Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Temporal regularity of cerebral activity at rest correlates with slowness of reaction times in intellectual disability

Julie Palix [a,c,d,*], Fabienne Giuliani [b], Guillaume Sierro [c], Catherine Brandner [c], Jérôme Favrod [d]

[a] Research Unit of Legal Psychiatry and Psychology, Department of Psychiatry, University Hospital Centre of Lausanne, Switzerland
[b] Consultation of Liaison Psychiatry for Intellectual Disability, Community Psychiatry Service, Department of Psychiatry, University Hospital Centre of Lausanne, Switzerland
[c] Brain Electrophysiology Attention Movement Laboratory, Institute of Psychology, University of Lausanne, Switzerland
[d] La Source School of Nursing, HES-SO University of Applied Sciences and Arts of Western Switzerland, Lausanne, Switzerland

ARTICLE INFO

HIGHLIGHTS

- The intellectual disability group does not differ from the control group in brain entropy.
- The intellectual disability group has significant slower reaction times than the control group.
- Slow reaction times in the below-average IQ group is associated with increased EEG regularity.

ABSTRACT

Objective: Intellectual disability (ID) is described as a general slowness in behavior and an inadequacy in adaptive skills. The present study examines whether behavioral slowness in ID could originate from abnormal complexity in brain signals.

Methods: Participants (N = 29) performed a reaction times (RTs) task assessing their individual information processing speeds. Half of the participants had moderate intellectual disability (intelligence quotient (IQ) < 70). Continuous electroencephalogram recording during the resting period was used to quantify brain signal complexity by approximate entropy estimation (ApEn).

Results: For all participants, a negative correlation between RTs and IQ was found, with longer RTs coinciding with lower IQ. This behavioral slowness in ID was associated with increased temporal regularity in electrocortical brain signals.

Conclusions: Behavioral slowness in ID subjects is closely related to lower brain signal complexity.

Significance: Brain signal ApEn is shown to correspond with processing speed for the first time: in ID participants, the higher the regularity in brain signals at rest, the slower RTs will be in the active state. ID should be understood as a lack of lability in the cortical transition to the active state, weakening the efficiency of adaptive behavior.

1. Introduction

1.1. Intellectual disability & general aim

Intelligence can be defined as general mental abilities related to reasoning, problem solving, and learning. Significant limitations in intelligence affect approximately 3% of the world population (World Health Organization, 2001), and the prevalence of physical disabilities (+∼30%), mental health impairments (+∼30%), and hearing (+∼10%) and vision impairments (+∼20%) is higher in these individuals than in individuals in the general population (Ouellette-Kuntz, 2005). Intellectual disability (ID) is mainly described as the presence of a below average intellectual quotient

(IQ < 70–75, APA, 1994) (Luckasson et al., 2002, Schalock and Luckasson, 2004), appearing in early development and combining with adaptive deficits in daily life in adulthood (i.e., communication, social skills and self-care). The diagnosis of ID is mainly based on psychometric evaluation scores. The intelligence quotient distribution of the general population is 100 ± 30. In a large proportion of cases, the cause of ID is unknown, but it has been estimated that 40–60% of all the etiologies of patient deficits could be explained by genetic factors, pre- or postnatal insults, an unhealthy environment or care provided by relatives. Most studies have presented male-to-female ratios ranging from 40 to 80% male, depending on the considered samples (Maulik et al., 2011), reflecting a sex effect in genetic factors and enhanced vulnerability in the male central nervous system (McLaren and Bryson, 1987). Below average intelligence is also described in most developmental genetic syndromes that are known to be highly prevalent in males, such as Fragile X, Aarskog-Scott, Rett, and Börjeson-Forssman-Lehmann syndromes and autistic spectrum disorders (Ropers and Hamel, 2005). This wide range of causes for below average intelligence poses the question of whether dysfunction in the whole central nervous system, including metabolic/genetic abnormalities, is related to intellectual disability. Many pathogenic processes could result in low IQ scores, and today, more than 350 potential causes of low IQ have been enumerated. As a consequence of this heterogeneity, few neuroimaging studies have focused on the shared cerebral specificities of ID patients. However, when considered as a unitary syndrome of generalized impairment, some specific behavioral patterns can be revealed, particularly related to the slowness of behavioral responses to a simple stimulus. This atypical slowness, demonstrated by a high variance in reaction times (RTs), is a well-known effect that has been reported for a long time in ID individuals (Baumeister and Kellas, 1968, Berkson, 1960, Deary, 2000, Nettelbeck and Brewer, 1981). Our aim here was to examine whether this recurrent behavioral slowness in ID originates from specific abnormalities in the flow of brain signal transmission. In particular, because the presence of less "healthy noise" has been described in brain signals at rest in neurological and psychiatric patients, here, we wanted to examine whether this is also the case in ID individuals. The relationship between this signal irregularity and the slowdown in RTs was the focus of our investigation.

