Epilepsy and autism: How does age at seizure onset factor in?

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SUMMARY
Introduction. Three neuropathological conditions and two neurosurgical situations have been reported to present significantly earlier seizure onset in cases with autism than without. These are tuberous sclerosis, Angelman syndrome, the PCDH19 mutation, vagal nerve stimulation and epilepsy surgery.
Method. We reviewed the case-report literature to determine the extension of this autism-specific early seizure onset effect across all relevant neuropathological conditions. Published clinical cases were collected fulfilling two inclusion criteria: age at seizure onset stated and presence (N = 1885 cases) or absence (N = 4907 cases) of autism. We also documented the type and tractability/intractability of the epilepsy, genetic abnormality, neurologic syndrome, structural brain imaging findings and presence of intellectual disability when available.
Results. Cases with autism presented significantly earlier seizure onset than cases without autism in 38 neuropathological conditions out of 162, including the previously established five. These 38 neuropathological conditions typically involved intractable epilepsy caused by focal cortical dysplasia located in the social brain, with the ictal or interictal electrical focus also located in the social brain. Within these 38 neuropathological conditions, in the cases with autism, the median seizure onset occurred between 50 days and 24 months after birth.
Conclusion. Onset of severe seizure disorder during an early critical post-natal interval, caused by brain damage specifically located in the social brain, strongly associates with subsequent autism.
Key words: seizure • age at onset • autism • social brain • critical period

INTRODUCTION
Post-natal events are established risk factors of autism
We are in the midst of a second scientific revolution or paradigm shift in autism research. From the late 1940s through the '60s, the dominant view was that autism is caused by poor parenting. According to Frith (1991), Leo Kanner, the first formulator of the autism syndrome, held this belief for a few years around 1944.
Scientists discovered in the 1970s that autism is not caused by poor parenting and is highly heritable – marking the first paradigm shift. Since at the time there was no evidence of cell, tissue or organ failure occurring after birth in autism it seemed reasonable to assume that autism is biologically determined, once and for all, entirely before birth.
There is an increasing awareness that the etiopathology of autism often involves morbid events occurring in the brain after birth. This suggests that post-natal pathological events could heavily contribute to onset of autism and characterizes the second paradigm shift. In
fact, very little brain abnormality, if any at all, is found in newborns who will later receive a diagnosis of autism (Elsabbagh and Johnson, 2010). Brain imaging has established that there is an early post-natal peak of brain overdevelopment (high cerebral volume) in idiopathic autism spectrum disorder (ASD) at about one year of age, followed by overcompensation (low cerebral volume) in later childhood, followed by normalization (normal cerebral volume) in puberty and early adolescence; a pattern termed “triphasic” (Lange et al., 2015; Zielinski et al., 2014). The post-natal anomaly of MRI termed cortical anisotropy also peaks and reaches significance soon after birth in idiopathic autism, then dips and then normalizes, suggesting that subtle dysplasia of tertiary cortex and/or migrational disorder also follows the triphasic developmental pattern.

The now well established “epigenetic failure” etiology of autism (Ciernia and LaSalle, 2016), the “imbalanced microbiote” etiology (Vuong and Hsiao, 2017), the “immune/inflammatory” etiology (Masi et al., 2015), and the “defective gamma aminobutyric acid (GABA)-conversion” etiology (Ben-Ari, 2015) are all post-natal. These new perspectives on post-natal etiologies of autism led LeBlanc and Fagiolini (2011) to propose that there exists a critical post-natal period of vulnerability to autistic brain disorder in infancy. The “defective GABA-conversion” etiology of autism is particularly relevant to the high risk of epilepsy known to affect people with idiopathic autism.

Seizure onset is a post-natal event with a precise ontogenetic tag, making it interesting for developmental understanding of autism

Seizure onset is a post-natal event with a precise ontogenetic tag, making it interesting for developmental understanding of autism. Severe seizures, as in West (WS), Lennox-Gastaut (LGS), Dravet or Ohtahara syndromes, or un interrupts prolonged electrical paroxysm as in status epilepticus, present with high rates of intellectual disability and are even occasionally fatal. This can entail enough stress on early brain development to cause a pervasive developmental disorder – which neurologists tend to label “severe encephalopathy”. However, most seizure onsets in idiopathic autism occur after the onset of autism and most persons with autism never have an epileptic seizure.

Nevertheless, even if epileptic seizures might not, of themselves, be a cause of autism, age at seizure onset in autism could time-tag (flag) post-natal central nervous system disturbance leading directly to autism. In particular, excessive neocortical synaptic excitability could be an obvious such vector (Brix et al., 2015; Brooks-Kayal, 2010; Kang and Barnes, 2013; Markram et al., 2007; Nelson and Valakh, 2015; Rubenstein and Merzenich, 2003). Weakness of the neural GABA inhibitory network is a commonly evoked mechanism postulated to underlie this anomaly in the autistic brain (Ben-Ari, 2015; Brix et al., 2015; Bozzi et al., 2018; Kang and Barnes, 2013; Van Kooten et al., 2005). Commensurately, patients with autism are averse to many sorts of stimulation (Oberman et al., 2007) and report feeling over-stimulated at all times (Grandin, 1992).

Idiopathic autism comprises a high risk of epilepsy, i.e., between 15% to 32% (Clarke et al., 2005; Matsuo et al., 2010; Tuchman et al., 2009). This is much higher than the 4% to 7.6% lifetime risk of epilepsy in the general population (Fiest et al., 2017; Pellock et al., 2016). When starting with epileptic cohorts, one also finds a high risk of autism that ranges from 5% to 35% according to the study and the type of epilepsy (Berg et al., 2011; Hesdorffer et al., 2011; Saemundsen et al., 2007). Patients with idiopathic autism remain so after their epilepsy is controlled by anticonvulsants (Wong, 1993; Tuchman, 2000), by vagal nerve stimulation (Danielsson et al., 2008) or by surgery, although their autistic symptoms may be slightly alleviated by these treatments (Nass et al., 1999; Szabó et al., 1999; Zaroff et al., 2005).

How might early seizure onset carry higher risk of autism?

A general law of developmental psychopathology and neuropathology was proposed by Braun (2000): The earlier an endogenous pathology expresses itself, the more severe will be its phenotype and the family recurrence will be higher. This principle holds for polygenic and monogenic pathologies. Even so-called single-gene disorders are themselves quite variably expressed. Diverse factors can affect severity of clinical phenotypes such as epigenetic variables interacting with genes, degrees or types of mutations, extent of copy number variations, mosaicism, involvement and expression of interacting genes and sex of the patient, to name only a few. If Braun’s principle applies to the age at epilepsy onset/autism connection, when autism is laden with aggravating factors, the earlier those factors will be expressed the higher the risk of autism will be, with each morbid
element contributing some specific variance to the effect. This supposes however that obtunded, prostrated or unresponsive cases be kept out of the equation because clinicians are understandably quite reticent to attempt an autism diagnosis in such cases.

On the other hand, it is also possible that age at seizure onset is a rather distinct marker of autism, independent of the global severity of brain morbidities affecting neurological patients at high risk for autistic comorbidity. Viewed in this manner, there could exist a specific interval, some time after birth; a critical period of vulnerability to some very specific insult to the brain selectively damaging only the brain structures necessary for implementation of interpersonal, social functions and abilities. This critical period could start quite early in life but not necessarily at birth (see LeBlanc and Fagiolini, 2011, for a detailed articulation of this proposal).

