels were lower than his overall verbal memory abilities and much lower than his superior Verbal I.Q. In Josh's pattern of results, the contrast was most notable between his impaired performance on tasks requiring visual memory processes and his above average verbal abilities (as in verbal fluency, Verbal I.Q. and verbal memory).

DISCUSSION

The main difference in the nature and level of cognitive dysfunction lay between the two patients with facial myoclonia (Sher and Bela) and those without (Josh and Jon). The finding that these two pairs varied in both neurocognitive dysfunction and biological mechanisms associated with their reflexive generalized seizures implies regional differences in the location and spread of brain hyperexcitability.

Sher and Bela

Sher and Bela shared similar neurocognitive deficits and facial myoclonia associated with visual stimuli. Severely impaired inhibition of automatic attention responses and compromised working memory abilities are neurocognitive deficits usually associated with the ventromedial prefrontal and anterior cingulate re-

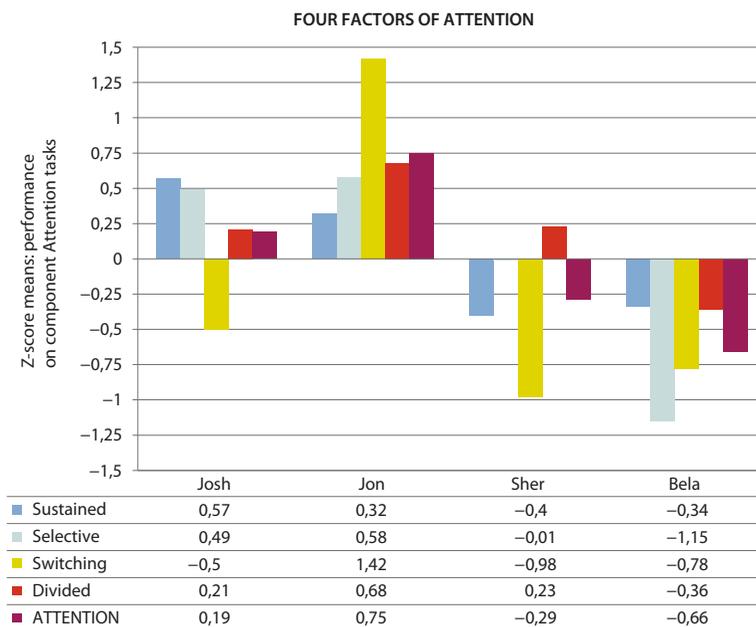


Figure 3. Individual performances in Attention for the GGE participants.

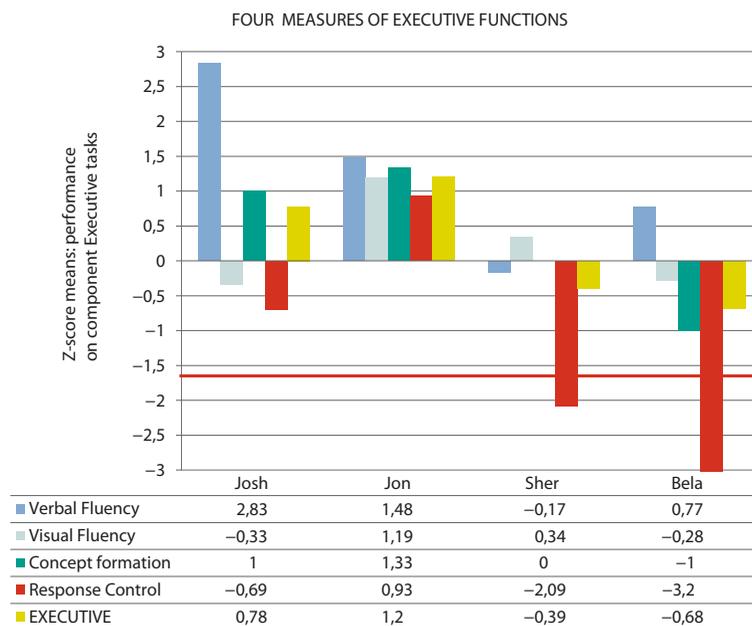


Figure 4. Individual performances in Executive Functions for the GGE participants.