1.2. Behavioral slowness

Despite the undeniable gap that could be observed between the tool of measurement [Spearman's g factor (Spearman, 1904), WAIS IQ (Wechsler, 1981)] and the trait being measured (human intelligence), experimental studies have revealed that intelligence scales can be linked to the general speed of behavioral processing. In clinical and nonclinical populations, individual IQ scores are highly correlated with the length and variance in RTs durations (Berkson, 1960, Jensen, 1980, 1992, Kail, 1992). The higher the intelligence score is, the faster the RTs are; this is the case regardless of whether simple or choice RTs tasks are used (Lynn and Vanhanen, 2002).

A general correspondence between intellectual fitness and neural properties has been proposed to explain this RTs slowdown in ID. The neural hypothesis considers that the link between RTs and IQ depends on the speed of processing between the appearance of a stimulus and the behavioral response. The speed of this transmission depends on the integrity of neurobiological processes such as nerve conduction velocity and synaptic transmission (Vernon and Mori, 1992) and myelin integrity (Miller, 1994). The neuronal adaptation hypothesis, in contrast, posits the idea that there are individual differences in speed reactions in the brain's economy mode and during functional arousal, and differences in

functional brain connectivity (Deary, 2000, Song et al., 2008). From this perspective, brighter subjects do not allocate more processing power when performing highly repetitive, predictable, or easy cognitive tasks (i.e., train of regular clicks) (Barrett and Eysenck, 1994, Haier et al., 1988, Neubauer and Fink, 2009, Robinson, 1989, Robinson and Behbehani, 1997) but do invest more cortical resources when the task difficulty increases. In contrast, low IQ individuals may be forced to allocate similar processing power regardless of the stimulus's predictability or complexity, as has been suggested in Down Syndrome studies (Jensen et al., 1981, Schafer and Peeke, 1982). The fundamental common idea here is the determination of the individual speed of information processing in efficient intelligence by the neural transmission efficiency (i.e., neural errors or quality of conductivity) and the functional mode (dynamics of resources), but so far, few neuroimaging studies have focused on transmission in those with below average intelligence.

1.3. Brain oscillations related to intelligence at rest

Regarding nonpathological individual differences in intelligence scales, evidence has supported the idea that during rest, cerebral recruitment is slower in brighter individuals than in individuals with lower intelligence. Consequently, higher synchronicity in the brain's alpha oscillations (Doppelmayr et al., 2005) and lower regional BOLD signal activation have been seen in high IQ individuals during relaxation but not in low IQ individuals (Neubauer and Fink, 2009). In this way, the impairment of general intelligence has been proposed to be related to more effortful cortical involvement during active states (Deary et al., 2010) and less refreshing rest states. As synchronous neuronal discharges in the alpha frequency range (8–13 Hz) represent rhythmic and ample potential fluctuations, known as the noncoding state of processing, increased power reflects a slowdown in cerebral activities. As a consequence, during effortful tasks, highly efficient subjects show higher transfer speeds between brain areas (Li et al., 2009, Miller, 1994, Robinson, 1989) and reach higher neural activation levels, corresponding to more desynchronized neural signals than subjects with low intelligence (Neubauer and Fink, 2009).

