Identification of Infants at High Familiar Risk for Language-Learning Disorders (LLD) by Combining Machine Learning Techniques with EEG-based Brain Network Metrics

The population of children with language-learning disorders (LLD) is heterogeneous with a mixture of language deficits and also sensorimotor deficits linked to dynamic processing of the speech information (Catts et al., 2002). The core of research focused mainly on the hypothesis of whether deficits on auditory spectro-temporal processing can cause phonological impairment that potentially can lead to reading and language disorders (Bishop and Snowling, 2004). To answer the aforementioned questions, neuroscientists performed longitudinal studies of infants at genetic risk using neuroimaging methods and experimental protocols with main scope to understand the effects of auditory information to the development of language skills (Leppanen et al., 2002 ; Lyytinen et al., 2004). An accurate understanding of the origin of LLD especially infants with or without high genetic risk will give an advantage for intervention strategies on individual level (for a review see Tallal and Gaab, 2006).

The major outcome of many epidemiological studies is that the most prominent feature of developmental disabilities are language learning problems (Beitchman et al., 1986). Although many studies support that the main deficit of LLD is phonological impairment (Snow et al., 1998), the precise origin of this disorder is still on debate. The major substrates of phonological deficits are linked to speech or to general domains like memory, attention, perception and sensorimotor constraints (Mody et al., 1997 ; Ramus et al., 2003). A consistent result of various hypotheses that

have been tested so far is that the speed of auditory information processing and/or its production disrupt core components that contribute to language learning such as the phonological representations (Farmer and Klein, 1995 ; Fitch and Tallal, 2003 ; Tallal, 2004). Two prominent hypothesis have been proposed after investigating sensorimotor deficits, the rate-processing constraint hypothesis (Farmer and Klein, 1995 ; Fitch and Tallal, 2003 ; Tallal. 2004) and the magnocellular hypothesis-theory (Livingstone et al., 1991 ; Stein et al., 2001). Consistent attributes of both hypotheses are the constraint of the temporal information processing of the speech and its production which both disrupt basic components of language learning like the acquisition of phonological representations. Both theories suggest that central auditory mechanisms of information processing particularly those involved in the dynamic spectro-temporal changes underline the major phonological deficits in LLD.

Tallal et al. proposed a link between the ability to analyse rapid spectro-temporal acoustic changes and the production of speech (Tallal et al., 2004). This hypothesis is based on the assumption that every language is characterized by a set of unique phonemes which composed of a complex acoustic spectrum that should be learned by daily practise and overrepresented in the auditory cortex as neural firing patterns (Kuhl et al., 1992). According to Hebb's proposal, neurons that are excited by many sensory cues that cannot be distinguished in time domain are coded as a unit, guiding individual experience and learning (Hebb, 1949). Further exposure generally to sensory input and specifically to the waveforms of speech will lead the cell assemblies to become more generalized and to decode individual syllables and phonemes of a language independently of the speaker or the context (Clark and Yallop, 1995). Additionally, the spectro-temporal segmentation of the ongoing speech into words and syllables will also be coded by auditory cortex

(Peeva et al., 2011). This statistical learning from the brain auditory cortex is referred as Hebbian learning in the literature (Sejnowski, 1999 ; Rao and Sejnowski, 2003).

The complex ability to recognize distinct changes of speech sounds in both amplitude and frequency domain is disturbed early in infancy in a subset of children (Choudhury and Benasich, 2011, Tallal, 2004). This deviation from normality results in LLD, such as dyslexia and language impairments (Bush, 2010, Lewis and Elman, 2008), sharing also a common spectrum with autism (Whitehouse et al., 2008). Electrophysiological and behavioural studies at infants and newborns demonstrated that differences of rapid auditory processing can be identified even in newborns with both familiar or genetic risk for LLD (Friedrich et al., 2004). Approximately, 30-60 % of infants with familiar risk for LLD are at high risk of developing learning disorders (Flax et al., 2003; Tomblin, 1989).

Previous neuroimaging studies have linked LLDs with brain structural alterations even before birth (Chu et al., 2015, Leonard et al., 2011). In those cases where a genetic risk for LLD was identified, anatomical differences are a cofactor to LLD (Choudhury and Benasich, 2011, Wong et al., 2013). To reveal potential biomarkers of developmental disorders in infants linked to higher genetic risk of LLD, longitudinal studies from the early infancy till the first five years of age have been conducted (for review see Benasich and Choudhury, 2012). Behavioral tests cannot provide neuroscientists with reliable biomarkers and for that reason neuroimaging approaches have been used in infant populations (Choudhury and Benasich, 2011, Maitre et al.,2013).

One of the very first studies that extended behavioural results to electrophysiological (EEG) measurements in infant group demonstrated significant correlations between the EEG estimated recorded at six months to the language outcome at twenty-four months in both groups of familiar (FH+) and non familiar history (FH-) (Benasich et al., 2006). Group differences were

observed on EEG measurements to the rapid presentation of deviant tone sequences (100 ms interval) but not to the same sequences of tones that were presented slowly (300 ms interval). Topological differences were observed mainly over frontal, central and fronto-central brain areas on the left hemisphere (see Figure 6 in Benasich et al., 2006).