**Does early seizure onset carry higher risk of autism in ordinary epilepsy?**

The first seizures occurring in idiopathic autism typically appear at around 4.7 to 14 years of age depending on the study (Mouridsen et al., 1999; Hara, 2007; Amiet et al., 2013), later than the age at which autism can be established which is now about two years of age. However, brains suffer before the first seizures manifest themselves (Berg et al., 2011) which means that endotypes or “essential comorbidities” accompanying certain epilepsies could still contribute to risk of autism.

Clarke and colleagues (2005), Juneja and colleagues (2018) and Reilly and colleagues (2014) reported epileptic case series typically seen by neurologists specialized in epilepsy. Such cases comprise a mixture of idiopathic and syndromic (typically more severe) epilepsies. They found that early seizure onset characterized autism. However, several studies of exceptionally large samples of cases, not limited to medical clinics specialized in epilepsy, found no link between idiopathic autism and early onset of seizures in what seemed to be mostly “idiopathic” (typically rather benign) epilepsy (Jokiranta et al., 2014; Wirrell et al., 2017).

As far as we could determine, age at seizure onset in autism has not yet been meta-analysed. At present, age at seizure onset is usually not documented in research on autism and epilepsy. When it is, types of epilepsy, types of central nervous system morbidity, presence/absence of autism and presence/absence of intellectual disability, are usually not fully documented. Given the state of current research on the association between epilepsy and autism, it is understandable that some authors have doubted that epilepsy is, in itself, a risk factor for autism at all in any respect (Pavone et al., 2004; Tharp, 2004), while others have reserved judgment in expectation of convincing data (Gabis et al., 2005).

**Are there specific neuropathological conditions or contexts in which early seizure onset is associated with autism?**

There are several hundred developmental neuropathologies that involve high risk of autism (Iossifov et al., 2012) and a varied minority of them, also involve a substantial risk of epilepsy. In these conditions, it could reasonably be expected that a high risk of epilepsy and a high risk of intellectual disability (ID) could conjointly carry a particular high risk of autism. However, even in the domain of so-called “secondary” or “syndromic” autism (autism thought to be caused by a well identified brain disorder), it has not been conclusively established that early onset seizures, of themselves, consistently contribute to risk of autism.

Only a few neurodevelopmental syndromes or contexts have been found to significantly carry increased risk of secondary autism significantly in association with earlier seizure onset. This has been reported in tuberous sclerosis complex (TSC), typically an autosomic monogenic pathology with high risk of epilepsy and autism (Asano et al., 2001; Numis et al., 2011). Humphrey and colleagues (2004) described two monozygotic twins with TSC, the first with autism and the second without. The first had his first seizure at three months and the other at seven months. Bakke and colleagues (2018) found that early seizure onset significantly associated with autism in Angelman syndrome which is another syndrome that is typically autosomic, monogenic and also carries a high risk of autism. In their study of 48 cases, age at seizure onset was negatively associated with the severity of autism ratings ($r = -0.61$, $p = 0.006$). Trivisano and colleagues (2018) found that early seizure onset significantly characterizes autism in patients with the X-linked PCDH19 gene mutation—a disorder which also carries a high risk of autism. This finding remains to be independently replicated within syndrome regarding the latter two syndromes. The relation has also been studied in patients with epilepsy treated with vagal nerve stimulation by Levy and colleagues (2010). The patients with autism presented significantly earlier seizure onset than the patients with-
out autism. This finding has not yet been replicated as far as we could determine. In patients with epilepsy needing cerebral surgical intervention, earlier seizure onset has consistently been found to significantly characterize the cases with autism (Taylor et al., 1999; Szabó et al., 1999; Zaroff et al., 2005; Nass et al., 1999; McLellan et al., 2005).

OBJECTIVES OF THE INVESTIGATION
The research questions were the following:
1. Does early onset epilepsy characterize cases with autism more than similar cases without autism in a wide array of specific biodevelopmental, neurological, neuropsychological, genetic or epileptological conditions?
2. If so, is there a specific interval of the lifespan during which this effect is particularly and typically statistically significant? and
3. Are there any brain morbidities that are common in, and specific to, these neuropathological conditions?

METHODS

Case collection and inclusion criteria
A literature search was conducted using Google Scholar to find articles presenting a single case or a case series of patients in which each case (to be included here) had been individually characterized for age at seizure onset and had also been determined to be autistic or not. These were the only two inclusion criteria.

Age at seizure onset and exclusion criteria for cases
Age at seizure onset was coded in days. Reports specifying only age in months or years at seizure onset were accepted and age was converted to days. Any determination of age less precise than to the year was excluded from the present report. For example, cases whose seizure onset was described as occurring in "childhood" or "adolescence" or "adulthood" were excluded.

Cases "last seen before two years of age" were excluded because autism cannot be reliably determined before that age. Cases without a specific mention of age last seen but with context indicating follow up any time from late infancy on were included, and age last seen was then coded as "missing". The median age last seen (follow up) of the patients with autism was 3467 days, mean = 4303 days, SD = 3223 days, N = 1606: age last seen was missing in 284 cases with autism (15%).

The median age last seen of the patients without autism was 3650 days, mean = 5004 days, SD = 4376, N = 4336. Age last seen was missing in 587 cases (12%). The cases without autism were significantly older at last evaluation than the cases with autism (Mann-Whitney U ranks Z = 3.4, p = 0.001). Cases characterized as obtunded, prostrate, or unresponsive were also excluded. However, we cannot guarantee that all such latter cases were excluded because some reports did not cover those dimensions explicitly.

Identification of autism
The diagnostic criteria of autism, both in the APA and ICD diagnostic psychiatry manuals, in all the revisions, have included three types of symptoms, one more heavily weighted (interpersonal/social isolation) and the others relatively less heavily weighted (underdeveloped language, stereotypic/repetitive behavior). To be included in the present investigation and coded as autistic, a case had to be explicitly labeled autistic. Absence of mention of autism was insufficient to characterize a case as non-autistic.

For a case to be categorized as non-autistic, one of the following six criteria had to apply:

1. A case (or the case series) was explicitly declared as non-autistic.
2. The methodology specified that patients were evaluated for autism and then cases not labeled with autism were considered non-autistic.
3. A table with a series of clinical cases included an explicit "autism" category with a rating of "present" versus "absent".
4. A case series included at least one case explicitly diagnosed with autism (it was then assumed that undiagnosed cases did not have autism).
5. A case was explicitly termed behaviorally or psychiatrically "normal".
6. A case received a formal psychiatric diagnosis (e.g., attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, depression) or neuropsychological diagnosis other than intellectual deficiency (e.g., Landau-Kleffner syndrome) with no mention of autism.

Neuropathological conditions and contexts
Many aspects of the epilepsy itself, of the epileptological, genetic, neurological or IQ test findings were noted qualitatively. These characterizations as a whole will
henceforth be referred to as the neuropathological conditions. As soon as any neuropathological condition characterized an autistic case, that characteristic was searched with Google Scholar. When any neuropathological condition emerged as prevalent in the autistic as well as non-autistic subgroups (10 cases, with at least 3 in each subgroup), a quantitative code was attributed to that neuropathological condition. It was then retroactively used to code all cases collected previously and then assigned to subsequent cases as well in view of performing statistical inference tests. In short, we searched for any and all neuropathological conditions that characterized any and all the patients meeting the inclusion criteria.