1.4. Entropy and the pathological brain

The electroencephalographic (EEG) approximate entropy (ApEn) estimation method (Pincus, 1991) consists of recording a few dozen seconds of spontaneous brain signals over the scalp of subjects and then extracting signal irregularities in the time series related to electrocortical fluctuations. The ApEn provides an estimation of the complexity and irregularity of the EEG signals. Steyn-Ross and colleagues (Steyn-Ross et al., 1999) matched the regularity in EEG to intracortical connectivity. Research findings have demonstrated that patients with neurological (Abasolo et al., 2006, Abásolo et al., 2005, Li et al., 2014) or psychiatric disorders (Akar et al., 2016, Kang et al., 2019, Pincus, 2006) display lower brain signal complexity than the general population. These findings all suggest that decreased EEG complexity at rest could be related to increased dysfunction. Based on numerous studies, the ApEn has been shown to correlate with subclinical changes and is thought to be predictive of subsequent clinical changes and individual longitudinal evolution, such as physiological aging, postsurgical recovery, and medical treatment. This loss of complexity also corresponded to fMRI entropy in the BOLD signal (Hager et al., 2017, Roy et al., 2018).

The advantage of this method of analysis is that it considers background EEG activity as an informative time series, unlike the more traditional methods seeking to eliminate as much "noise" as possible from the raw data before analysis (evoked potentials,

analysis frequency). Thus, ApEn has been proposed as a solution to the problem of noise contamination in EEG data and has been successfully applied to relatively small and noisy data sets (Natarajan et al., 2004, Pincus, 1991, Pincus and Goldberger, 1994). Furthermore, this method of analysis allows us to overcome any power or neuronal synchronization deficiencies related to a stimulus or a motor response and, thus, seems to be particularly appropriate for the population studied here, which is known to have difficulty concentrating and staying still and suffers from multiple sensory impairments.

Behavioral slowness and inefficiency in adaptive skills that characterize intellectual disability have been depicted for several developmental pathologies without finding consistent explanations. Our objective was to examine whether brain signal singularities related to behavioral slowdown correspond to intellectual disability. Indeed, Alzheimer's disease patients, for whom neural connectivity has been shown to decrease, not only demonstrate psychomotor slowness (Miller, 1974, Pirozzolo et al., 1981) but also general impairments in surface EEG signals (Jeong, 2004, Jeong et al., 2001) and abnormally low cortical signal complexity compared to controls (Abasolo et al., 2008). Because white matter integrity has been proposed to be related to general intelligence (Song et al., 2008), differences in ApEn were expected between participants with weak and normal intelligence. We hypothesized that the approximate entropy, i.e., an index of brain signal complexity, would be lower in the intellectually disabled group than in the control group, in line with the supposed global brain connectivity impairment and alterations in intracortical flow in the ID group.

2. Methods

2.1. Subjects

Twenty-nine young adults took part in the study, 14 (11 males) participants with moderate intellectual disability (IQ_{ID} = 57 ± 11) and 15 age- and gender-matched healthy controls (IQ_{HC} = 109 ± 11). ID participants were recruited from a group of patients who were followed by the mental development psychiatry mobile team of the Community Psychiatry Service at the University Hospital Center of Lausanne, Switzerland. IQ was individually evaluated with the WAIS-III instrument (Wechsler, 1981) by trained psychologists in the psychiatric department at the Lausanne University Hospital. All the ID subjects lived near their parents and/or were affiliated with an extended-care mental institution in the Lausanne area. No recognized medical or psychiatric pathologies other than mental retardation were diagnosed (DSM-IV-TR criteria, American Psychiatric Association, 2001), albeit most participants had been taking pharmaceutical medication since adolescence. All of the subjects personally, or through their legal representative, gave their written informed consent to participate in the study. Of the 14 subjects in the experimental group, one was excluded from the EEG results (contamination of vagus nerve electrical stimulation). The control subjects were volunteers who were recruited from the hospital (employees such as secretaries, human resources employees, and administrative, medical and educational staff) or from vocational colleges. A medical questionnaire confirmed the good health of the participants and the absence of any history of neurological disease in their families. The experiment was created with respect to the Declaration of Helsinki and was accepted by the Human Research Ethics Committee of the Canton de Vaud, Switzerland.