In the last five years, a few studies appeared that attempted to improve event-related potential (ERP) recordings from both magnetoencephalography (MEG) and EEG focusing on studying populations at-risk for the development of LLD (Barttfeld et al., 2011, Bosl et al., 2011) and infants at risk for autism (Stahl et al., 2012). The basic approach of averaging across trials at ERP studies in order to extract the amplitude and the latency at specific time instances with negative or positive polarity (N100, P300 etc) are not reliable in order to define robust biomarkers due to the variability of cognitive processes that can potentially alter the ERP components (Stets et al., 2012). Additionally, developmental studies with infants have an issue with artifacts due to movement of the participants during the recording session and in many cases a large part of the subjects need to excluded from the whole analysis.

Other studies analysed spontaneous EEG activity at the source level to detect predictors in populations early diagnosed with LLD (Heim and Benasich, 2011; Schiavone et al., 2014) or in other populations at risk (Gou et al., 2011). To extract meaningful features in order to discriminate the two populations (control vs target), wavelet analyses or Fast Fourier Transform (FFT) have been performed. This approach, even though it is more informative compared to amplitude and latency measurements of ERPs at specific scalp locations, cannot improve the statistical power to the level of introducing a reliable biomarker for any target group, e.g. LLD.

To solve all of the aforementioned issues regarding the prediction of a target group, classifiers have been built using EEG discriminative features to differentiate risk groups for a

specific disorder (Stahl et al., 2012). Employing machine-learning classifiers as an automatic separation strategy have been already proposed as a diagnostic procedure (Riaz et al., 2013). A recent study attempted to detect significant changes on the functional brain networks based on resting-state functional MRI between six and twelve months old groups of infants (Pruett et al., 2015). The hypothesis was that during the second six-month period, a dramatic transformation of social, motor and cognitive processes is realized. This study provided fundamental information that this period of life holds important information that can be linked to atypical development of social abilities (Elison et al., 2013) and to LLD (Zare et al., 2016 this issue).

A recent EEG study introduced an automatic classification approach based on network connectivity analysis and machine learning to firstly facilitate a framework for detecting infants at high familiar risk for LLD and secondly to provide features that can build a biomarker for the early detection of developmental disorders linked to language acquisition (Zare et al., 2016 this issue). The authors followed a network connectivity approach by first estimating a functional connectivity graph (FCG) derived from sixty two EEG (electroencephalogram) sensors during a resting-state condition and afterward by computing global efficiency and global/local clustering over original FCG and leaf / tree hierarchy indexes estimated over the unbiased unique Minimal Spanning Tree (MST) for each of the six studying frequency bands. Features extracted from the original FCG and the MST were complementary and further improved the classification accuracy to correctly classify FH+ and FH- around 80 % with specificity 89% and precision of 92 %. Global efficiency showed a decreased profile for FH+ in δ, θ and α_1 while clustering coefficient demonstrated a mixed pattern for δ, θ, α_1 and α_2. Interestingly, leaf and tree hierarchy were significantly higher for FH+ in δ band, suggesting more hierarchical brain networks for FH+ which can be interpreted as slower and inefficient information flow across the brain compared to FH-.

MST has been used as an alternative method that overcomes thresholding problems. Given a connected, undirected weighted graph, a spanning tree of the graph is a subgraph that is a tree and connects all the vertices together by minimizing the overall cost (Stam et al., 2014 ; Vourkas et al., 2014). MST will favour connections with high coupling strength but always supporting the objective criterion of connect all the nodes without introducing cycles. For that reason, a MST for a specific FCG can combine connections with a large range of strength. MST has already been used to EEG to detect network connectivity changes in children with math difficulties (Vourkas et al., 2014), through the development (Boersma et al., 2014), but this study is the first one that applied this unbiased method to infants (Zare et al., 2016 this issue). Features tailored to MST are the leaf number which is the percentage of nodes with only one link (e.g degree 1) while tree hierarchy is defined as the ratio of leaf number/(2mBC) where m denotes the number of edges in the MST and BC the highest betweenness centrality of any node in the MST.

To conclude, this study is the first one that combined machine learning techniques with EEG-based brain network analysis via the notion of MST to infants with main scope to discriminate children with a family history of LLD (FH+) from typically-developing infants without such a history (FH-) (Zare et al., 2016 this issue). At this developmental key time point, facilitation of a state of the art technique to distinguish those two groups is important due to the brain plasticity which is more flexible for intervention approaches. To further validate and improve the current analysis, a larger developmental data sets should be analysed by incorporating to the whole approach various functional connectivity estimators and also by adopting a dynamic functional connectivity analysis (Dimitriadis et al., 2010,2013,2015a,b, 2016).

Conflict of interest

The author has no potential conflicts of interest to be disclosed.

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