We retained, for statistical analysis, 24 such codes pertaining directly to details and characteristics of the patient’s epilepsy. For example, these codes detailed epilepsy characteristics such as scalp location, severity, tractability, type of seizure, etc. (described in Table 1 of the results section). There were 43 codes pertaining to single gene mutations on autosomes (described in Table 2 of the results section), 14 codes pertaining to single gene mutations on the X-chromosome (described in Table 3 of the results section), and 9 codes pertaining to whole or partial chromosome aberrations (described in Table 4 of the results section). Magnetic resonance imaging is one of the most informative neurological investigations currently available. In the case of autism, innovation in imaging has constantly and rapidly generated new descriptions of morbidity (e.g., subependymal giant cell astrocytoma or SEGA, radial migration tracks to nodular heterotopias in tuberous sclerosis, delayed myelination, focal cortical dysplasia, etc.). We retained 40 codes for MRI determinations (described in Table 5 of the results section). Finally, there were neuropathologically relevant conditions determinable from clinical neurology or from medical workups or IQ testing rather than MRI. These generated 32 codes (described in Table 6 of the results section). The list of these 162 neuropathological conditions is in tables 1 to 6.
of their operationalization are presented as and when necessary, in footnotes to those tables.

Statistical approach
Most distributions of age at seizure onset in the various neuropathological conditions failed the Kolmogorov-Smirnov tests of normality and had coefficients of variation so high (see figure 1c) as to preclude parametric testing. Accordingly, the non-parametric Mann-Whitney U test was used for all comparisons of age at seizure onset of independent samples, namely the autistic versus non-autistic patients, and central tendencies will be reported as medians rather than means (Tables 1 to 6 and figure 1 of the Results section). Each table ranks the conditions by decreasing Mann-Whitney Z value of the difference in ranks between the cases with versus without autism. To be included as a row in any table, a neuropathological condition had to comprise at least 10 cases and at least 3 cases in either group. Statistical analyses were done with SPSSv25. Alpha was set at .05 (two tailed).

A total of 6792 cases with epilepsy were collected and individually characterized for the present report. The list of 1440 references from which the cases were drawn in Word format is associated with the present report as a Supplementary data file. A PDF version of each of these 1440 articles is available upon request from the first author. The SPSS file used for statistical analysis, or converted to Excel for English language viewers, are available from the first author, allowing for complete verification of all raw data and statistics.

RESULTS

Neuropathological conditions amenable to an inference test of the hypothesis of a difference in age at seizure onset between cases with versus without autism
The 162 statistical inference tests reported in Tables 1 to 6 replicated all five relevant significant findings previously reported in the literature and reviewed by us in the introduction. Tuberous sclerosis, the PCDH19 mutation, Angelman syndrome, vagus nerve stimulation, epilepsy surgery each presented the same effect as reported by predecessors. Specifically, cases with autism had significantly earlier seizure onset than the cases without autism in all five of these neuropathological conditions. Beyond replication of previous findings, results expanded the autism specific early seizure onset effect to several additional neuropathological conditions. Most of the 162 neuropathological conditions associated with epilepsy did not present significant interaction between autism/non-autism and age at seizure onset (tables 1 to 6). This included many well-documented etiopathologies of epilepsy (and presumably of autism as well) such as mutations of so-called “epilepsy genes” and/or “autism genes”. This also included a large sample of 1859 cases with idiopathic epilepsy (row 22 of table 1).

To determine why certain neuropathological conditions present the autism-specific early seizure onset effect and not others, we next examined the direction of the significant findings (figure 1), ruled out statistical artifacts (figure 1) and identified commonalities in the significant findings which should contrast with the non-significant findings (see the discussion).

The autism-specific early seizure onset effect
Of the 162 neuropathological conditions, 39 (24%) did yield a significant difference. Of the latter, 38 (97%) respected Braun’s principle (Reilly et al., 2014) as well as the LeBlanc et al proposal (LeBlanc and Fagiolini, 2011), i.e., the cases with autism had earlier seizure onset and the ensemble revealed a tight post-natal critical period. The only exception was the “thin callosum” condition (row 11 of table 5) which significantly associated later seizure onset with autism. Altogether, the standard effect in secondary (or syndromic) autism, when significant, is earlier seizure onset in the cases with autism, i.e., the autism-specific early seizure onset effect.

The autism-specific early seizure onset effect occurs during a “critical period” of post-natal life
The autism-specific early seizure onset effect reached significance only in neuropathological conditions in which the cases with autism had median seizure onset after 50 days of life and no later than the second year of life (figure 1). The timing of this effect is critical for understanding how autism can be brought about by brain dysfunction. If the effect had been observed only in cases with seizure onset occurring years after the emergence of autism, it would have to be considered no more than an oddity. Rather, the effect occurred in the same time frame as cerebral overdevelopment and abnormal fractional anisotropy in idiopathic autism, i.e., during a brief post-natal critical interval of vulnerability (Braun et al., 2017), and it occurred before detectable onset of autism.
Table 1. Tests of a difference between autists and non-autists with regard to age at seizure onset in various epileptic conditions

| Epileptic condition                          | Number of autistic patients | Number of non-autistic patients | Median age at seizure onset of the autistic patients (days) | Median age at seizure onset of the non-autistic patients (days) | Whole sample coefficient of variation (%) | Mann-Whitney Z (∆ between ranks) | p          |
|---------------------------------------------|-----------------------------|---------------------------------|----------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------|----------------------------------|-----------|
| Intractable epilepsy+                       | 1146                        | 2923                            | 272                                                      | 730                                                             | 147                                      | 12.0                             | 2.9e-33   |
| Temporal lobe focus #                       | 128                         | 639                             | 546                                                      | 1825                                                            | 112                                      | 7.7                              | 1.4e-14   |
| Partial seizure                             | 187                         | 828                             | 300                                                      | 1095                                                            | 141                                      | 7.1                              | 1.4e-12   |
| Generalized tonic/clonic seizure            | 621                         | 1603                            | 365                                                      | 660                                                             | 146                                      | 5.7                              | 1.1e-8    |
| Frontal lobe focus #                        | 132                         | 384                             | 610                                                      | 1460                                                            | 114                                      | 5.3                              | 1.2e-7    |
| Focal seizure (not further specified)       | 283                         | 861                             | 330                                                      | 1095                                                            | 133                                      | 5.0                              | 5.3e-7    |
| Absence seizure                             | 177                         | 507                             | 700                                                      | 1278                                                            | 106                                      | 4.5                              | 0.0000006 |
| Status epilepticus awake                    | 154                         | 299                             | 240                                                      | 330                                                             | 154                                      | 2.9                              | 0.003     |
| ESES/CSWSS                                  | 67                          | 439                             | 1277                                                     | 1642                                                            | 70                                       | 2.7                              | 0.007     |
| Non-refractory epilepsy                     | 260                         | 999                             | 390                                                      | 600                                                             | 165                                      | 2.4                              | 0.018     |
| Lennox-Gastaut syndrome                     | 61                          | 152                             | 395                                                      | 815                                                             | 116                                      | 2.3                              | 0.020     |
| Parietal lobe focus #                       | 12                          | 39                              | 375                                                      | 1825                                                            | 168                                      | 2.3                              | 0.023     |
| Infantile spasms                            | 234                         | 364                             | 120                                                      | 150                                                             | 183                                      | 2.2                              | 0.027     |
| Febrile seizure                             | 175                         | 436                             | 270                                                      | 365                                                             | 136                                      | 2.2                              | 0.028     |
| Occipital lobe focus #                      | 51                          | 175                             | 730                                                      | 1095                                                            | 100                                      | 2.2                              | 0.030     |
| Tonic seizure                               | 101                         | 236                             | 300                                                      | 232                                                             | 158                                      | -1.9                             | 0.064     |
| Dravet/SMEI syndrome                        | 136                         | 235                             | 180                                                      | 180                                                             | 249                                      | 1.8                              | 0.071     |
| West syndrome/hypsarrhythmia                | 107                         | 186                             | 128                                                      | 150                                                             | 205                                      | 1.7                              | 0.092     |
| Atonic (drop) seizure                       | 87                          | 172                             | 450                                                      | 720                                                             | 101                                      | 1.6                              | 0.114     |
| Gastroenteritis-triggered seizure onset     | 4                           | 178                             | 1225                                                     | 570                                                             | 108                                      | -1.2                             | 0.238     |
| Ohtahara syndrome suppression burst         | 25                          | 60                              | 5                                                        | 3                                                                | 265                                      | 1.0                              | 0.930     |
| Idiopathic epilepsy *                       | 320                         | 1539                            | 1460                                                     | 1463                                                            | 106                                      | 0.9                              | 0.384     |
| Myoclonic seizure                           | 211                         | 497                             | 330                                                      | 365                                                             | 140                                      | 0.8                              | 0.400     |
| Vaccine-contiguous seizure onset            | 31                          | 36                              | 180                                                      | 180                                                             | 123                                      | 0.3                              | 0.800     |

