Auditory Prediction and Implicit Learning in Dyslexia

by

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ABSTRACT

More than a century of research has investigated the etiology of dyslexia, coalescing around 'phonological awareness' – the ability to recognize and manipulate phonemes – as a trait typically deficient in reading disorders. Meanwhile, the last few decades of research in neuroscience have highlighted the brain as a predictive organ, which subliminally calibrates sensory expectations according to experience. Do the brains of adults with dyslexia respond differently than those of matched controls to expected tones and unexpected omissions? While auditory oddball paradigms have previously been used to study dyslexia, these studies often interpret group differences to indicate deficit auditory discrimination rather than deficit auditory prediction. The current study takes a step toward fusing theories of predictive coding and dyslexia, finding that event-related potentials related to auditory prediction are attenuated in adults with dyslexia compared with typical controls. It further suggests that understanding dyslexia, and perhaps other psychiatric disorders, in terms of contributory neural systems will elucidate shared and distinct etiologies.

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CHAPTER 1

BACKGROUND

History of the Dyslexia Phenotype

"A well-grown lad, aged 14—is the eldest son of intelligent parents, the second child of a family of seven. He has always been a bright and intelligent boy, quick at games, and in no way inferior to others of his age.

His great difficulty has been –and is now –his inability to learn to read. This inability is so remarkable, and so pronounced, that I have no doubt it is due to some congenital defect."– "A Case of Congenital Word Blindness" -- W. Pringle Morgan, 1896

Developmental dyslexia describes those with otherwise normal intelligence who struggle uniquely with decoding letters and words; population prevalence estimates range from 5 to 9% (Francks et al., 2002; Pennington & Bishop, 2009; Peterson et al., 2007), though diagnosis is more common in boys than girls (Shaywitz et al., 1990; Romeo, 2022). However, while the DSM V defines dyslexia as a specific learning disorder (SLD) characterized by "a pattern of learning difficulties characterized by problems with accurate or fluent word recognition, poor decoding, and poor spelling abilities" (DSM V), individuals with dyslexia display a wider array of phenotypic differences than implied by the APA's definition. Broadening the DSM-V, the International Dyslexia Association notes "phonological weaknesses or disorders... are usually the underlying cause of the literacy problems associated with dyslexia" (Lowell et al., 2014). "Insufficient phonological processing" has long been associated with reading disorders (Lyon et al., 2003; for review see Lyon, 1994), but the neurobiological mechanisms responsible for phonological deficits are poorly defined.

Phonological Awareness and Statistical Learning

Phonological awareness – the ability to recognize and manipulate phonemes -- is a necessary capacity of learning to read in alphabetic languages; a budding reader's first step is to crack the letter-sound mappings of their language. Once a foothold is found, phonological awareness predicts reading ability, which in turn predicts phonological awareness (Hogan, Catts, & Little, 2005): the process of typical language development involves continuous updating of acceptable morphemic and syntactical structures. While intuition implies that phonological awareness would increasingly support reading in alphabetic languages with consistent letter-sound mappings, this capacity is uniquely important in orthographically deep languages like English (Ziegler et al., 2010).

This apparent paradox is resolved if phonological awareness is viewed in tandem with auditory statistical learning capacities. Statistical learning describes the automatic and unconscious updating of expectations (transitional probabilities) from one cognitive moment to the next (Frost et al., 2014), as well as the flexible adjustment of these perceptual expectations upon integration of conflicting information. Statistical learning has been shown to be relatively invariant over the developmental period (Amso & Davidow, 2012), pointing toward its involvement in impaired learning over an individual's lifetime.

The Endophenotype Concept

In 2003, Gottesman and Gould summarized endophenotypes as "measurable components unseen by the unaided eye along the pathway between disease and distal genotype", and while "they would ideally have monogenic roots…it is likely that many have polygenic bases". Endophenotypes are found in psychiatrically affected individuals and their unaffected relatives, implying that the measures reflect contributory, heritable risk factors for emergence of clinically relevant phenotypes.

Given the substantial overlap of dyslexia diagnoses with attention-deficit hyperactivity disorder (ADHD: 12-25%; Shaywitz, 2005), dyspraxia (up to 85%; Pauc, 2005), oppositional defiance disorder (17%; Pauc, 2005), anxiety (up to 29%; Rosen, 2017), and giftedness (2-5%; Gilger, 2017), it becomes apparent that the constellation of cognitive differences that characterizes reading difficulties is relevant for understanding cognitive diversity in the general population, not just for dyslexia.

Research into these neurodevelopmental disorders has enormously benefitted from big data and longitudinal approaches, which permit the assessment of biological perturbations alongside environmental confounds. These approaches reach back in developmental time (biomarkers and early behavior) to capture isolated deficits prior to their emergence as clinical phenotypes. Importantly, genome-wide association studies (GWAS) of these psychiatric conditions unveil the extreme genetic heterogeneity of these disorders (ADHD: Demontis et al., 2023, ASD: Morimoto et al., 2021, schizophrenia: Schwab & Wildenauer, 2013, and dyslexia: Gialluisi et al., 2021). This implies that the investigation of endophenotypes may lead to a clearer understanding of the genetic and neural networks that underlie clinically relevant phenotypes. It should be noted that a

2007 meta-analysis of endophenotypes showed that statistical genetics methods predicting clinically relevant phenotypes were just as successful as those predicting endophenotypes (Flint & Munafò, 2007), which does not support the idea that an increased pursuit in endophenotypes will elucidate genetic causes.

Despite these findings, researchers studying ADHD, ASD, schizophrenia, and dyslexia, among other disorders, have shifted to studying clusters of these behavioral, cognitive, and biological endophenotypes in hopes of capturing their developmental trajectories and interactions (Johnson et al., 2021), and while the panoply of potential predictors for developmental disorders is daunting, a survey of results is enlightening: early emotional and cognitive skills predict socioemotional functioning , academic achievement, and mental health (Calkins & Marcovitch, 2010), neonatal sleep predicts later emergence of attention disorders (Geva et al., 2016), and neuromodulator (dopamine, acetylcholine) dysregulation predicts emergence of attention-deficit hyperactivity-disorder (ADHD) and autism spectrum disorder (ASD) (Hellmer & Nyström, 2017).

The rationale for investigating endophenotypes related to dyslexia is increasingly apparent given recent evidence implicating the disruption of perinatal brain development in language disorders (Eising et al., 2019). While the clinically relevant phenotype of dyslexia is defined by reading disability, decades of research have coalesced around a phonological awareness hypothesis to explain differences in reading ability persisting through adulthood (Bruck, 1992; Wimmer & Schurz, 2010; for argument, see Share, 2021). This attribute is endophenotypic, predicting reading ability in undiagnosed individuals as well as those with formal diagnoses (Moll et al., 2010).

While the characterization of phonological awareness as an endophenotype is well-established, it makes little headway in understanding the etiology of dyslexia. However, investigating the neural architecture and neural response patterns partially responsible for phonological capacities can lead to development of treatments and approach understanding of cause.

Measuring Dyslexia with EEG

Much research in this area has focused on characterizing the mismatch negativity (MMN) response to the presentation of deviant auditory stimuli. This research is prompted by phonological awareness being dependent on auditory sensitivity. The "allophonic theory of dyslexia" even posits that the units available in long term memory of dyslexics are allophonic rather than phonemic, leading to disarray during letter-to-sound mapping (for review, see Serniclaes, 2018). While this theory certainly oversteps the available evidence, it does capture the deficit experienced by many individuals with dyslexia in distinguishing tones of close frequency, or syllables of differing voice-onset time.

In dyslexia, MMN has been used with marked success. For example, a diminished mismatch negativity (MMN) was observed in a dyslexic subgroup of 8-11 year old children at a latency of 250ms to syllable and tone changes (Lachmann et al., 2005). Another study found diminished (and abnormally shaped) MMN in a dyslexic group when listening to paired 90Hz tones with a 15Hz oddball at a similar latency (Baldeweg et al., 1999). And another found diminished late (300-700ms) MMN to deviant syllables in 10-to-15-year-old German children (Neuhoff et al., 2012). This lattermost study

involved measurement of unaffected relatives and ventured to deem the late MMN an endophenotype. While these studies are compelling, uniting their results under a common interpretation of dyslexia is difficult. One compelling interpretation is that dyslexia involves an auditory deficit related to the perception of slight auditory deviants, whether they be shifted in frequency or onset time, prompting an investigation into differences in the statistical learning capacity of adults with dyslexia.