Note: Red line of abnormality = -1.64

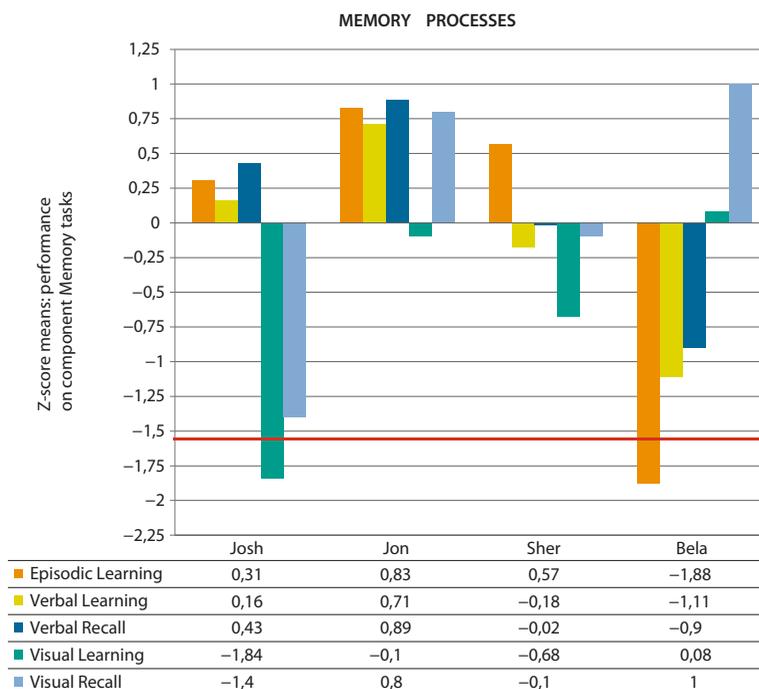


Figure 5. Individual performance in Memory processes for the GGE participants.

Note: Red line of abnormality = -1.64

gions. Their below average I.Q. scores imply cognitive dysfunction was generalized beyond the prefrontal regions, and the similarity in their set of deficits suggests these might be taken as neurocognitive markers for underlying hyperexcitability widespread across several contiguous cortices.

The presence of facial myoclonia associated with visual stimuli suggests involvement of the sensorimotor cortex. If some of Bela's perioral twitches were evoked by language-related stimuli such as reading, that would be consistent with the prefrontal regions associated with her more severe cognitive deficits. Reading epilepsy is known to activate regions of hyperexcitability across the dominant frontotemporal lobes (Wolf and Koepp, 2012), which would then account for her mildly impaired verbal episodic memory. The presence of facial myoclonia in both these cases raises the question whether they were serving as biomarkers for more extensive involvement of neuronal networks during spike-and-wave discharges (Archer et al., 2014a; Archer et al., 2014b).

Josh and Jon

Both Josh and Jon's seizures were precipitated by specif-

ic light stimuli with similar occipital lobe onsets. They both had high intellectual abilities and their only reduced or mildly impaired dysfunctions involved abilities requiring visual memory. Unlike the other two cases, Josh and Jon's sensitivity to light might have been confined to the occipital cortex.

There is considerable evidence from Balint's syndrome research that a person's occipital cortex is essentially divided into two functional streams (Levine et al., 1985):

- An occipital-parietal-frontal pathway that processes "where" information; and
- An occipital-temporal-frontal pathway that provides "what" information to the individual.

Either of these two visual-perceptual systems might be affected (Levine et al., 1985; Goodale, 2000; Barton and Caplan, 2001).

However, Josh's mildly impaired visual memory and Jon's brief spells of spatial disorientation suggest dysfunction of the occipital-temporal pathway which facilitates recognition of shapes, visual patterns and familiar landmarks (Levine et al., 1985; Turnbull et al.,

1997). The alternative occipital-parietal-frontal pathway as described in Turnbull et al. (1997) was not impaired in these two cases, as evidenced by their competent performance on the *Block Design* task which accesses the right parietal lobe and on *Judgment of Line Orientation* which measures spatial conceptualization of angles. It is thus likely that their GGE disorder had a region of hyperexcitability along the occipital-temporal-frontal pathways of the functional system.

CONCLUSIONS

The four GGE cases collectively show the presence of cognitive defects, ranging from mild and selective to moderate and generalized, depending on the nature of the cognitive and neural substrates of the functional systems involved. The traditional view of genetic generalized epilepsies as benign for cognition cannot explain the distinct patterns of reduced/mild visual dysfunction versus more widespread cognitive impairment in these four GGE cases. In contrast, the variation in the degree and type of cognitive impairment accords well with the more recent concept of “system epilepsies” which describes seizure onset mechanisms tied to functional-anatomical subsystems of the central nervous system (Wolf, 2006; Avanzini et al., 2012). The areas of hyperexcitability are said to be variable in their distribution and intensity, and the individual system’s responsivity to seizure precipitation can vary over time (Wolf and Koeppe, 2012). Where reflexive seizures are concerned, this may reflect fluctuations in internal seizure thresholds, which in turn may also change in response to environmental demands placed on the functional-anatomical subsystems. In clinical terms, these demands may also be represented by the patient’s life stress.

In conclusion, the four cases carry a few clinical implications. Availability of strong cognitive reserve might have diminished the levels of dysfunction associated with two of the GGE cases. This suggests that epilepsy need not always be associated with cognitive impairment. However, there is growing evidence in research on temporal lobe epilepsy to indicate that longer duration of seizures results in greater cognitive dysfunction. Previous work has documented this impairment in retentive memory, working memory and executive function domains (Kent et al., 2006; Schefft et al., 2008; Chapman Black et al., 2010). In conjunction with this research, the present findings highlight the importance of early identification and treatment of epilepsy in or-

der to minimize and perhaps prevent the possibility of subsequent cognitive impairment.

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CONFLICT OF INTEREST

The writers have no conflict of interest to declare.

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