Note
+ Intractable epilepsy was either reported as “intractable” or “refractory” or seizures were reported to have occurred during at least a year
# Temporal, frontal, parietal or occipital focus was coded here as any ictal or interictal electrical anomaly limited to a single lobe; the focus could be unilateral or bilateral
* Idiopathic epilepsy in the current report consisted of cases reported with no explanation or even a hypothesis of the etiology of the epilepsy
Table 2. Tests of a difference between autists and non-autists regarding age at seizure onset in subsamples with a mutation of a single gene on an autosome

| Mutated gene and its cytogenetic location | Number of autistic patients | Number of non-autistic patients | Median age at seizure onset of the autistic patients (days) | Median age at seizure onset of the non-autistic patients (days) | Whole sample coefficient of variation (%) | Mann-Whitney Z (Δ between ranks) | p     |
|------------------------------------------|----------------------------|-------------------------------|----------------------------------------------------------|----------------------------------------------------------|----------------------------------------|------------------------------|-------|
| DEPDC5/22q12.2-q12.3 mutation            | 8                          | 27                            | 51                                                       | 1095                                                     | 3.9                                     | 0.00009                      |       |
| CNTNAP2/7q35-q36 mutation                | 10                         | 17                            | 270                                                      | 730                                                      | 187                                     | 3.2                          | 0.001 |
| UB3A/15q11.2 mutation                    | 81                         | 33                            | 730                                                      | 1825                                                     | 108                                     | 2.6                          | 0.010 |
| SCN1A/2q24.3 mutation                    | 126                        | 277                           | 180                                                      | 180                                                     | 188                                     | 1.9                          | 0.053 |
| ASXL3/18q12.1 mutation                   | 5                          | 5                             | 730                                                      | 2190                                                     | 154                                     | 1.8                          | 0.074 |
| SLC6A1/3p25.3 mutation                   | 15                         | 23                            | 1085                                                     | 540                                                      | 66                                      | -1.7                         | 0.082 |
| SCN2A/2q24.3 mutation                    | 15                         | 23                            | 6                                                        | 240                                                      | 279                                     | 1.7                          | 0.083 |
| PTEN/10q23.31 mutation                   | 5                          | 10                            | 42                                                       | 2373                                                     | 132                                     | 1.7                          | 0.085 |
| HCN1/Spl2 mutation                       | 6                          | 29                            | 225                                                      | 270                                                      | 119                                     | 1.7                          | 0.095 |
| FOLR1/11q13.4 mutation                   | 4                          | 8                             | 1577                                                     | 41                                                       | 148                                     | -1.7                         | 0.109 |
| EEF1A2/20q13.33 mutation                 | 5                          | 15                            | 120                                                      | 90                                                       | 178                                     | -1.6                         | 0.114 |
| PNPO/17q21.32 mutation                   | 5                          | 31                            | 5                                                        | 1                                                        | 385                                     | -1.6                         | 0.207 |
| HNRNPU/1q44 mutation                     | 6                          | 10                            | 318                                                      | 392                                                      | 82                                      | 1.5                          | 0.125 |
| KCNA2/1p13.3 mutation                    | 4                          | 14                            | 180                                                      | 293                                                      | 207                                     | 1.5                          | 0.134 |
| ANKRD11/16q24.3 mutation                 | 7                          | 8                             | 1095                                                     | 365                                                      | 98                                      | -1.5                         | 0.143 |
| KCNB1/20q13.13 mutation                  | 12                         | 23                            | 378                                                      | 270                                                      | 82                                      | -1.4                         | 0.151 |
| Miscellaneous mutations*                 | 167                        | 455                           | 547                                                      | 720                                                      | 146                                     | 1.4                          | 0.163 |
| ALDH7A1/5q23.2 mutation                  | 5                          | 25                            | 2                                                        | 270                                                      | 223                                     | 1.3                          | 0.195 |
| KCNT1/9q34.3 mutation                    | 7                          | 10                            | 270                                                      | 913                                                      | 227                                     | 1.2                          | 0.221 |
| TSC1/9q34.13 mutation                    | 6                          | 21                            | 215                                                      | 540                                                      | 103                                     | 1.1                          | 0.316 |
| PACS2/11q32.33 mutation                  | 4                          | 9                             | 34                                                       | 257                                                      | -1.1                                    | 0.330                        |       |

Overview and depiction of age at seizure onset in autism vs non-autism and consideration of possible artifactual interpretations

Overview of tables 1 to 6 in a single figure (Figure 1) was planned to help the reader get a sense of the general profile of the findings (the 162 rows of tables 1 to 6) and gauge alternative explanations of the profile of effects, other than clinically meaningful, i.e., as artifacts. To this end, we scatterplotted the 162 effects, expressed as the Mann-Whitney Z values of the difference between ranks, in ordinate, and various parameters in abscissa. The main findings are depicted in Panel A of figure 1, illustrating that significant autism-specific effects of age at seizure onset a) virtually always consisted of earlier onset in the cases with autism than the cases without autism, and b) occurred during a clearly post-natal period of vulnerability before the onset of autism. Panel B of figure 1 depicts whether effects can be explained away as small-sample artifacts. Panel C of figure 1 depicts whether effects might be explained away as artifacts of dispersion of ages at seizure onset. Finally, panel D of figure 1 depicts whether a small proportion of cases with autism (a variant of small sample artifact) can explain away effects. See figure 1.

