Dissertation précis

Introduction

Dyslexia is probably the most prevalent and most studied learning disability. Research of dyslexia is targeted at a high-level aptitude – reading, while reading ability relies on simple perceptual skills that make this apparent high-level task automatic and implicit. Such a complex relationship between high-level cognition and basic perception calls for an integrative research which combines computational methods with rigorous psychophysics and neuroimaging tools. The traditional and most influential account for dyslexia is the Phonological Deficit Theory (Snowling, 2000). It proposes that dyslexics' deficit in reading stems from impaired sound representation of phonemes or from poor access to these representations. Both are necessary when decomposing oral language to the sounds encoded by the letter symbols and vice versa. However, many observations indicate that this account fails to explain many of dyslexics' common difficulties (e.g. auditory temporal difficulties; McAnally and Stein, 1996; Witton et al., 1998; Ahissar et al., 2000) as well as predicting some non-existing deficits (e.g. speech perception; Ramus and Ahissar, 2012).

In a series of studies conducted in our lab it has been found that dyslexics' main deficit is related to their difficulty in benefitting from stimuli that repeat across trials (Ben-Yehudah and Ahissar, 2004; Oganian and Ahissar, 2012). Based on these studies the Anchoring Deficit Theory was proposed. It aims to account for dyslexics' perceptual and verbal memory and reading deficits as stemming from a common failure in retaining and benefitting from repeated stimuli ("Anchor"; Ahissar et al., 2006; Ahissar, 2007). My PhD work extends the Anchoring Deficit Theory to a well-defined computational deficit in implicit inference of basic stimuli statistics, and aims to assess its neuronal basis.

Reading deficit is obviously uniquely human. Previous attempts to decipher the neural basis of dyslexia were thus based on human measurements. These ranged from trying to identify areas that show abnormal activity in dyslexia (e.g. MT for moving stimuli; Eden et al., 1996; but see Olulade et al., 2013) to searching for abnormal connectivity between frontal and temporal regions in the left hemisphere, associated with both oral and written language (Arcuate Facsiculus; Klingberg et al., 2000; Boets et al., 2013; Ramus, 2014). Other studies used ERP and MEG methods and characterized other aspects of abnormal brain responses, appearing as early as the brain stem responses (Hornickel and Kraus, 2013), and also in the auditory cortex, in the form of abnormally small mismatch negativity responses to frequency deviation (Baldeweg et al., 1999; though subsequent results were mixed, see Bishop, 2007). However, the role of the auditory cortex in the ethology of dyslexia remains open. A recent developmental longitudinal study suggested that the thickness of the auditory cortex is abnormal in children from families at risk of dyslexia (Clark et al., 2014), but its sample was small, and again its results are inconsistent with those of other developmental longitudinal studies (Kraft et al., 2015). In my PhD work, I found that neural activity in the auditory cortex has abnormal characteristics in dyslexia. In contrast to controls', it did not show sensitivity to experiment's basic statistics (mean frequency in my studies). I attribute this cortical abnormality to its shorter dynamics of adaptation. This work combines computational tools with neuroimaging methods into a coherent theoretical framework for the perceptual deficits in dyslexia.

My PhD thesis was composed of three studies:

The first study (Jaffe-Dax et al., 2015) extended the anchoring hypothesis to a well-defined computational deficits, and assessed its immediate predictions in a simple discrimination task. I used a model that was previously developed for the general population (Raviv et al., 2012) and studied it for the case of dyslexia, computationally, behaviorally and with EEG. This was a pioneer attempt to characterize the essence of dyslexia, both computationally and in terms of its neuronal basis. Computationally, we modelled perception process in simple discrimination task as an online heuristic approximation of Bayesian inference – a model which was developed in our lab. Using this model, we found that dyslexics sub-optimally use prior knowledge to compensate for their noisy observation. This weaker incorporation of information leaves them with poorer performance in specific cases which would have been improved by prior knowledge and intact performance in other cases. Neurally, we characterized P2 as an obligatory ERP component, which follows auditory stimuli at 200 ms, and its sensitivity to underlying distribution of stimuli. Specifically, P2 is enhanced with proximity to the central tendency of the distribution. We found that this enhancement was weaker among dyslexics.