2.2. Apparatus and procedure

The participants were seated comfortably in a dimly lit room in front of a table on which there was an HP computer screen (eyes-to-

screen distance = 57 cm). The subjects were instructed to stay still and to relax until the beginning of the experiment. Sixty-four active pin-type electrodes (BioSemi ActiveTwo EEG System acquisition, BioSemi B.V. WG-Plein 129 1054SC Amsterdam) had been attached to the Quick-Cap according to the 10–20 international position system (Jasper, 1958). The feedback loop provided by BioSemi ActiveTwo was used to ensure valid measurements. This system allows to avoid any abnormal range before recordings (common mode voltage) and to evaluate the good conductivity of signal at all electrodes 'sites (electrodes offset visualization). A continuous electroencephalogram was then recorded during the resting state (awake with eyes open) to be used *offline* in the estimation of the complexity of EEG resting activity. The EEG data were continuously acquired at a sampling rate of 4096 Hz with ActiView software (version 5.34) through 0.5–100 Hz filters.

The RTs task was the Poffenberger paradigm (Poffenberger, 1912), which measures participants' response latencies to a visual stimulus, usually a flash of light, appearing an equal amount of times in the right or left visual field, thus requiring an equal number of left or right hand responses. This paradigm has been selected for the population with mild intellectual disability because of its simplicity, as there is no ambiguity in the instruction: "As soon as picture appears on the screen, please press the button as fast as possible". It allows the easy testing of both visuals fields and the RTs of both hands and lateralized control impairment in this population. Here, the protocol was adapted, and the flashes were replaced by 140 different black line drawings (objects, animals, body parts) that were presented one by one on a uniform white background (3000 ms maximum duration). Next, the target stimulus onset after the preceding response occurred after a random interval between 500 ms and 1000 ms. For each trial, a black 5 mm by 5 mm fixation cross ('+') was centered on the monitor screen. The subjects were instructed to respond as fast as possible when an image appeared while maintaining their gaze on the central fixation point. Each image was lateralized to the left or the right of the central fixation point (8° of the visual angle) and required the unimanual push of the button to disappear. Half of the trial responses were given with the right hand using the right button (Cedrus RB-530 Copyright 2009 Cedrus Corporation, P.O. Box 6309, San Pedro, CA 90,734 – USA), while the other half of trial responses were given using the left hand on the left button. The stimuli and responses were presented and recorded with E-Prime 2.0 Professional software (Copyright © 2007 Psychology Software Tools, Inc.).

2.3. Analysis

Reaction times: The means and standard deviations of all the data (for both hands and visual fields) were calculated for each subject after excluding outlier responses (150 ms < RTs > 1000 ms). Significant differences between the populations were assessed using Student's t-test.

EEG irregularity quantification: The EEG signal was re-referenced offline to virtual ear lobes (B.E.S.A. GmbH, Germany) and bandpass filtered (0.5–40 Hz) using a zero-phase shift second-order Butterworth filter. We also downsampled to 256 Hz, in accordance with the methods described by Abasolo and colleagues (Abasolo et al., 2006). The EEG data that were free from electro-oculographic and movement artifacts (amplitudes below ± 120 μV) were carefully selected for nonlinear analysis. Further data pre-processing was not applied as the ApEn calculation is robust or even insensitive to extreme values and artifacts (Pincus, 2001): Extremely ample and minor artifacts have little impact on the ApEn calculation if they appear infrequently. The idea is also that the presence of broadband activity of EEG is required for a proper evaluation of complexity (Azami et al., 2017). Additionally