Could the global period of vulnerability to the autism-specific early seizure onset effect seen in Panel A of Figure 1 be a small sample artifact? Panel B of Figure 1 argues otherwise. If there was a bias, it was in the opposite direction – which would further support a properly clinical interpretation of the findings. Could this global period of expression of the autism-specific early seizure onset effect be an artifact of dispersal of ages at seizure onset, i.e., are the significant effects observed primarily in the conditions with high coefficients of variation (CV)? Panel C of figure 1 suggests otherwise. The significant autism-specific early seizure onset effects are in a low mid range of CVs. This profile would be expected if they were primarily reflecting between rather than within variance. Could the profile of neuropathological conditions yielding significant autism-specific early seizure onset effects be an artifact of an extremely small proportion of cases with autism? It ap-
Table 2. Continued

| Mutated gene and its cytogenetic location | Number of autistic patients | Number of non-autistic patients | Median age at seizure onset of the autistic patients (days) | Median age at seizure onset of the non-autistic patients (days) | Whole sample coefficient of variation (%) | Mann-Whitney Z (Δ between ranks) | p |
|------------------------------------------|-----------------------------|---------------------------------|----------------------------------------------------------|-------------------------------------------------|--------------------------------------|---------------------------------|---|
| CUX2/12q24.11-q24.12 mutation            | 4                           | 7                               | 273                                                      | 180                                             | 200                                  | -10.0                           | 0.412 |
| SETD1B/12q24.31 mutation                 | 9                           | 3                               | 990                                                      | 180                                             | 95                                   | -0.9                            | 0.354 |
| STHXBP1/9q34/ mutation                   | 26                          | 39                              | 44                                                       | 30                                              | 152                                  | -0.9                            | 0.355 |
| MEF2C/5q14.3 mutation                    | 16                          | 16                              | 345                                                      | 300                                             | 71                                   | -0.9                            | 0.395 |
| GABRA1/5q34 mutation                     | 6                           | 26                              | 330                                                      | 240                                             | 198                                  | -0.7                            | 0.465 |
| NF1/17q11.2 mutation                     | 4                           | 42                              | 1004                                                     | 1789                                            | 116                                  | 0.7                             | 0.486 |
| CHD2/15q26.1 mutation                    | 23                          | 35                              | 730                                                      | 875                                             | 94                                   | 0.6                             | 0.528 |
| TSC2/16p13.3 mutation                    | 46                          | 50                              | 180                                                      | 150                                             | 267                                  | -0.5                            | 0.605 |
| NBEA/13q13.3 mutation                    | 9                           | 6                               | 720                                                      | 720                                             | 139                                  | 0.5                             | 0.607 |
| GABRG2/5q34 mutation                     | 4                           | 8                               | 405                                                      | 660                                             | 82                                   | 0.4                             | 0.669 |
| MBDS/2q23.1 mutation                     | 8                           | 12                              | 560                                                      | 986                                             | 116                                  | 0.4                             | 0.670 |
| FOXG1/14q12 mutation                     | 3                           | 12                              | 150                                                      | 180                                             | 255                                  | -0.3                            | 0.770 |
| SPTAN1/9q34.11 mutation                  | 4                           | 23                              | 195                                                      | 120                                             | 211                                  | -0.3                            | 0.756 |
| KCNQ3/8q24.22 mutation                   | 8                           | 8                               | 900                                                      | 1004                                            | 90                                   | 0.3                             | 0.792 |
| SCN8A/12q13.13 mutation                  | 16                          | 57                              | 180                                                      | 165                                             | 140                                  | -0.3                            | 0.794 |
| KCNQ2/20q13.33 mutation                  | 13                          | 60                              | 4                                                        | 3                                               | 282                                  | -0.2                            | 0.838 |
| SYNGAP1/6p21.32 mutation                 | 26                          | 34                              | 900                                                      | 785                                             | 75                                   | -0.2                            | 0.840 |
| GRIN2A/16p13.2 mutation                  | 13                          | 48                              | 1460                                                     | 1460                                            | 497                                  | 0.2                             | 0.880 |
| GABBR3/15q12 mutation                    | 8                           | 4                               | 180                                                      | 270                                             | 226                                  | 0.1                             | 0.898 |
| POGZ/1q21.3 mutation                     | 6                           | 9                               | 1186                                                     | 912                                             | 69                                   | -0.1                            | 0.906 |
| DNLM1/9q34.11 mutation                   | 5                           | 15                              | 210                                                      | 210                                             | 58                                   | 0.1                             | 0.930 |
| SHANK3/22q13.33 mutation                 | 7                           | 13                              | 2555                                                     | 2555                                            | 68                                   | 0.00                            | 10.0 |

Note: The reader is cautioned that duplications, deletions and mosaic variants were included here in a same condition (table row) because we are interested in the eventuality of age at seizure onset being linked to the physiopathological pathway more than the global severity of the phenotype. *The label "Miscellaneous mutations" assembled all cases with a mutation too infrequent in the current database to appear in the table.

pears that this was not the case. Rather, this distribution, depicted in Panel D of figure 1, suggests that autism-specific early seizure onset effects are more likely to emerge in neuropathological conditions with a percentage of cases with autism around 30%, probably because this represents a balance between the neuropathological condition being a true generator of autism and a consistent generator of epilepsy.

DISCUSSION

Details of the autism-specific early seizure onset effect as a "critical period"

None of the neuropathological conditions locked to and limited to birth or the first month of life (except neonatal adenylosuccinate lyase deficiency) carried the autism-specific early seizure onset effect, namely fetal distress during pregnancy or at birth (including specifically maternal diabetes, or jaundice, asphyxia, or hy-
Table 3. Tests of a difference between autists and non-autists regarding age at seizure onset in subsamples with a mutation of a single gene located on the X chromosome

| Mutated gene and its cytogenetic location | Number of autistic patients | Number of non-autistic patients | Median age at seizure onset of the autistic patients (days) | Median age at seizure onset of the non-autistic patients (days) | Whole sample coefficient of variation (%) | Mann-Whitney Z (Δ between ranks) | p |
|------------------------------------------|-----------------------------|---------------------------------|----------------------------------------------------------|----------------------------------------------------------------|------------------------------------------|-----------------------------------|---|
| PCDH19/Xq22.1 mutation                   | 130                         | 192                             | 270                                                      | 315                                                             | 127                                      | 3.1                               | 0.002 |
| SLC6A8/Xq28 mutation                     | 18                          | 13                              | 1278                                                     | 2555                                                            | 75                                       | 1.3                               | 0.185 |
| MECP2/Xq28 mutation                      | 13                          | 11                              | 1095                                                     | 730                                                             | 101                                      | -10.0                             | 0.361 |
| KIAA2022/Xq13.3 mutation                 | 8                           | 4                               | 420                                                      | 605                                                             | 79                                       | -10.0                             | 0.368 |
| FMR1/Xq27.3 mutation                     | 10                          | 16                              | 1460                                                     | 913                                                             | 79                                       | -0.9                              | 0.354 |
| SYN1/Xp11.3 mutation                     | 3                           | 8                               | 1450                                                     | 3103                                                            | 123                                      | 0.9                               | 0.376 |
| CNKSR2/Xp22.12 mutation                  | 3                           | 16                              | 730                                                      | 1077                                                            | 78                                       | 0.9                               | 0.392 |
| WDR45/Xp11.23 mutation                   | 3                           | 15                              | 780                                                      | 450                                                             | 116                                      | -0.8                              | 0.426 |
| ARX/Xp21.3 mutation                      | 5                           | 10                              | 30                                                       | 120                                                             | 286                                      | 0.4                               | 0.664 |
| CDKL5/Xp22.13 mutation                   | 63                          | 35                              | 42                                                       | 45                                                              | 343                                      | 0.3                               | 0.747 |
| PIGA/Xp22.2 mutation                     | 5                           | 5                               | 180                                                      | 150                                                             | 106                                      | -0.3                              | 0.750 |
| IQSEC2/Xp11.22 mutation                  | 16                          | 10                              | 730                                                      | 730                                                             | 111                                      | 0.2                               | 0.811 |
| SPTAN1/9q34.11 mutation                  | 14                          | 5                               | 528                                                      | 540                                                             | 141                                      | 0.1                               | 0.888 |
| SLC9A6/Xq26.3 mutation                   | 14                          | 5                               | 529                                                      | 540                                                             | 136                                      | 0.1                               | 0.888 |