The second study (Jaffe-Dax et al., 2017) described the dynamics of dyslexics' behavioral and neuronal adaptation in three different experiments. Altogether, these experiments converged to shorter dynamics of context effects in dyslexia, associated with shorter neural adaptation, at the range of ~5-9 sec among dyslexics versus > 15 sec among controls. I proposed that the faster decay of adaptation underlies dyslexics' impaired usage of sound statistics. This study deepened our quest into the mechanism of dyslexics' impairments, both behaviorally and in terms of their neural basis. We related these impairments to the dynamics of adaptation. As the intervals between consecutive stimuli increase we expect a stronger neural response; i.e. decay of adaptation to previous stimuli. We found that this adaptation decay occurs faster among dyslexics and that its dynamics mirrors the retention of memory of previous stimuli. Taken together with the first study, these findings suggest that faster recovery from neural adaptation is the basis of dyslexics' perceptual difficulties. Following this study (Beyond the scope of my PhD), we have conducted an imaging study using fMRI, to localize the cortical regions that undergo fast recovery from adaptation among dyslexics. The imaging results suggest that throughout the cortex, dyslexic have shorter adaptation than good readers (Jaffe-Dax, et al., submitted). These findings support the hypothesis of cross-modal, multi-domain shorter adaptation in dyslexia.

The third study (Jaffe-Dax et al., 2016) asked whether a similar deficit is also observed in the visual modality. Using similar statistics of stimuli and a similar analysis of visual serial spatial frequency discrimination, we found the same group difference, suggesting that dyslexics' deficit in benefitting from basic stimuli statistics is domain-general. This study excluded the possibility of modality-specific impairment. In a visual discrimination task, we found similar behavioral pattern of sub-optimal usage of prior information among dyslexics. This finding extends our basic auditory-based mechanism to a broader cortical property of dyslexia which is cross-modal and multi-domain.

Chapter 1 – Impaired Bayesian inference accounts for dyslexics' perceptual difficulties

We used computational methods to analyze dyslexics' performance in simple two-tone frequency discrimination task and found that their impoverished performance in this task can be accounted by

impaired Bayesian inference. Namely, dyslexics underweight prior knowledge to compensate for their noisy observation. In the two-tone frequency discrimination task, subjects are sequentially presented with two pure tones and are asked to indicate which tone had a higher pitch. Raviv et al. (2012) have formulized the incorporation of prior with current observation in this task using a heuristic model of implicit memory: in each trial, subjects compare the second tone with a mental representation of the first tone. This mental representation is incorporated with a prior to compensate for the memory decay that occurred during the inter-tone time interval. Using this model, individual performance in this task can be quantified by the level of internal noise (which captures overall performance) and the weight that is assigned to the prior to compensate for this noise (Bayesian inference weight). For each noise level, we calculated the optimal weight of prior, that is required to achieve the best performance. We found that adequate readers' prior weighting is close to optimal. By contrast, dyslexics' weighting of prior was lower that optimal.