Predictive Coding

Expectation and prediction describe the brain's tendency to preactivate subsets of neurons and is partly responsible for subjective feelings of perceptual continuity. In this framework, feedback connections from higher-level areas in perceptual hierarchies (vision, audition, sensation) successively preactivate lower levels in an error-minimizing fashion (Friston, 2010). The biological plausibility of a predictive coding theory has been demonstrated in models of such a hierarchical network, which give rise to "simple-cell-like receptive fields" using natural images (Rao & Ballard, 1999). Meanwhile, auditory neuroscience has named an ERP after the 'error signal' observed upon the presentation of a deviant stimulus: the aforementioned mismatch negativity (MMN) (Näätänen et al., 1978; for recent review see Näätänen et al., 2011). Though the MMN component has been interpreted as the result of an "automatic comparison" in a bottom-up manner (Uwer & Suchololetz, 1998), which makes little sense given its varying latency, the component has otherwise been understood within the context of auditory predictive coding (Winkler & Czigler, 1998, 2012; Garrido et al., 2009). The latter interpretation is further supported by models of trial-by-trial changes in MMN with Bayesian inference (Lieder, 2013),

which postulates that models upcoming sensory stream are continuously generated and updated according to prediction errors (for review of the 'free energy principle' in neuroscience, see Friston, 2010).

Expected Tone "Match" Response

When an expected tone is presented, a typical pattern of components can be observed in the ERP, consisting of the P50, N100, and P200. Gamma band activity has also been found to increase during the early (20-60ms) time window (Bendixen et al., 2011).

The P50 is a positive going waveform with a maximum occurring ~50ms after the onset of an auditory stimulus that has been interpreted as reflecting initial auditory processing. It is attenuated as auditory stimuli are repeated as a result of sensory gating, or automatic filtering of irrelevant information. The P50 sensory gating ratio is even used as an endophenotype in schizophrenia research (Patterson et al., 2008).

The N100 is a negative going waveform with a maximum occurring ~100ms after stimulus onset and is thought to reflect automatic auditory processing, as it does not diminish in contexts of noise. Using paired tones, an N100 sensory gating effect was demonstrated, and adults with dyslexia showed lesser gating ratios than typical controls (Peter et al., 2019).

The P200 is a positive going waveform with a maximum occurring ~200ms after stimulus onset and is thought to reflect attentional processing of auditory stimuli. Attenuation of the P200 as a result of repeated presentation has been used alongside the

P50 and N1 to measure sensory gating, though with mixed results (Lijffijt et al., 2009, Peter et al., 2019).

Early gamma band activity has been observed occurring 40-100ms after stimulus onset in auditory oddball paradigms, with higher gamma for the expected stimulus relative to the deviant (Schadow et al., 2009; Bendixen et al., 2011) and has also been observed when participant expectations purportedly originate from long-term memory (Hermann et al., 2004). When this activity stems from processing auditory-pattern information, it is thought to reflect the activity of the ventral auditory stream, whereas when it stems from auditory-spatial information, it is thought to reflect activity of the dorsal auditory stream tasks (Kaiser & Lutzenberger, 2005). In the present study, gamma band power in the condition with two tones is expected to exceed that of the deviant omission condition during the aforementioned time window, supporting its interpretation as being involved in cognitive matching process rather than deviant detection.

Omitted Stimulus Response

When an expected tone is omitted, a different, though also typical, pattern of components can be observed in the ERP, consisting of a mimic P50, a mimic N1, and a P300.

The mimic P50 is thought to be the result of auditory prediction, as it appears even in the absence of a stimulus (Bendixen et al., 2009, for review see Bendixen et al., 2011). However, this interpretation seems to conflict with its interpretation as reflecting sensory gating.

The mimic N1 has been observed in the context of long-term memory (Janata, 2001) when participants explicitly imagined the continuation of known melodies, though it was not expected in the context of this experiment. This would be an interesting topic of future investigation in adults with dyslexia, given recent interpretations of sensory gating as impairing the "stable word representation", or encoding, storage, or retrieval of lexemes from long-term memory (Peter et al., 2019).

The P300 ERP has been observed in the context of error coding or "context updating" (Donchen & Coles, 1988; Polich 2006; for review, see Linden, 2005) in the visual domain even in the absence of conscious awareness (Bernat, 2001) and in the auditory domain, the P300 is attenuated by repetition (Linden et al., 2004). It has been separated into two biological generators, the first "P3a" component having a frontal generator and reflecting attentional orienting and the second "P3b" component having a temporoparietal generator and reflecting long-term memory updating (Polich, 2007).

Of some relevance to the current study, research with patients with left inferior frontal cortex lesions showed an attenuated (visually 'flattened') P300 to frequency-shifted deviants (80% 600Hz paired tones and 20% second tone was 660Hz; Jakuszeit et al., 2013).

Neurobiological Correlates of Statistical Learning

Statistical learning describes the proclivity of cognitive systems to extract transitional probabilities from sensory streams and is thought to involve primarily domain-specific mechanisms, and what evidence does exist supporting between-modality transfer of subliminally learned sensory regularities has been critiqued (Frost et al.,

2014). An account constrained by human neurobiology and explanatory of the 'lack of transfer' results is provided by domain-specific processing streams whose computations follow the same set of neurobiological rules, following largely from Hebbian and reinforcement learning. Of relevance to the current study are neurobiological correlates of auditory statistical learning, which is required at each level of language learning, from infantile segmentation (Jusczyk et al., 1999) of the auditory stream to the transitional regularities of syntax (Thompson & Newport, 2007).

The following neurobiological correlates are extracted from the review by Frost & colleagues (2014) and, for auditory statistical learning, include the inferior parietal lobule (IPL) and superior temporal gyrus (STG). Meanwhile, for visual statistical learning, they include the cuneus (C) and fusiform gyrus (FFG). Counter to the observation that little modality-transfer is observed with statistical learning, brain areas have been observed in both auditory and visual statistical learning paradigms. These include the caudate (CA), hippocampus (H), thalamus (T), and inferior frontal gyrus (IFG). A more recent review has found similar regions and significantly broadens the task summary (Batterink et al., 2019).

Investigations of auditory deviance detection have yielded similar results. An auditory frequency-discrimination task using simultaneous EEG and fMRI recordings found bilateral learning-related activation of the STG and left IFG (de Souza et al., 2013). Relevant to the current study, gamma band power from these two areas predicted behavioral performance. In another study, an auditory frequency-discrimination task was used with NetStation EEG source-localization tool 'sLORETA' (described in procedure) to localize generators of deviant-related ERPs, finding them in right STG, lingual gyrus

bilaterally, and in the right and left insula (Justen & Herbert, 2018). Intracranial recordings directly from STG of patients with medically refractory epilepsy find a high frequency band (70-150Hz) response to auditory omissions (Fonken et al., 2019: not certified by peer review).

Linking the auditory-specialized STG to the domain-general IFG, another group of researchers utilized the event-related optical signal (imaging light-scattering properties of neurons) to investigate the omission stimulus response, and found that right STG activity preceded right IFG activity during deviant omission processing (Tse et al., 2006), a result that was replicated when participants were focused on watching a movie while the tones were presented (Tse & Penney, 2007), indicating these activations are related to automatic and subliminal evaluation of auditory predictions.

Research using functional near-infrared spectroscopy, an imaging technique utilizing differential light-absorption of oxygenated and deoxygenated hemoglobin, has additionally supported these results, with one study finding that oxygenated hemoglobin increased in the left inferior frontal cortex during a statistical sequence condition but not a random sequence condition (Alba & Okanoya, 2008). And a study of ten non-aphasic patients with left inferior frontal lesions found they were insensitive to the sensory aspects of syntactic analysis, as evidenced by responses and ERPs, in which they demonstrated regular P300s but irregular N2b components (Jakuszeit et al., 2013), the latter of which is attention-dependent, but still interpreted as deviance detection and frequently shows up as a MMN (Näätänen et al., 2014).

To contextualize the role of the IFG in the current study, cognitive neuroscience has found time and time again that the IFG is involved with reading (D'Mello & Gabrieli,

2018). Interestingly, the activity of the IFG is attenuated for older readers, suggesting decreased reliance for more advanced readers, though this result is not apparent in those with dyslexia, who show hyperactivation of the IFC during reading across developmental time (Hoeft et al., 2007).

Taken together, these results suggest statistical auditory learning involves the right superior temporal gyrus and is in part dependent on the left inferior frontal gyrus.

Research Questions & Hypotheses:

1) Do adults with dyslexia demonstrate a lesser attenuation of the auditory ERP to a repeated tone than do typical controls? We hypothesize that the failure to attenuate the neural response to repeated presentation of a stimulus observed in previous studies (Perrachione et al., 2016; Peter et al., 2019) can be observed in conditions of uncertainty, namely, when the expected stimulus occurs only 80% of the time (Hypothesis 1a). Furthermore, while previous research on this topic has studied the longitudinal time course of neural adaptation over 30 seconds in the case of speaker identity (Perrachione et al., 2016), and around 3 minutes in the case of repeated tones (Peter et al., 2019), we hypothesize that typical adults will successively attenuate their response to repeated stimulus, whereas adults with dyslexia will fail to do so to the same extent (Hypothesis 1b).