Note. The reader is cautioned that duplications, deletions and mosaic variants were included here in a same condition (table row) because we are interested in the eventuality of age at seizure onset being linked to the physiopathological pathway more than the global severity of the phenotype.

base, there were 189 cases with and 468 cases without autism with seizure onset before 50 days of life, altogether. The cases with autism had later median onset (8 days) than the cases without autism (4 days)! And the two cohorts did not differ significantly regarding age at seizure onset (MWUz = 1.9, p = 0.057). As for neonatal adenylosuccinate lyase deficiency, which is a genetic metabolic disorder manifest in plasma at birth, though the cases with autism did have a significantly earlier seizure onset than the cases without autism, the median age at seizure onset of the cases with autism was 84 days. We thus provide plenty of evidence that very early brain morbidity with very early seizure onset (before 50 days) is not part of the spectrum of the autism-specific early seizure onset effect.

There were 29 neuropathological conditions in the current database with median age at seizure onset occurring after two years of life in the autists. Not one of these carried a significant autism-specific early seizure onset effect (see figure 1 for a general view). Altogether, there were 3011 cases with onset of seizures after two years of age, 650 cases with autism and 2361 without. Though the cases with autism had significantly earlier onset (Mann-Whitney Z = 3.0, p = 0.003), the Z value and effect size were modest compared to several of the morbid conditions tested in tables 1 to 6. There were 2472 cases with seizure onset later than three years of age (500 with autism and 1972 without), and the slightly earlier onset of the cases with autism was not statistically significant (Mann-Whitney Z = 0.6, p = 0.556).

In short, the autism-specific early seizure onset effect is a misnomer in an important respect. It is correct to conclude that within each of the 38 neuropathological conditions presenting the autism-specific early seizure
onset effect, looked at individually, the earlier the seizure onset, the higher was the risk of autism. In addition, however, the significant age-related effects observed comprised median seizure onset of the cases with autism between 50 days (not before in any of the neuropathological conditions) and 24 months (not later in any of the neuropathological conditions). It is thus exclusively during a distinct and clearly post-natal critical period that we observed the autism-specific early seizure onset effect, as proposed by LeBlanc and Fagiolini (2011), albeit limited to secondary autism. The effect was not observed at all in idiopathic epilepsy (see row 20 of table 1).

**Intractability of the seizures is of prime importance in the autism-specific early seizure onset effect**

In the present study, the main carrier of the autism-specific early seizure onset effect was intractability of the epilepsy (row 1 of table 1). This explains why the autism-specific early seizure onset effect is quite significant in vagal nerve stimulation and consistently so in epilepsy surgery in the literature: they both exclusively comprise patients with epilepsy that is extremely intractable.

It is possible that intractability of seizures is the main driver of the autism-specific early seizure onset effect because the active morbidity, either the epilepsy itself, or more likely, the underlying brain disorder, or both, must compromise a period of life when the infant should begin to be socialized. Indeed, the infant should be first engaging in dyadic play and imitation, learning to communicate, pronouncing the first words, developing deep empathy and theory of mind, global active benevolence, etc. In other words, we believe that pure autism is more likely to occur when a brain disorder severely disrupts development exclusively during the early socialization phase occurring AFTER the 50th day of life and BEFORE two years of age (Porter-O’Grady, 2011).

As will be detailed in the next two sections, we propose that there is a second very important factor in the autism-specific early seizure onset effect, namely that it is specifically the part of the brain that is predestined to manage interpersonal and social function that is damaged. In other words, we suspect that autism is probably "sociodevelopmentally" overdetermined in the 38 neuropathological conditions presenting the autism-specific early seizure onset effect. Indeed, the brain is critically stressed at just the right time critical for social development (this section and the previous one) and in just the right place also critical for social development (next two sections).
Focal cortical dysplasia (FCD) is key in the autism-specific early seizure onset effect

Another major carrier of the autism-specific early seizure onset effect in the current case review was neuronal FCD (row 3 of table 5). FCD is a disorder of neuronal migration considered to originate during fetal life. However, it is important to understand that the anatomy and physiology of FCD evolves after birth in association with numerous ongoing changes such as myelination and universal conversion of GABA neurons from excitatory to inhibitory synaptic function. It takes special expertise to detect FCD clinically with MRI. It is not often reported and still appears exotic, though that will surely change soon. Given the plethora of etiologies proposed for idiopathic autism, we easily forget that post-mortem investigation of idiopathic autism has consistently found FCD (Bozzi et al., 2018) and that MRI studies of fractional anisotropy in the cortex of patients with idiopathic autism suggest a disorder possibly reflecting dysplasia occurring in an early and small developmental interval, a brief critical period (Braun et al., 2017).

In the present study the prevalence and timing of FCD's role in the autism-specific early seizure onset effect can be gauged relative to competing models. Glial damage (white matter hyperintensity, delayed myelination, leukomalacia) did not carry the autism-specific early seizure onset effect. The major childhood diseases of white matter (leukodystrophy, encephalomyelitis) were absent in the autism/epilepsy case report literature reviewed by us. This suggests that the autism-specific early seizure onset effect is specifically neuronal, not glial. Mass lesions (porencephaly, cerebrovascular accident, arteriovenous malformation, head trauma) did not carry the autism-specific early seizure onset effect in the current database. FCD highly significantly carried the autism-specific early seizure onset effect in the present study, and it was detected across many

