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# Psychomotor slowing is associated with anomalies in baseline and prospective large scale neural networks in youth with epilepsy

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A B S T R A C T

*Purpose:* Psychomotor slowing is a common but understudied cognitive impairment in epilepsy. Here we test the hypothesis that psychomotor slowing is associated with alterations in brain status reflected through analysis of large scale structural networks. We test the hypothesis that children with epilepsy with cognitive slowing at diagnosis will exhibit a cross-sectional and prospective pattern of altered brain development.

*Methods:* A total of 78 children (age 8–18) with new/recent onset idiopathic epilepsies underwent 1.5 T MRI with network analysis of cortical, subcortical and cerebellar volumes. Children with epilepsy were divided into slow and fast psychomotor speed groups (adjusted for age, intelligence and epilepsy syndrome).

*Results:* At baseline, slow-speed performers (SSP) presented lower modularity, lower global efficiency, higher transitivity, and lower number of hubs than fast-speed performers (FSP). Community structure in SSP exhibited poor association between cortical regions and both subcortical structures and the cerebellum while FSP presented well-defined communities. Prospectively, SSP displayed lower modularity but higher global efficiency and transitivity compared to FSP. Modules in FSP showed higher integration between and within themselves compared to SSP. SSP showed hubs mainly from frontal and temporal regions while in FSP were spread among frontal, temporal, parietal, subcortical areas and the left cerebellum.

*Implications:* Results suggest the presence of widespread alterations in large scale networks between fast- and slow-speed children with recent onset epilepsies both at baseline and 2 years later. Slower processing speed appears to be a marker of abnormal brain development antecedent to epilepsy onset as well as brain development over the 2 years following diagnosis.

## 1. Introduction

Commonly appreciated neuropsychological complications of epilepsy include anomalies in memory, language, and executive function (Dodrill, 2004; Elger et al., 2004; Lin et al., 2012). Cognitive and psychomotor slowing is a less frequent focus of research as a core complication of epilepsy, but it appears as an abnormality in the cognitive status of adults with chronic epilepsy (Piazzini et al., 2006) as well as children with established cryptogenic localization-related (van Mil et al., 2010) and uncomplicated epilepsies (Boelen et al., 2005), as well in children and adults with new onset epilepsies prior to initiation of medications (Oostrom et al., 2003; Prevey et al., 1998; Taylor et al., 2010). Furthermore, especially in adults, psychomotor slowing worsens over time and can exceed the rate of change in other cognitive abilities (Baker et al., 2011; Hermann et al., 2006a). Cognitive and psychomotor slowing is a known complication of seizure medications (Vermeulen and Aldenkamp, 1995; Eddy et al., 2011; Loring et al., 2007; Park and Kwon, 2008), representing an impact that may be added to the intrinsic slowing observed antecedent to medication initiation in pediatric and adult new onset epilepsies (Oostrom et al., 2003; Taylor et al., 2010). With epilepsy remission and cessation of treatment with epilepsy medication there can be improvement in psychomotor speed in both children (Aldenkamp et al., 1993, 1998) and adults (Lossius et al., 2008), as well as following successful pediatric epilepsy surgery with

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reduction in medications (van Schooneveld et al., 2013). However, even with terminal remission of epilepsy a signal of persisting slowing has been reported (Aldenkamp et al., 1993; Berg et al., 2008).

While there is a long and extensive history of interest in processing speed and its relationship to intelligence and other cognitive abilities (O'Brien and Tulsky, 2008), the amount of research dedicated to characterizing the underlying neurobiological correlates of cognitive/psychomotor slowing in epilepsy in particular has been modest and varied. Dow et al. (2004) examined mental scanning speed in adults with temporal lobe epilepsy and found performance related to global white matter volume. Alexander et al. (2014) reported that increased FA of the left fornix was related to faster processing speed in temporal lobe epilepsy patients without hippocampal sclerosis. Van Veenendaal et al. (2017) examined the relationship between central information processing speed and rs-fMRI network efficiency and found no relationship between speed and network analysis in 55 patients with localization-related epilepsy. Normal aging in the general population is known to be associated with slowing of psychomotor speed (Era et al., 2011; Salthouse, 1996; Salthouse and Madden, 2008), an effect that has been attributed to age-related disruption of both cerebral white (Lu et al., 2011) and gray matter (see Seidler et al., 2010 for review). Clearly, much remains to be learned regarding the underlying neurobiology of psychomotor slowing as well as its impact on the efficiency of other cognitive processes in patients with epilepsy.