2) Do adults with dyslexia differ from typical controls in their generation of a pre-attentive 'mimic P50' ERP in response to an omitted, but expected, stimulus? We hypothesize that while typical controls will generate a P50 expectation component to an omitted stimulus, adults with dyslexia will fail to do so to the same extent (Hypothesis 2).

3) Do adults with dyslexia differ from typical controls in their generation of a P300 ERP in response to the presentation of a deviant omission? We hypothesize that adults with dyslexia will display an attenuated P300 to the omitted stimulus relative to typical controls (Hypothesis 3).

4) Do adults with dyslexia learn to discriminate auditory oddballs as quickly as typical controls? We hypothesize that auditory statistical learning, as measured by the reaction time slope of the first 100 trials of an auditory oddball paradigm, will take place to a greater extent in typical controls than in adults with dyslexia (Hypothesis 4a), and that this difference will be related to the number of orthographically irregular 'sight words' that each participant can name (Hypothesis 4b; untested).

5) To what extent can psychophysical endophenotypes be used to predict phonemic decoding efficiency (PDE) and sight word efficiency (SWE) as measured by the TOWRE? We predict that a backwards step-wise regression consisting of all measured endophenotypes as independent variables will significantly predict PDE (Hypothesis 5a) and SWE to a lesser extent, given that sight word reading is phenotypically downstream from phonemic decoding **(**Hypothesis 5b), in both adults with dyslexia and in typical controls.

6) Do adults with dyslexia display differences in the gamma band range (25-55HZ) when processing expected tones? Previous research has documented increased power in the gamma range (30-100Hz) during processing of auditory spatial and pattern information in typical adults, and separately over the frontal region during top-down tasks (Kaiser & Lutzenberger, 2005). We hypothesize that gamma band power will be

increased in the even relative to the odd condition (Hypothesis 6a) and that a group difference is observed with respect to gamma band power (Hypothesis 6b)

7) Do adults with dyslexia activate the left Superior Temporal Gyrus and Inferior Frontal Gyrus to the same degree as controls when processing expected tones & deviant omissions? We predict that more right-lateralized (Hypothesis 7a) or visual learning (Hypothesis 7b) areas will be activated in dyslexics than controls when listening to both expected tones & deviant omissions, and that dyslexics will show a lack of left frontal activation during and subsequent to the presentation of the deviant omission (Hypothesis 7c).

Component	Hypothesis	Prediction
N100 & P200 H1a & H2a	Adults with dyslexia have trouble filtering irrelevant auditory information	Greater attenuation in typical controls over time than adults with dyslexia
P50 & P300 H2 & H3	Adults with dyslexia preactivate auditory cortex to a lesser extent (P50) when expecting auditory stimulus and thus generate an attenuated error signal (P300)	Significantly greater P50 and P300 components in typical adults than in adults with dyslexia
Response Time Slope H4	Typical controls extract regularities from sequences and become more sensitive to find-grained auditory difference over time, whereas adults with dyslexia fail to show the same response	Typical controls will get faster over time at discriminating auditory stimuli whereas adults with dyslexia will not
Regression H5a & H5b	Phenotypes relying on fewer contributory neural systems are more predictable with ERPs than are phenotypes relying on more contributory neural systems	A higher degree of variance in phonemic decoding efficiency will be explained than in sight word efficiency
Gamma Band H6	Adults with dyslexia do not rely on the ventral auditory stream to the extent that typical controls do for extracting temporal pattern information from auditory sequences; high frequency synchrony supports the ability to extract auditory regularities	Higher gamma band power in typical controls in response to second stimulus; gamma band power is disrupted when stimulus fails to appear. This relationship is not observed to the same extent in dyslexia
sLORETA H7	Typical controls rely on information processing by the STG & IFG to extract pattern information from auditory sequences, whereas adults with dyslexia rely less strongly on this circuit	STG & IFG response will be tightly linked with the presentation or omission of the second tone in typical controls, whereas adults with dyslexia will demonstrate a different response pattern

CHAPTER 2

METHODS

Participants

This study was conducted with the approval of the Institutional Review Board at the University of Washington. All participants gave written consent.

Participants were 19 adults with dyslexia and 18 typical controls. Group differences for age and sex were not significant according to previous analyses with the same participants (Peter et al., 2019). All participants included in analysis passed a hearing test at 20dB for .5, 1, 2, and 4kHz, though one typical control failed and was excluded from analysis. Typical controls did not have a history of sensory, cognitive, psychological, or neurological disorders that could confound this study. Controls had no previous diagnosis of dyslexia and scored, at minimum, a standard deviation below the mean on the administered tests of reading and spelling (see "Behavioral Measures" below). Individuals diagnosed with dyslexia were included in this study if their score on at least one of the five administered tests of reading and spelling was lower than a standard deviation below the mean (Berninger et al., 1998). Typical controls obtained scores above one standard below the mean in all five tests.

Behavioral Measures

Participants were administered a series of verbal tests: the Woodcock Reading Mastery Tests-Revised's Word Identification (WID) and Word Attack (WATT) measure untimed sight word reading and non-word decoding ability, respectively (Woodcock et

al., 2001), the Test of Word Reading Efficiency's Sight Word Efficiency (TOWRE SWE) and Phonemic Decoding Efficiency (TOWRE PDE) subtests (Torgesen et al., 1999) measure their namesake, the Spelling (SP) subtest from the Wechsler Individual Achievement Test-II (Wechsler, 1992) does likewise, and two verbal and two nonverbal subtests from the Reynolds Intellectual Assessment Scales (RIAS) provided the basis for the verbal intelligence index (VIX) and Nonverbal Intelligence Index (NIX) (Reynolds & Kamphaus, 2003).

EEG Recordings

During the experiment, participants were seated in a quiet room in front of a blank, unchanging computer monitor. Participants were instructed to keep their eyes open and loosely focused on a fixation cross, which was displayed on the screen while they listened to auditory stimuli.

Stimuli used in this experiment were a pair of pure tones (25ms duration, 500ms inter-stimulus interval) where the second tone was NOT presented in 20% of trials, creating an "omitted stimulus oddball". The stimulus timeline thus has 4 events: stimulus onset at 0ms, stimulus offset at 25ms, stimulus onset at 525ms, and stimulus offset at 550ms.

Continuous EEG recordings were collected using a 128-electrode net (HydroCel Geodesic Sensor Net) at 1000Hz sampling frequency with a recording system running NetStation2.0 (Electrical Geodesics Incorporated, Eugene, OR), including electrodes for recording eye movements (vertical and horizontal) and an electrode on each mastoid. Impedance of all electrodes stayed below 40kOhms during recording. Offline data

analyses were conducted using the NetStation 2.0 toolbox according to the pipeline specified in Dennis Molfese's NetStation 2.0 Manual. These processing steps included:

1) Raw EEG signals were band-pass filtered with a low-pass cutoff at 55Hz and a high-pass at .1Hz.
2) Filtered EEG files were segmented into epochs of 1000ms, extending 100ms before the onset of the first stimulus and 350ms after the offset of the second stimulus.
3) Segmented files were then passed through the automatic artifact detection software in NetStation 2.0, which has several criteria for artifact detection:
4) Bad channels were those with amplitude ranges of 200 microvolts over 640ms. Other parameters were set as suggested by the NetStation5.0 Manual (Geodesic)
    a. Eye blinks were detected as those amplitude ranges of 140 microvolts over 640ms. Blink duration was then extended by 20ms to ensure successful removal. Eye movements were detected as those amplitude ranges of 100 microvolts over 640ms.
    b. A channel was marked bad for all segments if greater than 40% of segments met a criterion above.
5) Bad channels were replaced using the built-in NetStation 5.0 tool.
6) Cleaned files were then re-referenced using the average of the two mastoids for the ERP analysis and re-referenced using the average of all other electrodes for all other analyses.
7) All files were then baseline corrected based on the first 100ms of each epoch.

8) All files were averaged, once according to condition (grand averages) and once according to participant (individual averages).
9) The grand average files were processed through a statistical extraction tool, which output minimum/maximum amplitudes for the P50, N1, P2, and P3a components, which were defined as the largest positive component occurring between 35 and 95ms (Pratt, 2008), largest negative component occurring between 70 and 130ms (Peter et al., 2019), the largest positive component occurring between 150 and 250ms (Peter et al.,2019), and the largest positive component beginning at 225ms (Kujala et al., 2003) and ending at 325ms (Rinne et al., 2006) post-stimulus, respectively. This extraction was also performed on the average of the same 19 frontocentral electrodes analyzed in Peter et al., 2019.