the parameter *r* of the ApEn formula plays *de facto* the role of filter: noisy data of a magnitude below the tolerance width of *r* (0.25 × standard deviation) will have no incidence in the calculation (Pincus, 1991; Pincus, 2001; Abásolo et al., 2005). As a check for the presence of an acceptable signal-to-noise ratio (SNR) in the EEG signals of both groups, evoked potentials were calculated stimulus-locked on the images presentation, individually for each participant. On average, 86% ± 16 SD of raw signal were retained (59 epochs/70), without groups distinction (p = .57). The SNR was equivalent to 1.97+/-0.28 SD (B.E.S.A. GmbH, Germany), and comparable in both groups (p = .75), providing a satisfactory estimate of 2:1 ratio between the signal power and noise.

Then, for entropy estimation, EEGs at rest were divided into 5 s epochs (~1280 data points) and exported for electrodes P7, P3, POz, P4 and P8 as ASCII files for offline analysis. A total average of 35 s ± 2 (9000±~500 data points) was used for each electrode and for each subject to estimate the approximate entropy, which is considered to be highly sufficient for classifying such complex systems (at least 1000 data points are advised) (Pincus, 1991). The number of raw EEG data points used to estimate the entropy was equivalent between both groups (*t*-test applied for independent variables; p > .7).

The MATLAB routine previously used by Pincus (1991) was then applied to each time series for each subject independently (see the online Supplementary Material). ApEn can be defined as the negative logarithmic probability that a sequence of length *m* predicts a new sequence of *m* + 1 points to within an error range of 'r', typically set at 0.25 × standard deviation. In a regular signal, most sequences will thus successfully predict the next data points, and the ApEn will be low. In an irregular signal, there will be few successful predictions, and the ApEn will be correspondingly high (Pincus and Goldberger, 1994, Sleigh et al., 2004).

According to Pincus (Pincus, 2001) and Abásolo et al (Abásolo et al., 2005), ApEn provides effective discriminatory capability in instances in which spectral analyses exhibit minimal distinctions. This entropy estimator might be complementary to spectral and autocorrelation analyses to reveal hidden characteristics of biosignals that can remain undetected with linear (spectral) analysis. This routine has been introduced to quantify regularity in the data (in short and noisy data sets) without any a priori knowledge about the system generating them (Pincus and Goldberger, 1994).

The ApEn values for the ID subjects and controls were compared on the 5 posterior electrode sites in a 2 (groups) × 5 (electrodes) factorial design analysis of variance because these electrodes represent the brain default network (in which alpha activity is stronger) and will avoid contamination from eye movement artifacts. Differences were considered to be statistically significant if the P value was lower than 0.05. Post hoc comparisons were performed with Fisher's LSD test, and the normality of the data and homogeneity of variance was assessed with the Shapiro-Wilk test and the Brown & Forsythe test, respectively, before performing ANOVA. Then, a multilinear regression analysis was conducted to predict RTs duration, with IQ, ApEn and age as independent variables. In this last analysis, the average ApEn of the 5 posterior electrode sites was used. All analyses were performed with the software StatSoft, Inc. (2014) STATISTICA (data analysis software system), version 12.