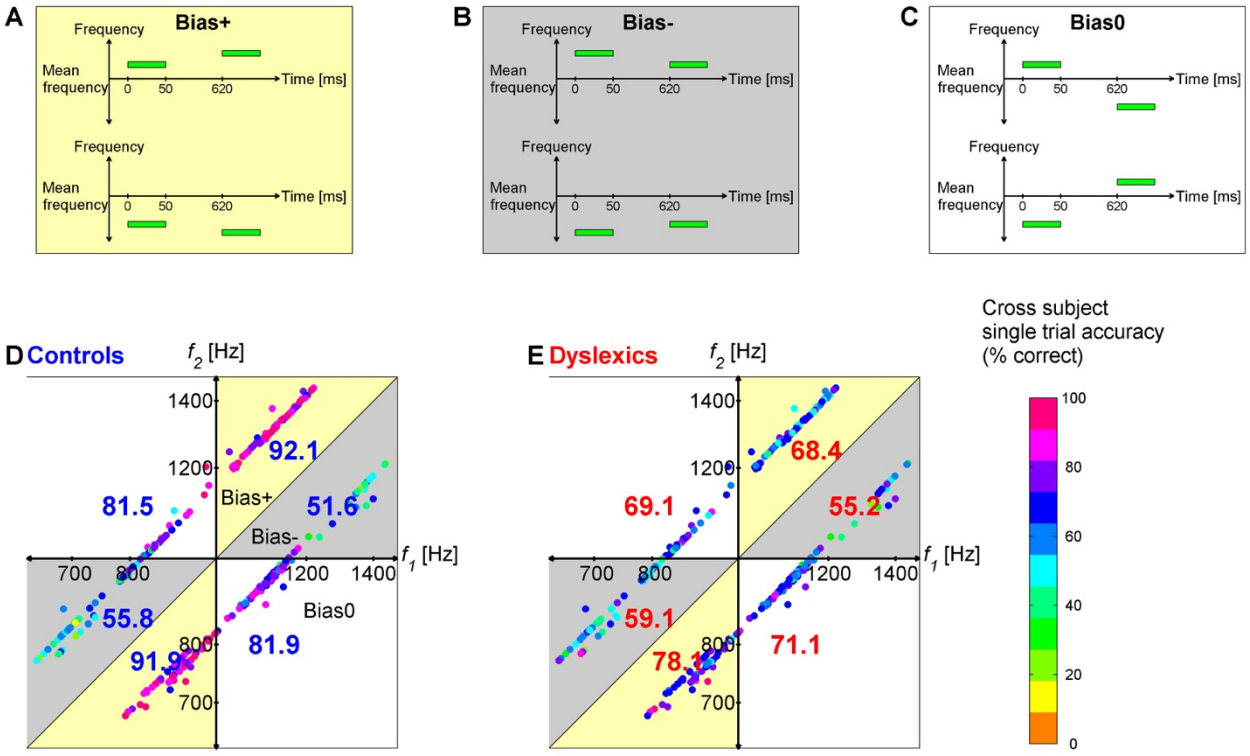

Figure 1. Performance of controls and dyslexics differentially depend on trial type. ***A-C.*** Schematic examples of the three types of trials. (A) in *Bias+* trials the first tone is closer to the mean. (B) in *Bias-* trials the first tone is farther from the mean. (C) in *Bias0* trials the two tones flank the mean. ***D-E.*** Mean performance (% correct) of controls (***D***; n = 14) and dyslexics (***E***; n = 14) in the six sub-regions of trial types, plotted on the frequency plane of the second tone f_2 as a function of the first tone f_1. *Bias+* zones (denoted in yellow) are above the diagonal when both tones are above the mean frequency (second tone is higher) and below the diagonal when both tones are below the mean frequency (second tone is lower). *Bias-* regions (denoted in gray) are complementary with respect to the diagonal, and *Bias0* trials (denoted in white) are those trials associated with the two remaining quarters. Each dot denotes f_1 and f_2 of a trial (tested across individuals). The color of each dot denotes the cross-subject average performance for that pair of stimuli. Numbers denote the average percent correct in each region.

Weighting of prior can be illustrated by dividing the trials in this task into three types according to the impact of prior on performance. Incorporating the prior into perception contracts the representation of the first tone closer to the mean of all previously perceived tones (prior). In *Bias+* trials (Fig. 1A), this

contraction increases the perceived difference between the two tones and improves performance. In *Bias-* trials (Fig. 1B), contraction of the first tone's representation towards the mean decreases the perceived difference between the two tones in the current trial and hampers performance. In *Bias0* trials (Fig. 1C) the contraction has an ambiguous impact on performance. The individual performance difference between *Bias+* trials and *Bias-* trials can represent the weighting of the prior. Among good readers, this difference in performance was about 40% in accuracy rate (Fig. 1D). By contrast, among dyslexics, this difference was less than 20% in accuracy rate (Fig. 1E).

While measuring EEG from subjects performing this task, we found that among good readers, the automatic response of their auditory cortex was different between these two trial types. However, this difference was not observed among dyslexics. The underlying mechanism that gave rise to this bio-marker of dyslexia was the focus of the next chapter.

Chapter 2 – Shorter adaptation in dyslexics' cortical activity

Neural adaptation – the attenuation of neural response to repeated similar events – is the simplest evidence for memory, i.e., the retention of representation in a neural tissue. The time-scale of adaptation and the time-scale of implicit memory have been found to be correlated across individuals (Lu et al., 1992), suggesting that adaptation carries implicit memory. Based on this observation and on the findings of chapter 1, we hypothesized that both adaptation to tones' related response and implicit memory for tones' frequency should be shorter among dyslexics compared to good readers.

In order to test this hypothesis, we manipulated the temporal intervals between the trials of the two-tone frequency discrimination task and measured the event-related response to the onset of the trials (using EEG) and the behavioral evidence for implicit memory for the tones' prior (using contraction bias). As the temporal interval between the trials increased, we found that the event-related response was augmented (Fig. 2A), i.e., adaptation decreased. In parallel, the impact of the prior on performance also decreased, i.e., contraction bias towards the mean of previous tones was weaker in larger inter-trial intervals. In other words, both the memory for previous tones and the neural evidence for this memory (adaptation) decayed as we increased the inter-trial temporal intervals.