Additional analyses were performed to attain three additional results from EEG.

1) A wavelet extraction tool was created using a frequency scale factor of 7 with a step of 1Hz, which collected frequencies from .1 to 50Hz (Molfese). This wavelet extraction tool processed individual files after baseline correcting according to step 7 above. The wavelet files were then processed through a statistical extraction tool, which output power estimates for Theta (4-7Hz), Alpha (7-12Hz), Beta (12-30Hz), and Gamma (30-50Hz) bands occurring in the 40-100ms time window (Bendixen et al., 2011).
2) An alternate segmentation strategy was implemented to test Hypothesis 1b, whereby the even trials (those where both tones were presented) were split by their presentation order: categories 1, 2, 3 and 4 consisted of the first, second, third, and fourth set of 50 even trials. Processing steps 3-9 were then repeated on

these files, yielding a grand average file with four averaged waves, representing groups of trials split into four epochs.

3) Neural generators of the ERPs were estimated with sLORETA software (University Hospital of Psychiatry, Zürich, Switzerland). Source localization was conducted on grand average data. In sLORETA, the regularization setting was set to .001, the based on a real head model rather than a sphere (FDM imputes source from tissue geometries and their conductivities) and with the setting "2mm Atlas Man", where each dipole is made up of three dipoles in the X, Y, and Z orientations (Geosource 2.0).

Before statistical analysis, three participants' ERP components were imputed from the group average due to more than 40% of their ERP segments being removed because of ocular artifacts.

Statistical Analysis

All statistics were conducted using the IBM SPSS Statistics 28 software package. A summary is available in Figure 1.

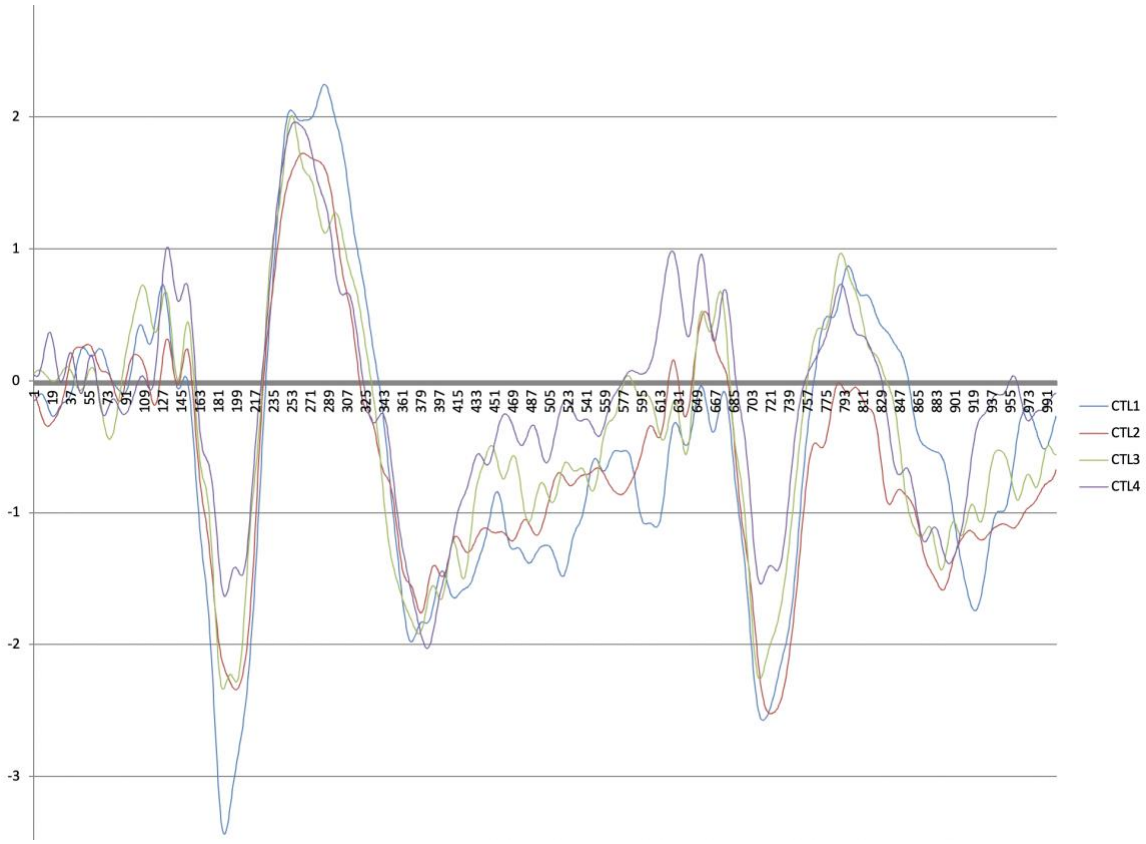
Affected		EP5.1	OP5.1	EN1.1	ON1.1	EP2.1	OP2.1	EP5.2	OP5.2	EN1.2	EP2.2	EOSR	OOSR	TOWRE_PDE	Slope100	TOWRE_SWE
1	Mean	1.30	1.74	-3.72	-3.45	2.50	3.53	.85	2.21	-3.14	1.17	.44	3.11	97.50	-2.18	98.7778
	N	18	18	18	18	18	18	18	18	18	18	18	18	18	16	18
	Std. Deviation	.667	1.323	2.281	2.318	1.682	1.688	1.223	2.092	2.594	1.753	1.509	2.788	9.263	2.486	15.95418
2	Mean	1.41	1.40	-4.47	-5.17	3.30	3.26	.79	-.03	-3.64	1.62	.46	1.32	77.32	.01	94.6316
	N	16	16	16	16	16	16	16	16	16	16	16	16	19	16	19
	Std. Deviation	.642	1.471	1.936	2.360	2.493	1.894	1.118	1.608	1.810	1.670	1.344	1.454	7.341	2.507	12.96238

Figure 1: Summary statistics between groups for ERP components and behavioral measures

CHAPTER 3

RESULTS

(H1) To test for a sensory gating difference between groups (H1a), an independent samples t-test was conducted on the N1 and P2 amplitudes in response the first and second tones. This analysis was not significant for the first N1 amplitude ($F(32)= .066$, $p=.314$), nor the second N1 amplitude ($F(32)=.303$, $p=.524$). Furthermore, this analysis was not significant for the first P2 amplitude ($F(32)=1.975$, $p=.272$), nor the second P2 amplitude ($F(32)=.062$, $p=.452$). However, there is some evidence for a longitudinal gating effect (H1b), which was not statistically tested because standard deviations are not available from the NetStation 2.0 output of the grand average files. However, the the visual results of this analysis are intriguing, and are depicted in Figure 2.



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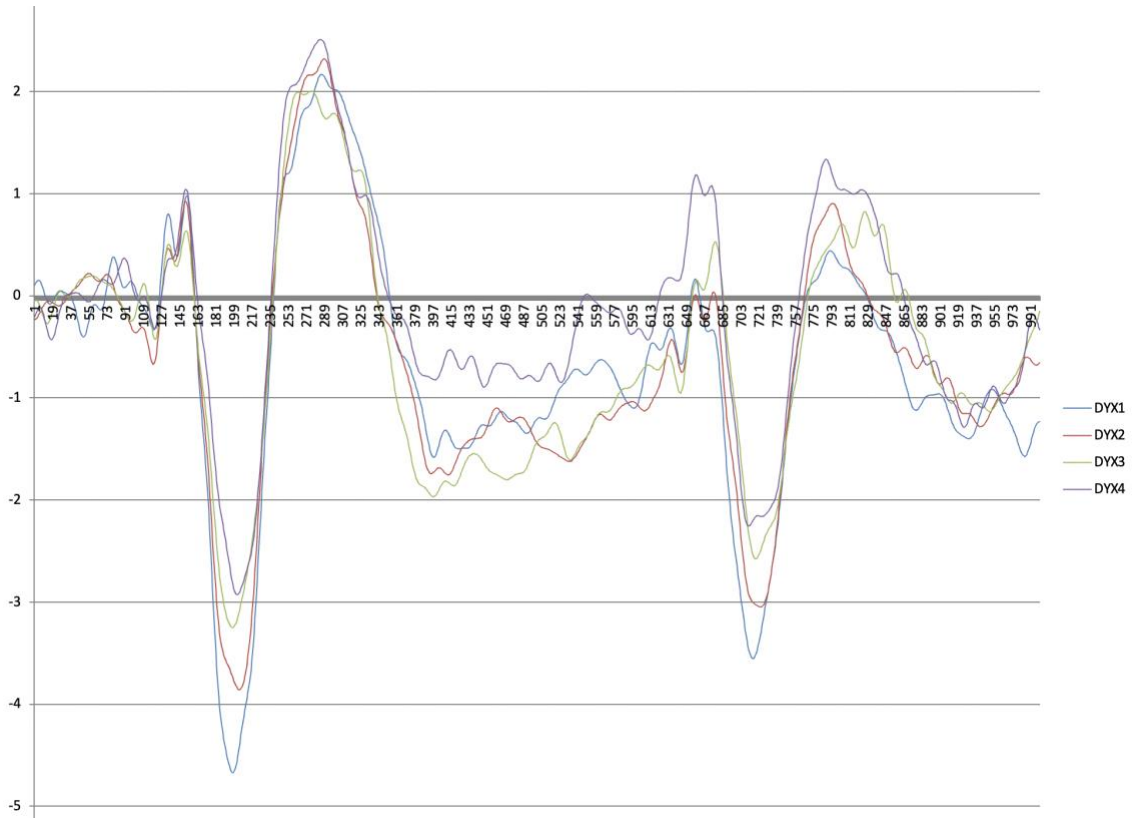