3. Results

Both groups (experimental group (N_{ID} = 14, 11 males) and healthy controls (N_{HC} = 15, 11 males)) were comparable (p_{min} = 0.53) in age (ID = 33 ± 11 SD; HC = 35 ± 9 years old), skull perimeter (ID = 57.5 ± 2.7; HC = 57.5 ± 1.5 cm), height (ID = 174 ± 9; HC = 174 ± 9 cm), weight (ID = 79 ± 20; HC = 77 ± 17 kg) and BMI (ID = 26 ± 5; HC = 25 ± 5). IQ was significantly lower in ID individ-
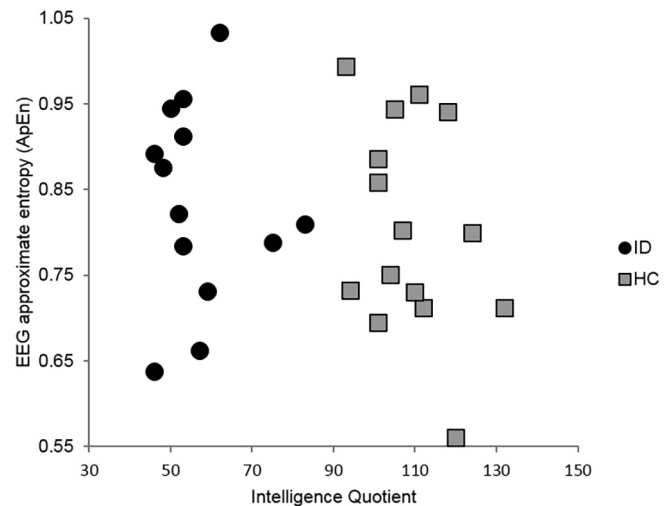

Fig. 1. Intelligence quotient (IQ) was significantly lower for the intellectual disability subjects (ID, block dots: 57 ± 11SD) than for the healthy control subjects (HC, gray squares: 109 ± 11SD; p < .001). No correlation between IQ and the EEG approximate entropy (ApEn) was noted.

uals (57 ± 11) than in HCs (109 ± 11; p < .001). Parametric assumptions were tested with success for all variables. The Shapiro-Wilk W test was significant only for the age distribution of the ID group.

3.1. Reaction times

Outlier RTs (150 ms<>1000 ms), representing an average of 5/140 for the ID subjects and 0.5/140 for controls, were excluded from the calculations. The RTs were longer for the ID subjects (309 ms ± 69) than for the HCs (270 ms ± 27; p < .05), with almost twice the standard deviation in the ID subjects (97 ± 40) than in the HCs (48 ± 9 ms; p < .001). The variance was higher in the ID subjects than in the HCs (Brn-Fors $F(1,26)$ = 17.9; p < .001). When combining all participants (N = 28), RTs were negatively correlated with IQ (r = −0.43, p < .03), indicating that the processing speed tended to decrease with the decline in IQ. The RTs StDevs correlated with IQ even more clearly (r = −0.73; p < .001).

3.2. Brain signal complexity

The ApEn values in the ID group did not differ from those in the HC group (p = .48; $ApEn_{I.D.}$=0.835 ± 0.12, $ApEn_{CTRL}$ = 0.805 ± 0.12). When all the participants' data were combined, IQ and ApEn did not seem to be related (Fig. 1), and no correlation was found between RTs and ApEn (p = .15).

However, when considered separately, the groups showed different patterns. The results of multilinear regression analyses, with RTs duration as the dependent variable and IQ, ApEn and age as independent variables, were significant for the ID group (($F(3, 12)$ = 3.95, p < .05, R^2 = 0.57, CI 95% (1.25–0.13)). Only ApEN predicted a significant increase in RTs duration (see Fig. 2left). Thus, for ID patients, the lower the brain signal complexity, the longer the RTs were. The other predictors were not significant (see Table 1a). For the HC group, the model was not significant (R^2 = 0.18, n.s. see Fig. 2right, Table 1b).