Among dyslexics however, this decay was faster. Both behavioral and neural evidence for their memory of previous tones short-lived compared to good readers'. Their decrease in contraction bias as a function of inter-trial interval was faster than that of good readers. In parallel, their neural adaptation also decreased faster. We quantified the behavioral impact of previous tones by contrasting performance in *Bias+* trials and *Bias-* trials in each inter-trial interval (ITI) condition. We fitted this performance difference ($\Delta d'$) to an exponential decay as a function of ITI and found that dyslexics' decay time was shorter than good readers' (Fig. 2B dotted line and Fig. 2C). We quantified neural adaptation as the difference between P2 amplitude and the asymptote level of the decay function and found that here too, dyslexics' decay was faster than that of good readers (Fig. 2B solid line and Fig. 2C).

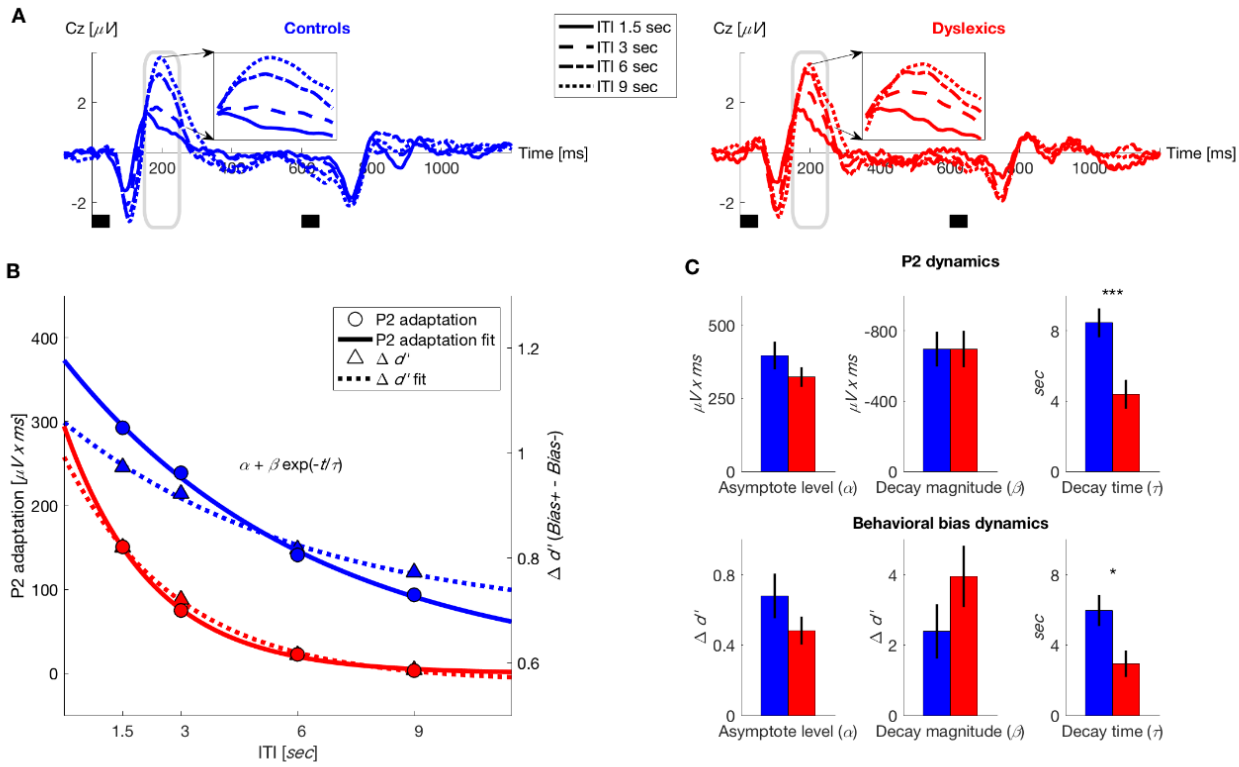

Figure 2. Dyslexics' decay of both neural adaptation and behavioral contraction bias was faster than controls'. ***A.*** Grand average ERPs, plotted separately for blocks with different ITIs, for controls (n = 23; blue, left) and dyslexics (n = 25; red, right). Timing of the 2 tones in each trial is denoted by the short black bars under the plots. ***Middle insets***: P2 range (denoted in gray) enlarged. Dyslexics' P2 area was similar for 6 and 9 second ITIs, whereas controls' P2 was larger for the 9 second interval. ***B***. The decrease in P2 adaptation (solid lines, circles, left scale; estimated magnitude at asymptote minus fitted curve) and the decrease in contraction bias (dashed lines, triangles, right scale; reflecting implicit memory decay) as a function of ITI. Symbols denote groups' means, and plotted curves were fitted to these means. ***C.*** Groups' means and SEMs of the individually fitted parameters (to an exponential decay) of both P2 adaptation (***top***) and behavioral contraction bias (***bottom***). In both, dyslexics differed from controls only in the estimated rate of decay (P2: $p < 0.0005$; $\Delta d'$: $p < 0.05$).