Table 5. Tests of a difference between autists and non-autists regarding age at seizure onset in subsamples with various MRI anomalies

| Neurologic morbidity                              | Number of autistic patients | Number of non-autistic patients | Median age at seizure onset of the autistic patients (days) | Median age at seizure onset of the non-autistic patients (days) | Whole sample coefficient of variation (%) | Mann-Whitney Z (Δ between ranks) | p       |
|---------------------------------------------------|-----------------------------|--------------------------------|-----------------------------------------------------------|---------------------------------------------------------------|------------------------------------------|----------------------------------|---------|
| Abnormal MRI                                      | 625                         | 1704                           | 300                                                       | 720                                                           | 156                                      | 7.4                              | 1.1e-13 |
| Focal temporal lobe damage*                       | 96                          | 299                            | 240                                                       | 1825                                                          | 130                                      | 7.1                              | 1.1e-12 |
| Cortical dysplasia                                | 187                         | 400                            | 210                                                       | 730                                                           | 168                                      | 5.7                              | 1.4e-8  |
| Focal frontal lobe damage*                        | 85                          | 196                            | 240                                                       | 1021                                                          | 147                                      | 4.5                              | 0.000007 |
| Subcortical dysplasia                             | 115                         | 206                            | 330                                                       | 1020                                                          | 152                                      | 4.4                              | 0.00001 |
| Tumor@                                            | 35                          | 114                            | 300                                                       | 1806                                                          | 138                                      | 4.1                              | 0.00004 |
| Hippocampal sclerosis                             | 18                          | 76                             | 210                                                       | 1460                                                          | 118                                      | 40.0                             | 0.00007 |
| Nodular periventricular heterotopia               | 40                          | 53                             | 233                                                       | 1020                                                          | 190                                      | 3.9                              | 0.0001  |
| Focal parietal lobe damage*                       | 43                          | 142                            | 180                                                       | 1369                                                          | 163                                      | 3.6                              | 0.0004  |
| Focal occipital lobe damage*                      | 27                          | 121                            | 330                                                       | 1062                                                          | 168                                      | 3.4                              | 0.001   |
| Thin corpus callosum                              | 81                          | 142                            | 690                                                       | 150                                                           | 185                                      | -2.9                             | 0.004   |
| Thick cortex                                      | 10                          | 14                             | 195                                                       | 1460                                                          | 108                                      | 2.7                              | 0.007   |
| Dysembryoplastic neuroepithelial tumor            | 7                           | 45                             | 730                                                       | 2993                                                          | 86                                       | 2.6                              | 0.009   |
| Gray/white matter boundary blurring              | 9                           | 12                             | 300                                                       | 1004                                                          | 141                                      | 2.5                              | 0.013   |
| Delayed myelination                               | 50                          | 95                             | 270                                                       | 120                                                           | 181                                      | -20.0                            | 0.050   |
| Arterovenous malformation¢                         | 11                          | 34                             | 210                                                       | 695                                                           | 161                                      | 1.5                              | 0.144   |
| Ulegyria                                          | 3                           | 9                              | 912                                                       | 2555                                                          | 84                                       | 1.4                              | 0.165   |
| Cerebellar anomaly+                               | 62                          | 76                             | 635                                                       | 730                                                           | 144                                      | 1.4                              | 0.172   |
| Double cortex                                     | 3                           | 27                             | 1460                                                      | 2190                                                          | 56                                       | 1.4                              | 0.176   |
| Encephalomalacia                                  | 7                           | 12                             | 243                                                       | 874                                                           | 120                                      | 1.4                              | 0.170   |
| Hypothalamic hamartoma                            | 27                          | 122                            | 365                                                       | 420                                                           | 173                                      | 1.3                              | 0.194   |
| Central nervous system cyst∆                     | 27                          | 63                             | 365                                                       | 365                                                           | 173                                      | 1.2                              | 0.225   |
etioologies (see table 5). Among the neuropathological conditions that we found to significantly carry the autism-specific early seizure onset effect, nearly all are known to comprise FCD. This has been demonstrated to be the case frequently in tuberous sclerosis (Randle, 2017), in the PCDH19/Xq22.1 mutation (Trivisano and Specchio, 2018), in the DEPDC5/22q12.2-q12.3 mutation (Baulac et al., 2015), in the CNTNAP2/7q35-q36 mutation (Strauss et al., 2006), in dysembryoplastic neuroepithelial tumor (Daumas-Duport et al., 1988), in electrical status epilepticus in sleep or continuous spikes and waves during sleep ESES/CSWS (Caraballo et al., 2013), and occasionally in ganglioglioma (Sarfaty and Flores-Sarnat, 2015) and astrocytoma (Pravson and Estes, 1995).

FCD is the most common cause of medically refractory epilepsy (Kabat and Król, 2012). Several reports of repeat MRI in children describe undetectability of FCD at first MRI reading but salient detection upon a repeat MRI (Jeon et al., 2017; Yoshida et al., 2008). Evidence from MRI and from post-mortem histology (Miyata et al., 2013; Sprefaco, 2010) has recently established that FCD progresses after birth by exacerbating or entailing any combination of the following: focal white/grey matter blurring, proliferation of localized patches of abnormally giant cortical neurons, focal changes in cortical and callosal thickness, focal neuronal heterotopia (or dyslamination), post-natal brain enlargement, focal disruption of myelin, focal calcification, ganglioglioma, and even focal gyral/sulcal malformation (polymicrogyria, ulegyria, pachygyria, lissencephaly, schizencephaly). Adverse perinatal events such as asphyxia, brain bleeds and shunted hydrocephaly are significantly associated with FCD (with the latter always detected later with MRI), and several authors reporting these findings believe that the former causes the latter more than the latter the former (Redfearn et al., 2005).

Most importantly for our purposes here, several findings have documented synaptic and chemical changes in FCD, occurring after a post-natal interval, thought to directly cause seizure onset (Marin-Valencia et al., 2014).

We note that Angelman syndrome (AS), however, could be in a special category; not explainable by FCD. AS, which significantly manifested the autism-speci-
fic early seizure onset effect in the present study, involves direct damage to the GABAergic inhibition network necessary to stave off epilepsy. AS has apparently not yet been investigated post mortem for FCD, except in one study in which FCD was detected only in a minority of a small sample of cases with autism. In our own subset of 145 cases with the Angelman phenotype, only two cases, both with autism, were reported to manifest FCD.

The social brain is the most damaged and dysfunctional in the autism-specific early seizure onset effect

In the present study, another major carrier of the autism-specific early seizure onset effect was morbidity occurring in the social brain, far more than other brain areas. In their authoritative and exhaustive review of the social brain Adolphs and colleagues (Falck-Ytter et al., 2013) define its function as consisting of “reward evaluation, perception of people’s actions, motivation, theory of mind, feeling, empathy, moral emotion and social emotion”. They also clearly stated that the social brain includes the temporal and frontal lobes, but not the parietal or occipital lobes, nor the brain stem, nor the diencephalon. The latter four can be considered part of the “emotional brain” but not the “social brain” per se. The social brain has been proposed by several authors as the critical site of brain dysfunction in autism. The evidence supporting that point of view has consisted so far of subtle and controversial evidence from structural and functional imaging research in idiopathic autism (Pelphrey et al., 2011; Sato and Uono, 2019). Here, we introduce structural MRI and EEG scalp topography as additional new unequiv