4. Discussion

Our objective was to determine whether brain signal irregularities in individuals with intellectual disabilities were less prominent than in healthy controls and whether this difference could explain the specific behavioral slowdown related to ID. We found no differences between the ID subjects and the controls in their
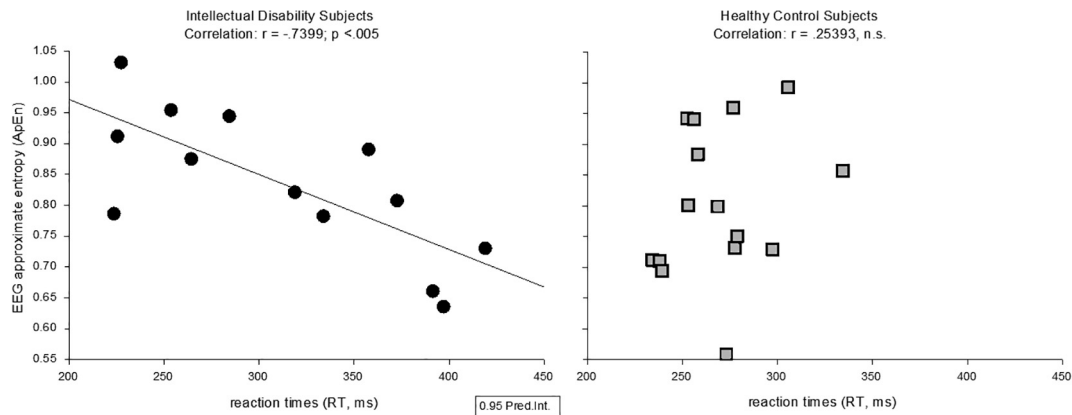
Fig. 2. Left. EEG signal complexity estimates by approximate entropy (ApEn) predicts reaction times length for intellectual disability subjects (N = 13). Right. No such effect is found for healthy control subjects (N = 15).

Table 1
Multilinear regression analyses.

Predictor	β	R	95% CI for p
a. Predicting reaction times of intellectual disability subjects			
Intelligent Quotient	−0.07	−0.06	−0.59, 0.44
EEG approximate entropy estimation	−0.69*	−0.74**	−1.25, −0.13
Age	0.12	0.43	−0.46, 0.69
b. Predicting reaction times of healthy control subjects			
Intelligent Quotient	−0.38	−0.40	−1.03, 0.27
EEG approximate entropy estimation	0.13	0.25	−0.51, 0.76
Age	0.09	0.02	−0.52, 0.70

$^*p < .05; ^{**}p < .01.$

respective brain signal complexities, with no relation to IQ. However, strong negative correlations between posterior signal irregularities and RTs were found in the ID group.

4.1. Brain signal complexity does not differ between HC and ID groups

First, this study provides strong evidence in favor of the feasibility of EEG for investigating and extracting common cerebral factors in ID patients using EEG nonlinear analysis. The neural activations that characterize distributed and interconnected brain areas during the resting state have been poorly described in relation to intelligence disability. However, two studies from the 1980s showed that electrical brain dynamics in individuals with low intelligence were distinguished by higher coherence in interconnected cortical area activations (Gasser et al., 1987, Thatcher et al., 1983). One of the reasons why we did not find any differences in our results may be that the population here comprised adult ID subjects, not school-aged ID subjects. In addition, EEG coherence analysis specifically measures coupling between cerebral areas, while entropy measures the regularity of EEG signal information flow. From this point of view, it seems important for us to emphasize the absence of a distinction between individuals with ID and individuals with normal IQ within the general population. Thus, the decrease in entropy described in many pathologies, e.g., in patients with Alzheimer's disease, even in the early stages, or in epilepsy, schizophrenia, depression and mood disorders (Coronel et al., 2017, Glenn et al., 2006, Li et al., 2008, Pincus, 2006, Urigüen et al., 2017), was not observed in intellectual disability in our study.

4.2. Negative correlations between posterior signal irregularity and RTs slowdown in ID

However, despite this point of correspondence between the two groups, the ID population had significantly slower RTs than the controls, an effect that was highly correlated with the level of irregularity in the brain signal: the higher the regularity in the brain signal at rest, the slower the RTs were in response to stimuli in the active state. As this link between RTs and ApEn was not found for all the individuals in both groups, it could not be considered representative of a general rule with a linear function. It should be noted, however, that subjects with an IQ between 60 and 90 should be tested in future investigations to complement our work and improve this interpretation. However, the correlation between ApEn and processing speed in overt behavior could help us better understand the origin of behavioral slowness and the disrupted skills that characterize intellectual disability in the diagnosis of an IQ below 70.