To assess the relevance of our findings to reading, we conducted a fast-reading experiment which was designed to measure the impact of memory on reading speed. Subjects were asked to read as fast and as accurate as possible. Each word appeared twice in the course of the experiment (Fig. 3A). Obviously, by the second presentation, the word was read faster (Reading benefit). Importantly, this benefit decreased as the temporal interval between the two presentations increased, with more intervening words between the two presentations of the same word. The minimal inter-stimulus interval (ISI) between two presentations of the same word was one second (one intervening word), at that interval, dyslexics and good readers had the same benefit (Fig. 3B left). However, good readers' benefit lasted longer than dyslexics'. At intervals greater than two seconds (more than one intervening word), dyslexics' benefit was smaller than good readers' (Fig. 3B right).

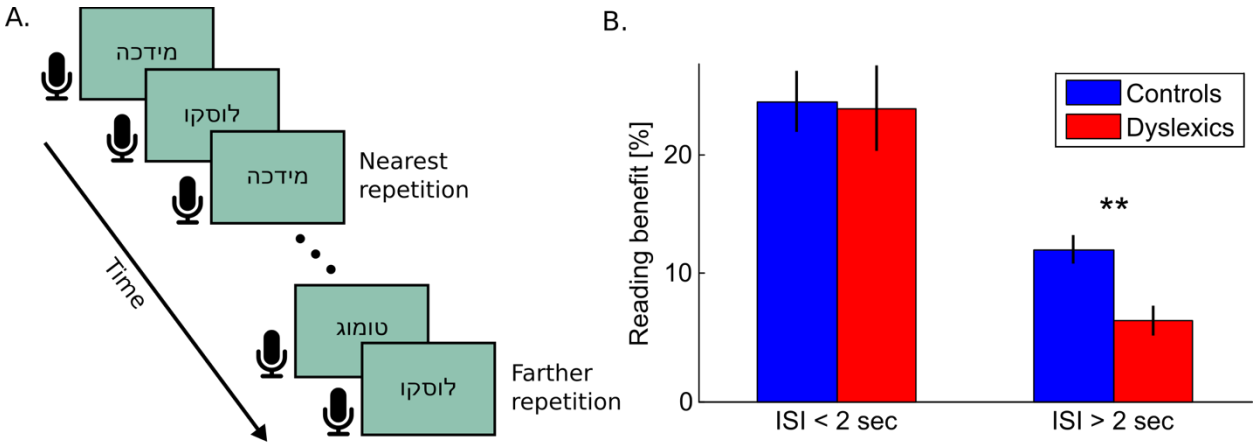

Figure 3. Dyslexics' benefit from a previous exposure to the same non-word decayed faster than controls'. ***A.*** Schematic illustration of the reading task. Subjects were asked to read the non-words aloud as quickly as possible. Presentation switched to the next word with the subject's voice offset. The closest repetition of the same non-word was with one intervening non-word (i.e. an ITI of < 2 sec). ***B.*** Benefit in RTs (response times from visual word presentation to vocal onset) as a function of the time interval between the first and second presentation of the same non-word. Improvement was calculated as the difference in RT between the first and second presentation of the same non-word in the block. At very short intervals (< 2 sec) the benefit was similar for both groups. However, this benefit decayed faster (at interval > 2 sec) among dyslexics (red) than among controls (blue; $p < 0.005$). Error bars denote standard error (SEM).