Table 6. Tests of a difference between autists and non-autists regarding age at seizure onset in subsamples with medical diagnoses not primarily based on MRI or in subsamples not receiving surgery for intractable epilepsy

| Neurologic morbidity                        | Number of autistic patients | Number of non-autistic patients | Median age at seizure onset of the autistic patients (days) | Median age at seizure onset of the non-autistic patients (days) | Whole sample coefficient of variation (%) | Mann-Whitney Z (∆ between ranks) | p     |
|---------------------------------------------|------------------------------|---------------------------------|-------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------|-----------------------------------|-------|
| Epilepsy surgery                            | 168                          | 595                             | 210                                                         | 1095                                                          | 138                                       | 9.2                               | 2.4e-20|
| Angelman syndrome phenotype                 | 91                           | 54                              | 730                                                         | 1630                                                          | 106                                       | 3.2                               | 0.001 |
| Tuberous sclerosis phenotype                | 162                          | 238                             | 180                                                         | 210                                                           | 246                                       | 3.1                               | 0.002 |
| Vagus nerve stimulation                     | 61                           | 199                             | 365                                                         | 1095                                                          | 124                                       | 2.6                               | 0.009 |
| Neonatal adenylosuccinate lyase deficiency  | 22                           | 8                               | 84                                                          | 1460                                                          | 114                                       | 2.1                               | 0.032 |
| Kabuki syndrome                             | 4                            | 13                              | 195                                                         | 1095                                                          | 87                                        | 20.0                              | 0.045 |
| Maternal diabetes                           | 6                            | 6                               | 273                                                         | 730                                                           | 77                                        | 1.9                               | 0.053 |
| Neonatal pyridoxin deficiency               | 13                           | 104                             | 14                                                          | 2                                                             | 660                                       | -1.9                              | 0.057 |
| Neonatal/infantile hypoglycemia             | 13                           | 51                              | 180                                                         | 730                                                           | 100                                       | 1.9                               | 0.059 |
| Hypotonia documented at birth               | 45                           | 49                              | 540                                                         | 330                                                           | 143                                       | -1.9                              | 0.062 |
| KBG syndrome                                | 8                            | 10                              | 2738                                                        | 468                                                           | 84                                        | -1.8                              | 0.074 |
| Bainbridge-Ropers syndrome                  | 5                            | 5                               | 2190                                                        | 730                                                           | 154                                       | -1.8                              | 0.074 |
| Various metabolic syndromes #               | 18                           | 24                              | 278                                                         | 730                                                           | 141                                       | 1.6                               | 0.117 |
| Hydrocephaly                                | 8                            | 24                              | 210                                                         | 727                                                           | 143                                       | 1.5                               | 0.127 |
| Encephalitis                                | 26                           | 69                              | 695                                                         | 1450                                                          | 110                                       | 1.5                               | 0.137 |
| Low Apgar score (<7)                        | 4                            | 17                              | 90                                                          | 453                                                           | 140                                       | 1.4                               | 0.150 |
| Microcephaly (OFC)@                         | 170                          | 254                             | 365                                                         | 270                                                           | 162                                       | -1.4                              | 0.174 |
| Intellectual deficiency                     | 950                          | 1475                             | 360                                                         | 365                                                           | 146                                       | 1.2                               | 0.219 |
Table 6. Continued

| Neurologic morbidity                      | Number of autistic patients | Number of non-autistic patients | Median age at seizure onset of the autistic patients (days) | Median age at seizure onset of the non-autistic patients (days) | Whole sample coefficient of variation (%) | Mann-Whitney Z (Δ between ranks) | p     |
|-------------------------------------------|----------------------------|--------------------------------|------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------|-----------------------------------|-------|
| Temple-Baraitser syndrome                 | 3                          | 9                              | 985                                                        | 270                                                          | 134                                      | -1.2                              | 0.226 |
| Cerebrovascular accident                  | 18                         | 91                             | 315                                                        | 240                                                          | 227                                      | -10.0                             | 0.302 |
| Rett syndrome phenotype                   | 49                         | 26                             | 960                                                        | 730                                                          | 112                                      | -10.0                             | 0.330 |
| Cornelia De Lange syndrome                | 11                         | 19                             | 1333                                                       | 150                                                          | 128                                      | -10.0                             | 0.331 |
| Neonatal folate deficiency                | 10                         | 17                             | 635                                                        | 132                                                          | 133                                      | -0.9                              | 0.393 |
| Congenital hyperbilirubinemia             | 11                         | 9                              | 300                                                        | 1095                                                         | 133                                      | 0.8                               | 0.403 |
| Nicolaides-Baraitser syndrome             | 12                         | 19                             | 638                                                        | 540                                                          | 118                                      | -0.8                              | 0.428 |
| Any severe fetal distress or at birth     | 155                        | 262                            | 450                                                        | 365                                                          | 151                                      | -0.9                              | 0.372 |
| Williams-Beuren syndrome                  | 6                          | 16                             | 303                                                        | 635                                                          | 138                                      | 0.9                               | 0.376 |
| Phelan-McDermid syndrome                  | 25                         | 12                             | 2555                                                       | 2008                                                         | 66                                       | -0.6                              | 0.569 |
| Asphyxia/anoxia at birth                  | 28                         | 54                             | 387                                                        | 348                                                          | 144                                      | -0.5                              | 0.649 |
| Autoimmune encephalitis*                  | 3                          | 22                             | 1934                                                       | 2445                                                         | 60                                       | 0.3                               | 0.738 |
| Periventricular leukomalacia              | 8                          | 16                             | 345                                                        | 1004                                                         | 103                                      | 0.3                               | 0.787 |
| Macrocephaly (OFC)@                       | 40                         | 52                             | 365                                                        | 870                                                          | 144                                      | 0.2                               | 0.822 |
| Various mitochondrial syndromes           | 18                         | 8                              | 450                                                        | 1095                                                         | 123                                      | 0.2                               | 0.845 |
| Head trauma                               | 6                          | 33                             | 2463                                                       | 2555                                                         | 114                                      | 0.0                              | 0.969 |

Note. AED – Antiepileptic drug; # – Excludes pyridoxine and aldehyde deficiencies; * – All cases had Rasmussen's encephalitis except one autist who had anti-NMDA receptor encephalitis; @ OFC – occipitofrontal circumference (3 percentile limit), measured at birth except occasionally in childhood.

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they should be linked to nothing but autism. It is enlightening that intellectual deficiency in the present study did not at all carry the autism-specific early seizure onset effect (see row 18 of table 6). Thus, the autism-specific early seizure onset effect seems to be exactly what it states: highly specific to autism.

Summary of how age at seizure onset factors into the autism/epilepsy association

An autism-specific early seizure onset effect is common but not universal in specific neuropathological conditions, and this effect occurs within a critical post-natal interval. Within each neuropathological condition in which age at seizure onset associates with autism the cases with autism have earlier seizure onset, but across those conditions, median age at seizure onset in the cases with autism is never before 50 post-natal days and never after 24 months. The strongest driver of the autism-specific early seizure onset effect, across the wide range of relevant neuropathological conditions probed here is intractability of the lesions. Another strong driver of the autism-specific early seizure onset effect is focal cortical dysplasia, which we also noticed is common across several of our otherwise defined neuropathological conditions significantly manifesting the autism-specific early seizure onset effect. Finally, focal neuropathology in the brain documented either by MRI or by EEG in which neuropathological conditions present an autism-specific early seizure onset effect is far more statistically significant when the morbidity is in the temporal or frontal lobes than when it is in the parietal or occipital lobes. Altogether, these findings inspire us to believe that in those conditions in which the autism-specific early seizure onset effect is significant it is stress on and damage to the social brain, occurring within the period during which development of social skills would be expected, that causes both autism and seizure onset.

ACKNOWLEDGMENT

This research was inspired by and is dedicated to the 500 or so students of the first author who took his graduate course on the neuropathology of autism over a span of 15 years. These students, striving to dedicate their professional lives to caring for persons with autism, were some of the kindest persons he had the honor of serving.

CONFLICT OF INTEREST DISCLOSURES

The authors declare no competing interests.

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