Figure 2: Control & Dyslexic response to four successive epochs of 50 paired tones: the blocks are ordered such that CTL1 is the first epoch of 50, while CTL 4 is the final epoch of 50. Suggestions for statistical analysis are welcomed.

(H2/3) To test for a group difference in the P50 'mimic' and early P3a in response to the deviant omission (H2 & H3), an independent samples t-test was conducted on the components' respective amplitudes in response to the deviant omission. This P50 test was significant ($F(32)=12.017$, $p=.002$), though the P50 was also significantly different between conditions, complicating the interpretation of this result. The test for the early P300 was nominally significant ($F(32)=5.247$, $p=.028$).

(H4) To measure individual statistical learning rate, the reaction time slope from the first 100 trials of the INTER paradigm was calculated (Peter & colleagues, unpublished). This is an auditory oddball experiment presented to the same participants, in which 80% of the stimuli are tones not phase-shifted and 20% are deviants that were phase shifted to create the percept of a 45-degree spatial deflection. The task was to press "front" or

"side" as quickly as possible to indicate the direction from which the tone came. To uncover whether adults with dyslexia differ in their statistical learning rate (H4), an independent samples t-test was used on the response time slopes. This test was nominally significant (F(32)=.023, p=.019). Results are available in Figure 3.

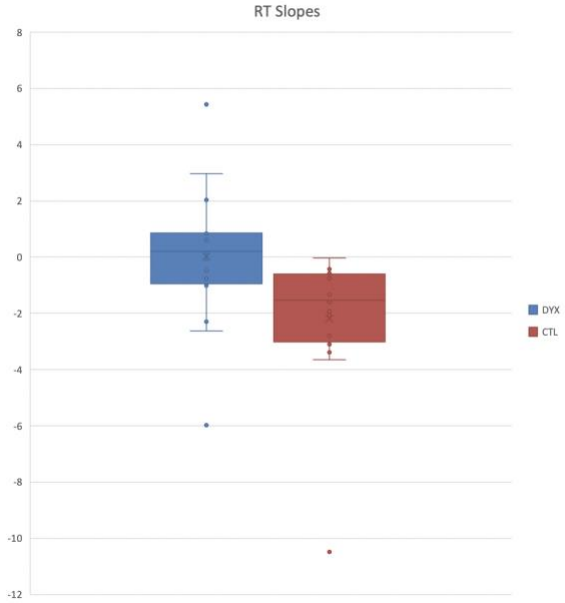

Figure 3: Box and Whisker plot of reaction times to deviant detection when deviant was difference in interaural timing

(H5) To test whether a significant proportion in sight word reading efficiency (TOWRE SWE) and phonological decoding efficiency (TOWRE PDE; H5) could be predicted with the endophenotypes measured, a reverse step-wise regression was conducted using P50, N1, and P2 responses to the first tone (+3), P50, N1, P2, and early P3a ERP maximum/minimum amplitudes to the second tone or its omission (+8) as well as the statistical learning rate (1) for a total of 12 starting predictors.

In the prediction of PDE, variables were dropped in the following order: first N1, the mimic P50, the first P50, second P50 and P200 mimic in the same step, which made the omnibus significant for the first time at the .05 level (F(7)=2.787, p=.032). As the analysis continued, the second P2 was dropped, then the first P2, then the N1 mimic, then

the early P300 to the second tone, then the second N1, and finally, the statistical learning rate. The adjusted R^2 peaked at .316, and that model included the amplitude of the second N1, the early P300 in response to omission, and the statistical learning rate. These results are summarized in Figure 4. It is remarkable that nearly 30% (adjusted R^2= .316) of the variation in phonemic decoding efficiency is captured by the variance in minimum/maximum ERP amplitude from the measures selected, and that those are in response to 250 trials of paired and deviant stimuli. A progression of R^2 and adjusted R^2 as a function of predictors included in analysis is included in Figure 5.

The reverse step-wise regression on SWE proceeded according to the same steps outlined above and variables were dropped in the following order: the early P300 to the second tone, the first N1, the second P50, the P2 mimic, the second N1, the omission P300, the P50 mimic, the first P50, the second P2, the statistical learning rate, the first P2, and finally, the N1 mimic. At no point was the omnibus test for this analysis significant. These results are summarized in Figure 6. Interestingly, the N1 mimic is purportedly the product of auditory predictions originating in long term memory, which has a clear interpretation as predicting sight word reading efficiency.

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	2663.807	6	443.968	3.213	.020[b]
	Residual	3040.055	22	138.184		
	Total	5703.862	28			

a. Dependent Variable: TOWRE_PDE

b. Predictors: (Constant), EOSR, Slope100, ON1.2, EN1.2, EP2.1, OOSR

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.
1	(Constant)	87.822	5.713		15.372	<.001
	EP2.1	1.367	1.302	.216	1.050	.305
	EN1.2	1.983	1.221	.324	1.624	.119
	ON1.2	2.219	1.556	.306	1.427	.168
	OOSR	2.517	1.323	.443	1.902	.070
	Slope100	-1.463	.831	-.283	-1.760	.092
	EOSR	-3.430	1.900	-.351	-1.805	.085

a. Dependent Variable: TOWRE_PDE

Figure 4: Significant results of backwards step-wise regression on Phonemic Decoding Efficiency. Key: EP2.1 = P200 to second tone, EN1.2 = N100 to second tone, ON1.2= N100 to omission, OOSR = early P300 to omission(previously called "omission stimulus response" in my analysis), Slope100 = response time slope to the first 100 trials of the INTER paradigm, EOSR = early P300 to second tone. Note the negative effect of a P300 when the stimulus is unexpected versus the positive effect of a P300 when it is not expected. This is in line with previous findings of P300 indexing typical neural response. Negative relationship of Slope100 is due to learning being reflected as a negative slope (faster over trials).

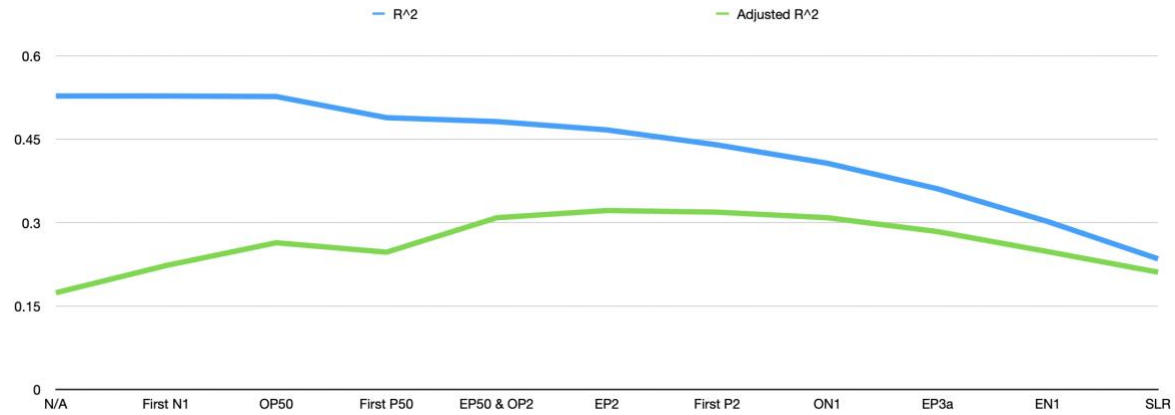

Figure 5: R^2 and adj R^2 change as a function of predictors on Phonemic Decoding Efficiency.