Although beyond the scope of my dissertation, it is worth mentioning a complementary fMRI study that we conducted, to try and locate the cortical region which exhibits faster decay of adaptation in dyslexics. We asked participants to perform the two-tone frequency discrimination task under varying inter-trial interval conditions and quantified their adaptation decay time using similar methods as described above. We found that throughout the responsive cortex, dyslexics' adaptation was shorter than good readers'. This difference was not restricted to auditory-specific regions and stretched across to multi-modal associative regions, suggesting that shorter adaptation in dyslexia is a general cortical tissue property and not modality-specific. The third chapter of my dissertation assessed behaviorally, whether weaker contraction bias in dyslexia is exhibited only with auditory stimuli, or whether it can be measured with other stimuli, implying for a cross-modal deficit.

Chapter 3 – Evidence for domain-general implicit memory deficit in dyslexia

In order to assess whether dyslexics' impaired Bayesian inference is restricted to audition, or whether it extends to a more general cross-modal deficit, we conducted a visual version of the two-tone frequency discrimination task and measured contraction bias. In the visual experiment, subjects were requested to indicate which of the two sequentially presented gratings had a higher spatial frequency (Fig. 4A). As in the auditory experiment, trials could be divided according to the impact of previous trials (prior) on performance. *Bias+* trials were those in which contraction of the first grating towards the mean of previous trials increased the perceived difference between the two gratings and improved performance. *Bias-* trials were those in which contraction bias towards the mean decreased the perceived difference and hampered performance (Fig. 4B). Individual contraction bias can be quantified as the difference in performance between these two types of trials. Dyslexics' difference in performance between these two trial types was

found smaller than good readers' (Fig. 4C), suggesting that their poor usage of prior to compensate for noisy observation is apparent in vision and not restricted to audition. Namely, dyslexics' Bayesian inference impairment is domain-general and not modality-specific.

