Summary of Research:
From brain activation to prevention of developmental dyslexia

Reading skills are central to our well-being, offer us access to a huge amount of information and, are a key factor for success at school, academics and professional life. Children with poor reading competence, such as those with developmental dyslexia (ICD-10: F81.0, DSM-5: 315.0) [1, 2], are more prone to develop social, emotional or psychological problems and often encounter disadvantages in job opportunities [3]. Developmental dyslexia runs in families [4-6] and it is well known that targeted interventions for poor reading children are more effective the earlier they start. Dyslexia, however, is usually diagnosed only months or even years after formal reading instruction has started, because accurate prediction of reading outcome in preschool children is still limited. Therefore, *new approaches to improve prediction are imperative*.

As one of the first groups worldwide, we used *multimodal neuroimaging techniques* with high spatial and temporal resolution to assess normal and impaired reading development with the aim to *better understand the neuronal basis of and the risk factors for poor reading development in children*. Characterization of the reorganization in cortical brain networks during reading acquisition and of deviant development in children with poor reading skills contribute not only to the ***identification of biomarkers*** at preschool age but also ***to advance the development of targeted and efficient training programs and interventions***.

Development of the brain network for reading in children [12,13]*:* During reading acquisition, children learn that only a specific set of culturally defined graphical patterns (graphemes) are associated with speech sounds (phonemes) and that they can be blended to form words with semantic and lexical content. These learning processes *initiate a reorganization of the left ventral occipto-temporal (vOT) cortex and a specialisation to process print* which is crucial for efficient, fluent reading. During the initial phase of learning to read, the brain acquires the ability to discriminate relevant graphical patterns such as word forms from meaningless, arbitrary patters. In adult readers, print-sensitive activation can be measured by the visual N1 event-related potential (ERP) of the electroencephalogram (EEG) after around 170ms [7-11] or the corresponding left vOT activation in functional magnetic resonance imaging (fMRI). However, little is known about the development of this functional specialization to print in the brain, which is a prerequisite for fluent and efficient reading. In our longitudinal EEG-fMRI studies, we showed that the occipito-temporal sensitization to print, shown as a left-lateralized negativity around 200ms after presentation of a word, emerges when children learn to read. Before reading acquisition, no characteristic print-specific N1 [11-14] and no specific activation of the corresponding occipito-temporal cortex [12] was found in kindergarten children. In second grade, however, after initial formal reading instruction at school, a pronounced difference between written words and visually matched symbol strings emerged [13, 14]. These longitudinal assessments clearly demonstrate the impact of learning to read on the reorganization of visual areas and the emergence of print sensitive processing. Because reading acquisition includes multiple steps, such longitudinal studies from preschool to school age cannot answer the question on which distinct processes drive the initialization of print sensitivity in childrens' brain. We specifically addressed this question by training illiterate kindergarten children grapheme-phoneme associations and tracked the brain correlates of letter-speech sound learning with ERPs and fMRI. We found that the N1 sensitivity to print and the corresponding activity in the occipito-temporal cortex developed rapidly (less than 3.5 hours of training) and emerged as a result of an eight-week grapheme-phoneme training, even though the children remained non-readers [12]. The results thus *provided for the first time direct evidence that the N1 and the corresponding ventral occipito-temporal cortex activation* do not reflect whole-word recognition or semantic processing at that age but rather the *association of written information with speech sounds*. This finding is not only crucial to better understand how reading acquisition initiates and impacts on the reading network but also pivotal to tackle deficient integration of letters and speech sounds, which is considered a core problem of children with developmental dyslexia. Enhanced training of grapheme-phoneme associations for children at risk for poor reading outcome may thus represent a promising strategy for early prevention.

Poor reading children show diminished print sensitivity and enhanced compensational activation in right hemispheric brain areas* [13, 20]*: In our longitudinal study, we not only concentrated on normal reading development but also included a group of children with poor reading abilities. As mentioned above, our studies showed that learning to read is accompanied by a specialization of specific brain regions for processing print. Interestingly, the ERP measure was sensitive to index poor readers, as second-grade children with developmental dyslexia showed a clearly reduced N1 after reading acquisition as compared to their normal reading peers [13, 15]. Importantly, grapheme-phoneme training in kindergarten seems to normalize the attenuated print sensitivity in poor-reading children, as shown by our longitudinal training study [13]. Whether or not such training may also diminish emerging reading problems at school has to be clarified in future studies. Due to the importance of phonological processes [16-18] in learning to read and the broad consensus about the phonological processing deficit [19] in children with developmental dyslexia, we also examined differences in poor and normal reading second graders in a covert reading task. *Our data* revealed that poor reading was associated with altered, more bilateral activity and *suggest that poor readers spent more resources for phonological processing and retrieval of lexical information*. The tendency to recruit right lateralized brain regions furthermore *indicates altered strategies and compensatory processing* in poor readers [20].

Neuroimaging measures improve the prediction of poor reading outcome at preschool age* [13, 21]*: Given the strong developmental effects of print sensitivity in the N1 and its relation to fluent reading, we also examined whether the initial print sensitivity and the corresponding left vOT activation after grapheme-phoneme training in kindergarten would predict the reading outcome of children in second grade. The combination of behavioural, fMRI, and ERP measures yielded a remarkable prediction: 84% of the variance in second-grade reading speed could be explained by measures of rapid automatized picture naming, print-sensitive activation in the vOT, and the amplitude of the print-sensitive N1 ERP [21]. Even though the prediction and classification results with the small sample available have to be interpreted with care, our results *impressively demonstrate the potential of combining multimodal neuroimaging and behavioural measures to improve prediction of reading outcome at preschool age*. We examined whether reading outcome at school age could also be predicted by the use of specific precursors of N1 print sensitivity measured before any form of reading-related training in kindergarten. An atypically right-lateralized negativity in the N1 time range was detected, which was more pronounced with words than with symbol strings and which differentiated between children with normal and children with poor reading outcome. Our data demonstrated that this atypical right-lateralized print sensitivity accounted for 22% of the variance in word-reading speed [13]. The prediction was improved (40%) when combined with behavioural measures. *Together, our prediction results strongly encourage the further investigation of neuroimaging markers to complement and improve behavioural prediction for developmental dyslexia.*

In conclusion, my presented work critically advanced the insights into the *neuronal underpinnings of learning to read in children with normal and poor reading skills* and especially the *development of print processing from kindergarten to school age* and the potential of *neuroimaging markers for early prediction of reading outcome*.

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