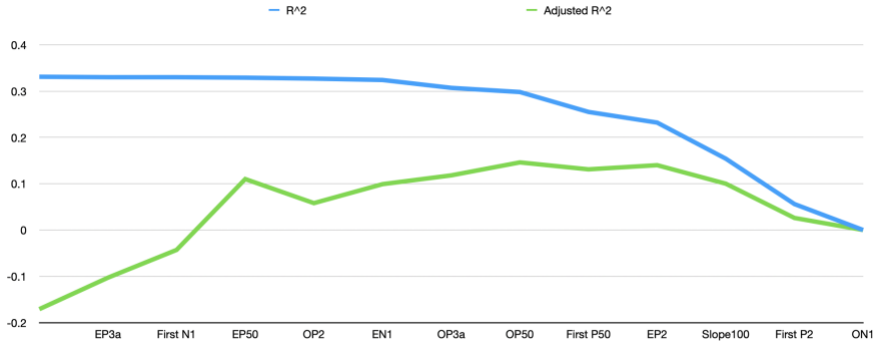

Figure 6: R^2 and adj R^2 as a function of predictors on Sight Word Efficiency

(H6) The investigation into group differences in the gamma band response to the paired or omitted tone is promising. Gamma band power is significantly increased when the second tone is presented versus when it is omitted ($F(33)=5.384$, $p<.001$), though there is no group difference in gamma band power during the presentation of the second tone ($F(32)=4.614$, $p=.078$) or when it is omitted ($F(32)=2.352$, $p=.780$).

(H7) Grand average ERP files were viewed with sLORETA low resolution brain electromagnetic tomography. The comparison between conditions & groups, with preliminary results available in Figure 7. These results should be interpreted with caution: the inverse problem of EEG is notoriously difficult to solve, though sLORETA was the best available option for source localization (Grech et al., 2008). "Visually significant results" include a typical auditory statistical learning response pattern by STG and IFG in the control group in both conditions, whereas adults with dyslexia displayed a pattern of activity more consistent with a typical visual statistical learning response pattern. Voxel analysis is warranted to produce statistically interpretable results, though sample output from the maximum probability source estimate during relevant time windows is available in Figure 7, and output during the omission period (and 5ms after offset or expected offset) in both groups has been replicated in Figures 8-11 for intrigue.

First Tone	P50	N100	P200
DYX	Medial fusiform gyrus, left lingual gyrus, bilateral superior temporal gyrus, right parahippocampal gyrus, left superior frontal gyrus	Right fusiform gyrus, left lingual gyrus, right superior temporal gyrus, left parahippocampal gyrus	Right fusiform gyrus, bilateral lingual gyrus, right parahippocampal gyrus, right superior temporal gyrus
CTL	Right fusiform gyrus, bilateral lingual gyrus, right amygdala, right medial temporal gyrus, bilateral superior frontal gyrus, right inferior occipital gyrus	Bilateral lingual gyrus, left fusiform gyrus, inferior occipital gyrus, right superior temporal gyrus	Left lingual gyrus, right amygdala, bilateral hippocampus, right fusiform gyrus, inferior temporal cortex, right superior temporal gyrus

Second Tone	P50	N100	P200	P300
DYX Match	Left inferior temporal gyrus, left superior temporal gyrus	Left inferior temporal gyrus	Left inferior temporal gyrus	Left inferior temporal gyrus
DYX Omission	Right fusiform gyrus, middle superior frontal gyrus	Right fusiform gyrus, middle superior frontal gyrus	Right fusiform gyrus, middle superior frontal gyrus	Right medial frontal gyrus
CTL Match	Left lingual gyrus, left inferior frontal gyrus, rectal gyrus, left superior frontal gyrus	Left lingual gyrus	Rectal gyrus, bilateral superior temporal gyrus	Left lingual gyrus
CTL Omission	Right superior temporal gyrus, left inferior frontal gyrus	Rectal gyrus, right superior temporal gyrus, left inferior frontal gyrus, left inferior temporal gyrus	Left inferior temporal gyrus, left inferior frontal gyrus, rectal gyrus	Rectal gyrus, left inferior temporal gyrus, left inferior frontal gyrus, bilateral superior temporal gyrus

Figure 7: Visually estimated activity patterns in sLORETA over the time course of stimuli presentation. Table 1 shows response to the first stimulus, Table 2 shows response to the second stimulus

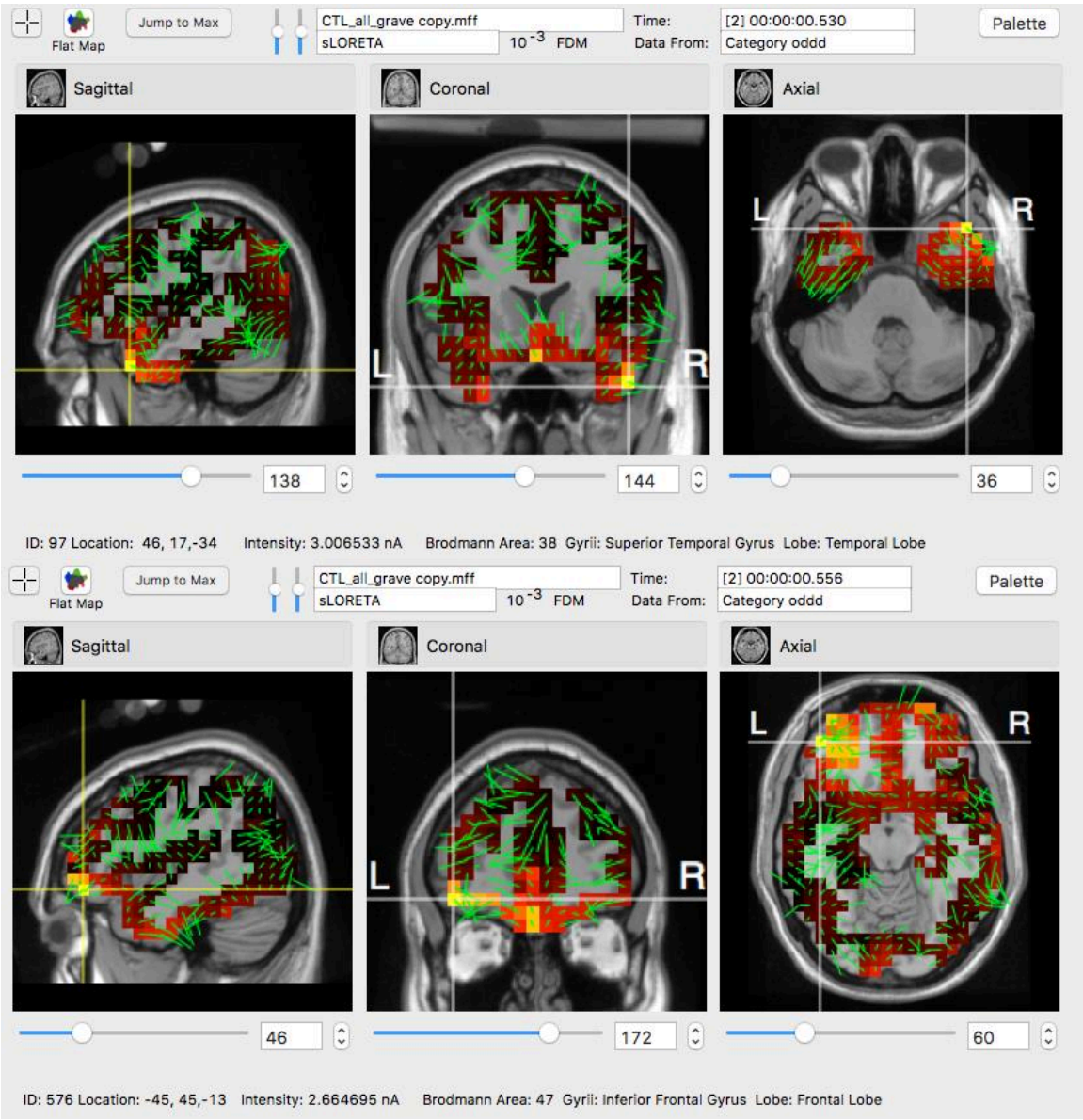

Figure 8: Controls respond to the deviant Omission by activation of Superior Temporal Gyrus followed by Inferior Frontal Gyrus