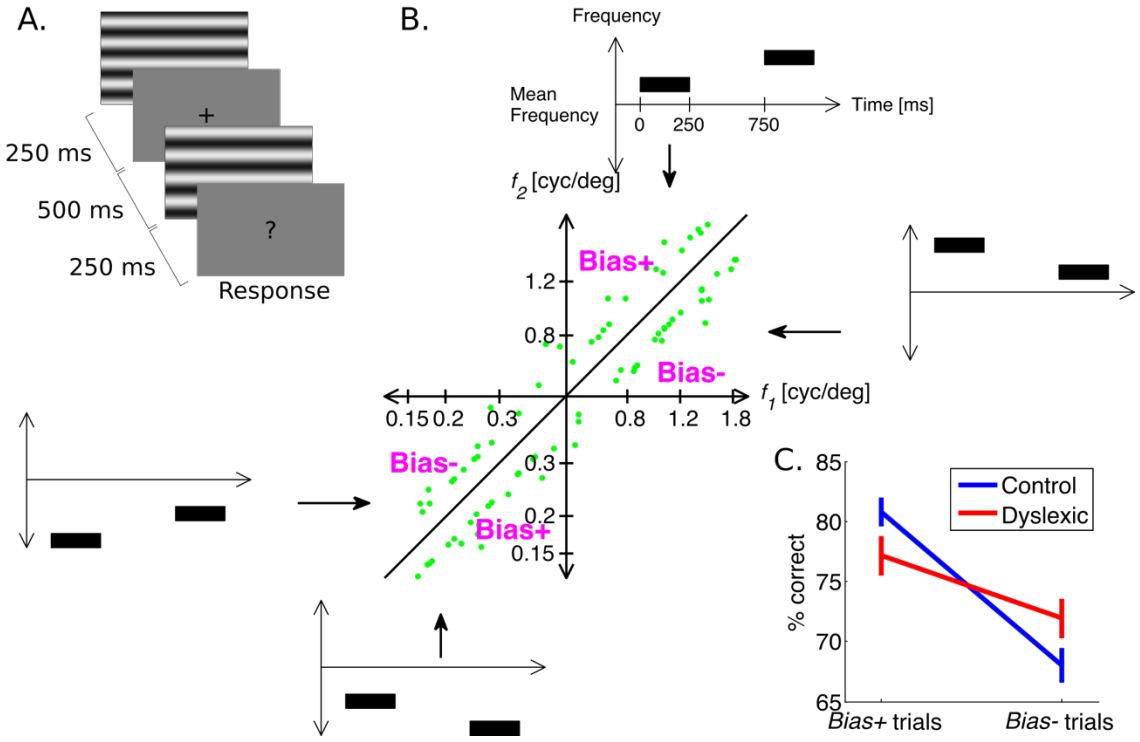

Figure 4. Visual two-gratings frequency discrimination study. ***A.*** The temporal structure of a single trial. The first grating was presented for 250ms, followed by an ISI of 500ms. The second grating was presented for 250ms. The observer was requested to indicate which of the two gratings had the higher spatial frequency (density). ***B.*** The contraction-bias division to trial types. The middle plot illustrates the distribution of single trials in the frequency plane (the frequencies of the first and second grating in each trial, respectively) for a typical subject. Each green dot denotes the pair of stimuli in a single trial. This plane illustrates the ranges of the different trial types. In *Bias+* trials the frequency of the first grating stimulus was closer to the mean frequency; thus, contraction of its representation towards the mean increased the perceived difference between the two gratings and consequently improved performance. In *Bias-* trials the first grating was farther from the mean; thus, contraction of its representation towards the mean frequency decreased the perceived difference between the gratings and hampered performance. **C.** Dyslexics' contraction bias is smaller than controls'. Contraction bias averaged across participants. Ordinate shows the percentage of correct responses for the two sub-divisions of trials (abscissa): *Bias+* trials (left), where the grating in the first interval is closer to the mean frequency of all previous trials, and *Bias-* trials (right), where it is reversed. Controls (n = 40) are denoted in blue, and dyslexics (n = 33) in red. Both populations performed better on *Bias+* than on *Bias-* trials. However, the difference, i.e., the contraction bias, was larger among the controls. Error bars denote SEM.

Discussion

The findings presented in this dissertation suggest that dyslexia can be grounded from the high-level description of its symptoms and implications to fundamental mechanistic principles of Bayesian inference in perception and adaptation time-scale. We capitalized on previously established findings of dyslexics' specific perceptual difficulties (Anchoring Deficit; Ahissar et al., 2006) and formulized their deficit using

concrete computational methods (chapter 1; Jaffe-Dax et al., 2015). We then found that adaptation time-scale - a basic neural property - underlay this computational deficit (chapter 2; Jaffe-Dax et al., 2017). Finally, we showed that dyslexics' perceptual difficulties are not modality-specific, but domain-general and reside in the computational level of perception (Jaffe-Dax et al., 2016; Jaffe-Dax et al., submitted).

Noteworthy, since the publication of these chapters, the deficient adaptation account for dyslexia has received support from another imaging study (Perrachione et al., 2016). In contrast to my suggestion for temporal adaptation deficit, Perrachione et al. showed that dyslexics exhibit poorer stimulus-specific adaptation, as revealed by fMRI repetition suppression. In other words, while this dissertation put forward the claim for dyslexics' shorter adaptation in the time domain, their work offered dyslexics' limited adaptation in feature space. Further work is necessary to determine whether dyslexics' adaptation is limited in time, in feature or both.

This dissertation pin-pointed the locus of dyslexics' difficulties at the computational level (Marr, 1982; Shagrir, 2010). This computational level allows broader explanation of the wide spectrum of difficulties that are associated with dyslexia than attributing dyslexia to deficits at the sensory level (e.g., Neural Noise Hypothesis; Sperling et al., 2005; Hancock et al., 2017). On the other hand, the computational level brings us closer to the source of this learning deficit than remaining at the phenomenological description level (e.g., Phonological Deficit Theory; Snowling, 2000).

Grounding dyslexia from its high-level description to its basic fundaments will allow early diagnosis of this prevalent learning disability, even before reading age. Such an early diagnosis might enable early interventions which would stop the "snowball of frustration" in learning to read when it is still small.

References

Ahissar M (2007) Dyslexia and the anchoring-deficit hypothesis. Trends Cogn Sci 11:458–465.

Ahissar M, Lubin Y, Putter-Katz H, Banai K (2006) Dyslexia and the failure to form a perceptual anchor. Nat Neurosci 9:1558–1564.

Ahissar M, Protopapas A, Reid M, Merzenich MM (2000) Auditory processing parallels reading abilities in adults. Proc Natl Acad Sci U S A 97:6832–6837.

Baldeweg T, Richardson A, Watkins S, Foale C, Gruzelier J (1999) Impaired auditory frequency discrimination in dyslexia detected with mismatch evoked potentials. Ann Neurol 45:495–503.

Ben-Yehudah G, Ahissar M (2004) Sequential spatial frequency discrimination is consistently impaired among adult dyslexics. Vision Res 44:1047–1063.