First, these results supported our initial hypothesis of a possible link between ID and brain signal regularity. More precisely, we showed that the higher the cerebral signal regularity, the more substantial the behavioral slowdown is. Given that this pattern was valid only for the clinical population with lower than normal IQs, one therefore wonders to what extent, if any, the ApEn values of this population are similar to the norm, as differences in this variable would indicate a resting state slightly different from that of the control population.

Indeed, one of the intelligence impairment explanations states that higher general arousal in the nervous system (Deary et al., 2010) amounts to global inefficiency. From this perspective, here, we wonder whether a higher level of activity occurring at rest in ID individuals, i.e., resting hyperarousal compared to the cortical resources at their disposal, would hamper the deployment of additional resources when sudden activity is needed. This explanation resonates with the results of previous studies regarding intelligence and neural efficiency (for review, see Neubauer and Fink, 2009). Therefore, the high predictability between ApEn during rest and RTs slowness during the active state should be understood as an impairment in the neural threshold permutation, more than an intracortical flow dysfunction in ID, and as a lack of lability in cortical activations in the active state, weakening the efficiency of adaptive behavior.

These considerations would also fit, in a broader sense, with our previous results concerning this particular population, noting that a heightened general state of excitation in the autonomic nervous system was identified at rest, producing normal-to-overactive parasympathetic activities (Palix et al., 2017). These internal constraints could be responsible for an increase in sensory anxiety, which is often reported in the case of sensory overload (Giuliani et al., 2011). These observations were related to a level of subordination / vulnerability in these individuals, with high levels of perceived stress and increased anxiety related to the abnormally effortful inhibition of negatively induced emotions (Palix et al., 2011), with good results being achieved with targeted therapeutic

interventions (El Korh and Giuliani, 2016, Favrod et al., 2015, Giuliani and Jacquemettaz, 2017). Indeed, poor intellectual skills may interact with environmental speed and complexity in a way that makes the world seem more threatening and keeps the alert system overactivated, degrading the resting state.

Our study has a few limitations. The sample is small, and the results should be interpreted with caution. However, the results are promising and should be replicated in a larger sample. It would be interesting to have a subgroup with IQ scores between 70 and 90, since the results are linear. Only the ApEn algorithm corresponding to the embedded time series analysis has been used. Supplementary algorithms could have been used to complete our exploration, such as Fuzzy entropy or Sample entropy (Amarantidis and Abasolo, 2019, Chen et al., 2009). Only visual inspection has been used to avoid artefacts. The EEG data that were free from electro-oculographic and movement artifacts were selected for the analysis. However, resting-state EEG of subjects can be influenced by other factors, which can be not be necessarily identified by data preprocessing (Kang et al., 2019). Finally, ApEn analysis cannot be considered as independent of other EEG dimensions such as spectral power. Thus, possible power confounds cannot be excluded. Equally, EEG reference choice and skin preparation remain probably relevant issues in order to reduce noisy reference which might produce confounding ApEn values.

5. Conclusion

Together, our results indicate that in addition to being useful for psychiatric or neurological diagnoses, brain signal irregularity estimation by nonlinear EEG analysis may be used as a marker reflecting unusual processing speed inefficiency. We speculated that signal irregularity in the ID group during the resting state, although similar to that of controls, could restrict brain efficiency and produce impairments in smooth adaptive behaviors in the active state. This speculation is in agreement with conclusions from ApEn BOLD signals in fMRI showing improvements in health-related quality of life and reduced depression. A healthy brain that is able to wander suggests flexibility in thinking (Lin et al., 2019, Shan et al., 2018). A more general hyperarousal of the neural alert system at rest in intellectual disability could be the origin of and could coincide with such a pattern; thus, hyperarousal must be taken into account in appropriate therapeutic follow-up from an early age. To our knowledge, this is the first time that cortical entropy has been shown to be correlated with a behavioral measure.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.04.174.

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