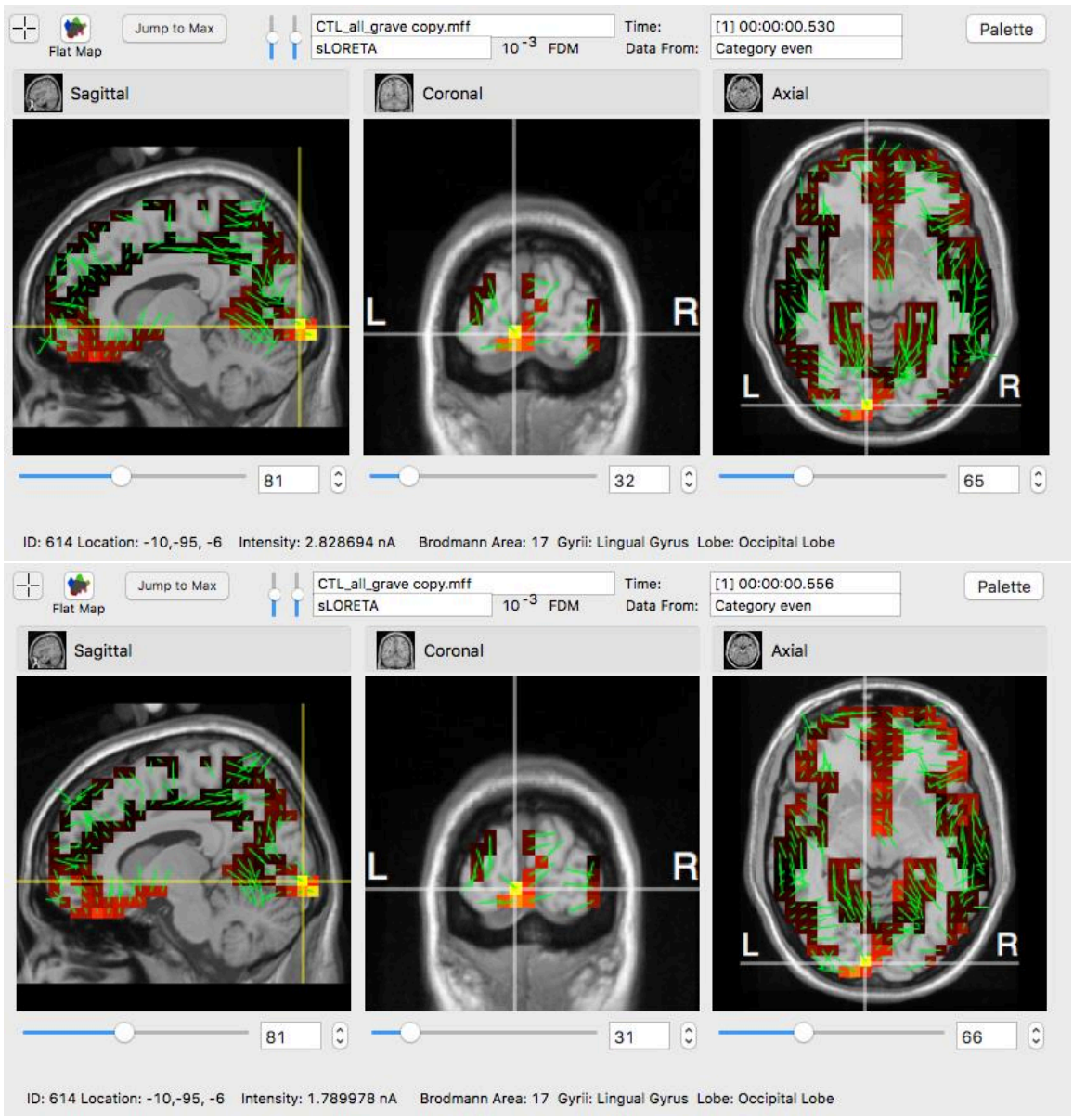

Figure 9: Controls respond to the expected presentation of a second tone by activation of Lingual Gyrus; this activity is maintained

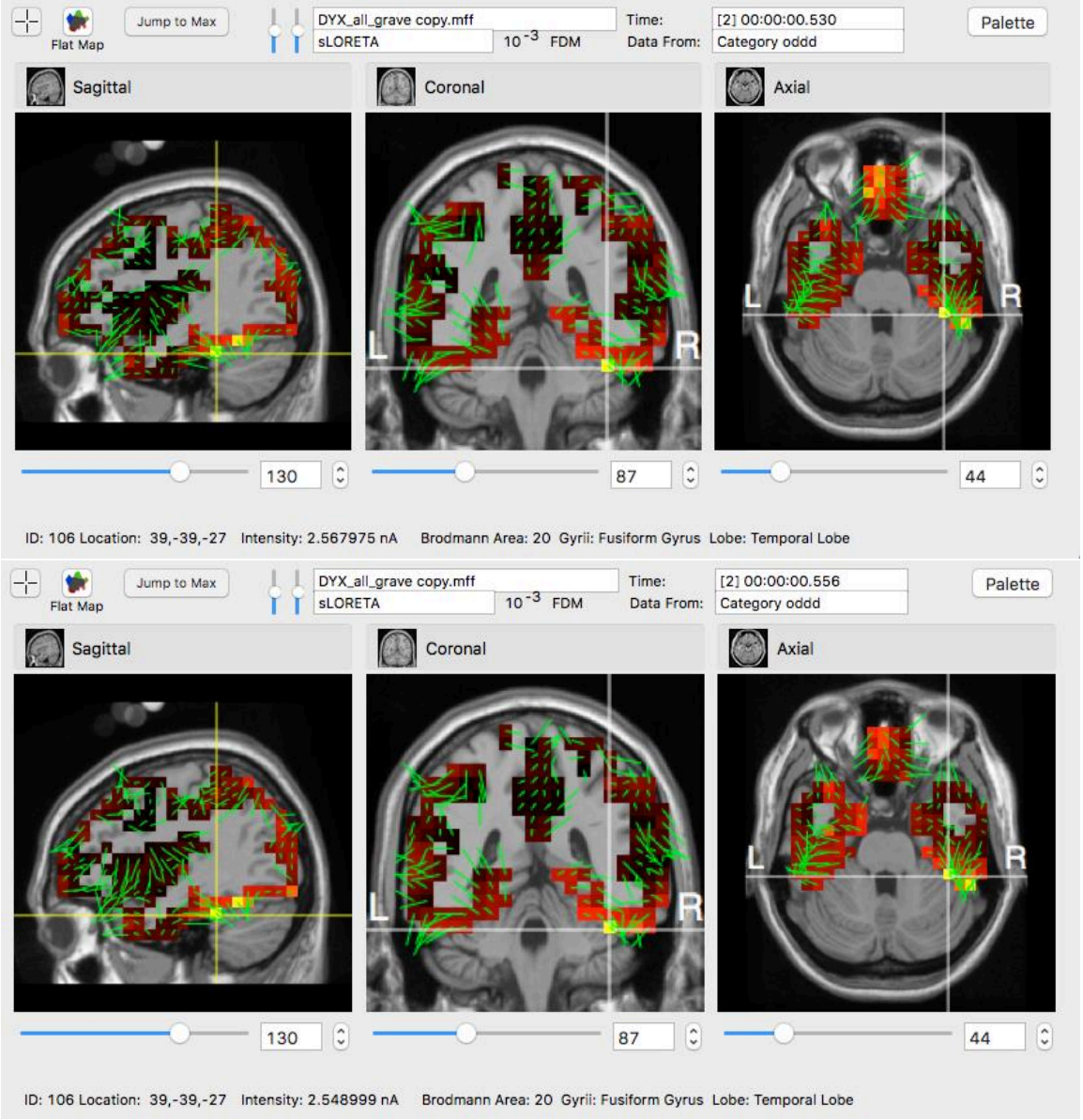

Figure 10: Dyslexics respond to the deviant Omission by activation of Fusiform Gyrus; this activity is maintained