Bishop DVM (2007) Using mismatch negativity to study central auditory processing in developmental language and literacy impairments: where are we, and where should we be going? Psychol Bull 133:651–672.

Boets B, Op de Beeck HP, Vandermosten M, Scott SK, Gillebert CR, Mantini D, Bulthé J, Sunaert S, Wouters J, Ghesquière P (2013) Intact but less accessible phonetic representations in adults with dyslexia. Science 342:1251–1254.

Clark KA, Helland T, Specht K, Narr KL, Manis FR, Toga a W, Hugdahl K (2014) Neuroanatomical precursors of dyslexia identified from pre-reading through to age 11. Brain 137:3136–3141.

Eden GF, VanMeter JW, Rumsey JM, Zeffiro T a (1996) The visual deficit theory of developmental dyslexia. Neuroimage 4:S108–S117.

Hancock R, Pugh KR, Hoeft F (2017) Neural Noise Hypothesis of Developmental Dyslexia. Trends Cogn Sci 21:434–448.

Hornickel J, Kraus N (2013) Unstable Representation of Sound: A Biological Marker of Dyslexia. J Neurosci 33:3500–3504.

Jaffe-Dax S, Frenkel O, Ahissar M (2017) Dyslexics' faster decay of implicit memory for sounds and words is manifested in their shorter neural adaptation. Elife 6:e20557.

Jaffe-Dax S, Lieder I, Biron T, Ahissar M (2016) Dyslexics' usage of visual prior is impaired. J Vis 16:1–9.

Jaffe-Dax S, Raviv O, Jacoby N, Loewenstein Y, Ahissar M (2015) A Computational Model of Implicit Memory Captures Dyslexics' Perceptual Deficits. J Neurosci 35:12116–12126.

Klingberg T, Hedehus M, Temple E, Salz T, Gabrieli JD, Moseley ME, Poldrack R a (2000) Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging. Neuron 25:493–500.

Kraft I, Cafiero R, Schaadt G, Brauer J, Neef NE, Müller B, Kirsten H, Wilcke A, Boltze J, Friederici AD, Skeide MA (2015) Cortical differences in preliterate children at familiar risk of dyslexia are similar to those observed in dyslexic readers. Brain 138:e378.

Lu Z-L, Williamson J, Kaufman L (1992) Behavioral Lifetime of Human Auditory Sensory Memory Predicted by Physiological Measures. Science 258:1668–1670.

Marr D (1982) Vision: A computational investigation into the human representation and processing of visual information.

McAnally KI, Stein JF (1996) Auditory Temporal Coding in Dyslexia. Proc R Soc B Biol Sci 263:961–965.

Oganian Y, Ahissar M (2012) Poor anchoring limits dyslexics' perceptual, memory, and reading skills. Neuropsychologia 50:1895–1905.

Olulade O, Napoliello E, Eden G (2013) Abnormal Visual Motion Processing Is Not a Cause of Dyslexia. Neuron 79:180–190.

Perrachione TK, Del Tufo SN, Winter R, Murtagh J, Cyr A, Chang P, Halverson K, Ghosh SS, Christodoulou JA, Gabrieli JDE (2016) Dysfunction of Rapid Neural Adaptation in Dyslexia. Neuron 92:1383–1397.

Ramus F (2014) Neuroimaging sheds new light on the phonological deficit in dyslexia. Trends Cogn Sci 18:274–275.

Ramus F, Ahissar M (2012) Developmental dyslexia: The difficulties of interpreting poor performance, and the importance of normal performance. Cogn Neuropsychol 29:37–41.

Raviv O, Ahissar M, Loewenstein Y (2012) How recent history affects perception: the normative approach and its heuristic approximation. PLoS Comput Biol 8:e1002731.

Shagrir O (2010) Marr on Computational-Level Theories. Philos Sci 77:477–500.

Snowling MJ (2000) Dyslexia. Wiley-Blackwell.

Sperling AJ, Lu Z-L, Manis FR, Seidenberg MS (2005) Deficits in perceptual noise exclusion in developmental dyslexia. Nat Neurosci 8:862–863.

Witton C, Talcott JB, Hansen PC, Richardson a J, Griffiths TD, Rees a, Stein JF, Green GG (1998) Sensitivity to dynamic auditory and visual stimuli predicts nonword reading ability in both dyslexic and normal readers. Curr Biol 8:791–797.