Complicating the situation in epilepsy, as well as general processing speed research in general, is the fact that cognitive and psychomotor speed has been assessed through a diversity of measures including simple and complex reaction time, finger tapping, mental scanning, motor assembly tasks, and other methods (Grevers et al., 2016; Martin and Bush, 2008) and the generalizability of findings across these diverse metrics is a persisting concern. At its most basic level, processing speed can be defined as the time required to complete a cognitive task or the amount of work that can be completed in a finite amount of time (DeLuca, 2008). One commonly used metric of “processing speed”, examined in epilepsy as well as across various clinical disorders, is the digit symbol substitution or number symbol substitution test, with applications to examine speeded performance in schizophrenia (Dickinson et al., 2007; Dickinson and Gold, 2008; Knowles et al., 2010; Morrens et al., 2007), bipolar disorder (Morsel et al., 2015), multiple sclerosis (Batista et al., 2012), chronic fatigue (Demaree et al., 2008), and other clinical groups (c.f., DeLuca and Kalmar, 2008, Dickinson and Gold, 2008), as well as normal aging (Salthouse, 1978, 2000). In a confirmatory factor analysis of an extensive neuropsychological test battery in 233 youth with epilepsy and normally developing controls (age 8–18), we identified a speed-based cognitive factor of which digit symbol was a composite test (Hermann et al., 2016), indicating its direct relevance to epilepsy as well.

The origin of the digit substitution test dates to the early 1900s (for review see Boake, 2002) which were initially thought to represent an assessment of incidental learning. However, careful deconstruction of the task has demonstrated that it is driven in part by speed-dependent processes (graphomotor speed, perceptual speed) with secondary contributions of visual scanning efficiency, learning/memory and executive function (Joy et al., 2003; Ashendorf and Reynolds, 2013). This easily administered and scored procedure has been included in all versions of the child and adult Wechsler intelligence scales since their inception (Dickinson and Gold, 2008). Overall, the digit symbol substitution test is an appropriate but not pure measure of processing speed, but one that has been used and investigated in diverse clinical disorders including epilepsy as well as normal and abnormal aging as well as diverse clinical groups including epilepsy.

Given that human cognitive processes are dependent on distributed neural networks, we first test the hypothesis that psychomotor slowing will be found to be associated with alterations in brain organization reflected through analysis of large scale structural networks. In addition, as baseline psychomotor slowing in children with new onset epilepsy has been shown to be predictive of behavior problems 3 years later (Austin et al., 2011), behaviors that have been demonstrated to be associated anomalies in brain structure (Dabbs et al., 2013), we hypothesize that those children with cognitive slowing at baseline will exhibit a pattern of altered prospective brain development as well. Hence psychomotor slowing may serve as a marker of potential anomalies in current as well as prospective brain structure, organization, and development. We test these hypotheses regarding morphological networks based on regional brain volumes in children with idiopathic epilepsies with fast and slow psychomotor speed performances tested close in time to their diagnosis of epilepsy and two years later.

## 2. Methods

### 2.1. Participants

Study participants included 78 children with idiopathic epilepsies who were recruited from pediatric neurology clinics at three Midwestern medical centers (University of Wisconsin-Madison, Marshfield Clinic, Dean Clinic) and met the following inclusion criteria: (i) diagnosis of epilepsy within the past 12 months; (ii) no other developmental disabilities (e.g. intellectual impairment, autism); (iii) no other neurological disorder, and (iv) normal clinical MRI. All children entered the study with active epilepsy diagnosed by their treating pediatric neurologists and confirmed by medical record review of the research study pediatric neurologist. Each child's epilepsy syndrome (Idiopathic Generalized or Localization Related Epilepsy) was defined in a research consensus meeting by the research pediatric neurologist who reviewed all available clinical data (e.g., seizure description and phenomenology, EEG, clinical imaging, neurodevelopmental history) while blinded to all research cognitive, behavioral, and neuroimaging data. All participants completed two waves of MRI and neuropsychological evaluations including baseline and 2-year follow-up assessments. Baseline evaluation was performed within 12 months of epilepsy diagnosis. At baseline, all participants attended regular schools (see Hermann et al., 2006b for further details).

### 2.2. Neuropsychological assessment

At baseline and 2-year follow-up, all participants were administered a neuropsychological test battery that included assessment of intelligence (Wechsler Abbreviated Scale of Intelligence [WASI-4) and psychomotor speed assessed by the digit symbol substitution test (Wechsler Intelligence Scale for Children III, Digit Symbol-Coding) (Wechsler, 1991). The Digit Symbol test was independent of the derivation of the WASI-4 intelligence quotient.

### 2.3. Psychomotor speed groups

In order to discern brain morphological differences associated with psychomotor speed performance, the epilepsy participants were separated into fast ($n = 29$) and slow psychomotor speed performers ($n = 47$) based on a median split (median = 8) of baseline age-adjusted WISC-III Digit Symbol performance (Wechsler, 1991), with those participants falling below the median value considered to be slow-speed performers. The number of participants is not identical in each group as many subjects exhibited the same median scale score and were considered slow-speed performers.

A summary of the demographic and clinical characteristics of the participants is provided in Table 1. The fast and slow processing speed groups both had full scale IQ scores that fell in the average range but with a significant difference in processing speed performance (13th percentile in the slow group and 58th percentile in the fast group). There were no differences between the groups in age, sex, SES, or medication number. The project protocol was reviewed and approved by the Institutional Review Board of the University of Wisconsin School