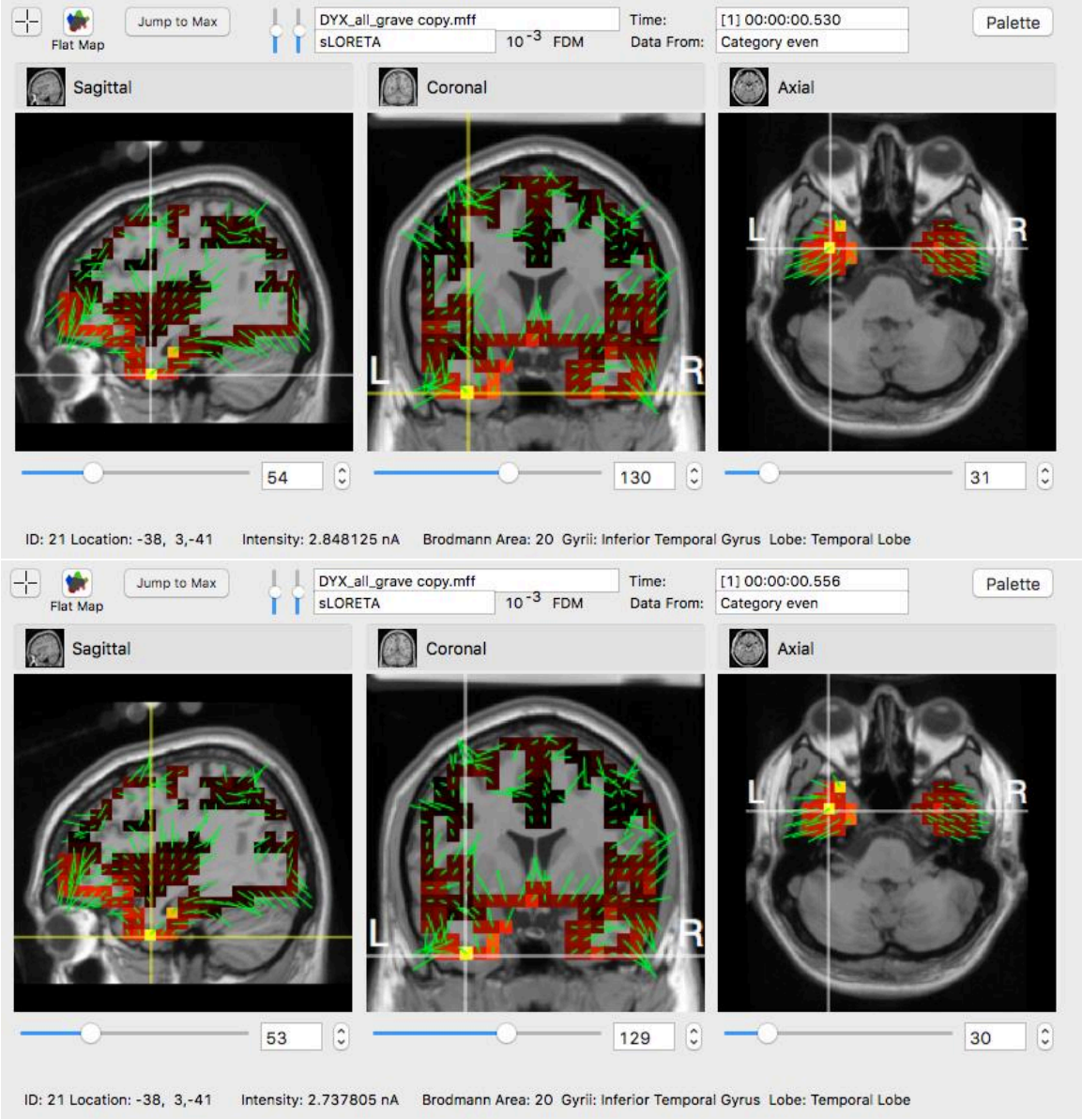

Figure 11: Dyslexics respond to the expected second Tone by activation of Inferior Temporal Gyrus; this activity is maintained

CHAPTER 4

DISCUSSION

While the initial sensory gating hypothesis did not replicate, the long term gating effect also provides evidence for storage of auditory information for use in the long run, as is implied by the significant correlation between the gating effect and performance on the word discrimination task as was observed in Peter et al,. 2019. Both the short-term gating effect, which can be interpreted as auditory sensory decay, and the long-term gating effect, which is evidence of expectation updating over multiple blocks of trials, are likely to represent endophenotypes, as was implied by the cluster analysis of the same study, and can likely be linked more precisely to neurobiological mechanisms.

The group tests for the P50 mimic, P300, reaction time slopes, gamma band power, and neurobiological generators were all meant to answer similar questions: is there a difference in the way adults with dyslexia process omissions of expected auditory stimuli? While the results are not overwhelming, they do imply a deficit in auditory statistical learning in adults with dyslexia compared to typical controls that is related to predictive processing carried out in part by circuits involving the right superior temporal gyrus and left inferior frontal gyrus. Previous research has found hyperactivation of the left IFG in dyslexic readers while this analysis found nearly none. Hyperactivation is often interpreted as overexertion, or inefficient processing, and the stimuli in this study were simple tones. Shaywitz & colleagues investigated the neurobiological correlates of dyslexia in 1998 by administering phonological tasks of increasing difficulty. Interestingly, activity in left IFG of dyslexics was hypoactivated relative to controls in the easiest condition, though it was a visual line discrimination task, and hyperactivated to

the most demanding task, a semantic category judgment from read words (are corn and rice in the same category?). This evidence suggests a lack of engagement of IFG in the processing of simple sounds, but an over-recruitment of left IFG to more complicated language tasks. Hyperactivity in these experiments is often a sign of inefficient processing, much like the interpretation of the N1 sensory gating deficit.

Meanwhile, the stimuli in this experiment were simple tones. Perhaps adult readers with dyslexia circumvent a developmental predisposition to hypoactivation of the left IFG in response to auditory statistical change (tone omission) when explicitly learning letter-sound mappings during instruction. In this view, dyslexia might involve an undersensitivity to auditory change that is related to activity in both the r-STG and left IFG. Future research should see if the relationship between phonological task difficulty holds with more controlled phonological tasks than were used in Shaywitz, 1998, such as making more fine-grained distinctions in frequency, or voice-onset time. This may elucidate the extent to which activity in a circuit involving r-STG and left IFG is involved in the auditory statistical learning deficit observed in dyslexia.

It would seem that the complex of ERPs observed in the typical controls indicates prediction (P50), violation (N1 disappears), and updating (P300) that is driven by activity in the r-STG and left IFG. Meanwhile, the affected group shows relatively decreased activity of the left right STG and in the left IFG, indicating that disruption to this process may take place in the prediction generation process. More research is needed to make this connection clear.

The ERP and behavioral predictors of PDE uncovered in the significant regression analysis were the second P2 amplitude, N1 amplitudes to both the presentation

and omission of the second tone, reaction time slope, the omission P300, and, interestingly, the P300 during the even presentation of the stimulus, which was not apparent and was not analyzed. However, there was no significant omnibus test involved the prediction of SWE, implying the lack of relevant variables included in the model. While exploratory in nature, the unexpected pattern of significant predictions on PDE may indicate the presence of signal within activity that is typically discounted as noise, warranting future investigation with black box big data approaches that can capture more of the variance in the ERP waveform.

In the endophenotype view, group differences along a particular axis should not be interpreted as 'individuals with dyslexia have a deficit along this axis,' but rather as indicators of a contributory endophenotype to the clinically relevant diagnosis. For example, the results of this analysis do not imply that individuals with dyslexia have a deficit in statistical learning, but rather that statistical learning is a trait that contributes to the clinical relevance of the reading phenotype.

Efforts studying endophenotypes have already proved insightful into the genetic etiology of dyslexia. A recent GWAS was run on rapid automized naming task results rather than composite measures that found new variants linked to dyslexia (Gialluisi et al., 2019). However, rapid naming is a downstream phenotype emergent from component neurobiological processes, one of which is surely auditory statistical learning, or deviant MMN. Future research might utilize GWAS techniques to investigate variation in neural responses to simple and well-known, such as can be done with the two-tone sensory gating paradigm and deviant variations. Gene networks interacting over time make brain

networks, which interact over time to affect behaviors, of which some are important enough to society to deem clinically relevant.

The results of the two regression analyses suggest that neural responses explain more variation in upstream phenotypes than downstream phenotypes if sight word efficiency is interpreted as being phenotypically downstream to phonemic decoding efficiency (if the former is dependent on the latter, which may be a point of theoretical and practical debate).

Furthermore, the results of this analysis suggest that some, but far from all, of the variance in reading ability is the result of auditory prediction capacities. Assuming fluent reading ability relies on several functionally integrated circuits, this analysis solely captures the impact of simple auditory prediction on phonemic decoding efficiency and explains little of the variance in sight word reading. However, it does imply that future genome-wide association studies might have success uncovering variants relevant for reading by studying those relevant for the contributory systems. This analysis suggests that subliminal auditory prediction is one such system.

Limitations and Future Studies

While this study does suggest a relationship between a subliminal auditory prediction mechanism and dyslexia, it was limited by the number of typical controls and adults with dyslexia that took part. All participants were diagnosed in English, limiting generalizability to other languages. Small sample size increases the probability of finding differences when there are none or failing to find differences when they exist, and it limits the ability to perform interaction analyses and to uncover the effect of individual

differences. Finally, there was limited ability to study the effects of developmental trajectory owing to age range in both the control and affected groups – presumably a subliminal auditory prediction mechanism would decrease in temporal resolution over the life span as binding novel auditory change to articulators or orthography becomes less behaviorally relevant.

Future research should increase the number of participants and administer a more comprehensive battery of tests, like in Ramus et al., 2003, to investigate the interactions of neural systems in dyslexia.

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