**Research Plan**

An influential conceptual framework suggests that Developmental Dyslexia (DD) arises from a selective disruption to procedural learning and memory; the type of learning that emerges when a complex, multifaceted motor or cognitive activity is repeated to the point that it is performed automatically, without the need for conscious control or directed attention [[1](#_ENREF_1), [2](#_ENREF_2)]. Despite evidence supporting this notion, procedural learning mechanisms in dyslexia are far from being understood. Research on procedural learning in DD suffers from two main limitations. First, group differences between participants with DD and neurotypicals in studies with small samples are taken as evidence for impairment. To establish the existence of a procedural learning deficit in DD, there is a need for large-scale studies involving multiple measures for improving power and for increasing generalizability. Second, tasks labeled ‘procedural’ in the literature vary widely, and we do not have a deep understanding of whether they draw on truly common processes even among neurotypicals. Without a better understanding of the different facets of procedural learning, it is impossible to define what may actually underlie the reported procedural learning deficits in DD. The aim of this bi-national research proposal between Israel (University of Haifa) and the United States (Carnegie Mellon University) is to investigate whether procedural learning is a unified or componential ability, whether procedural learning measurements are reliable **(Objective 1),** and whether there are systematic challenges to procedural learning abilities in dyslexia, independent of tasks that are best associated with dyslexia severity **(Objective 2).** Using a machine learning approach, we also aim to ascertain whether dyslexia can be identified solely on the basis of aggregated performance on a battery of procedural learning tasks **(Objective 3).** To address these objectives, we will conduct a large scale-study by establishing a novel online psychological testing platform to study multiple measures of procedural learning examined within the same individuals (DD and neurotypicals) accompanied by assessments of reading and language-related abilities. In this way we intend to develop an open source, freely available procedural learning test battery to help researchers to measure procedural learning in their own research fields. The findings from this project will be a first step towards developing better diagnostics (e.g., streamlined diagnostics that do not rely on reading and could be administered earlier in development) and may lead to the discovery of subclasses of dyslexia. At a basic science level, the results from this project will enable us to zero in on different aspects of ‘procedural learning tasks' (which are quite fuzzy in definition), and thus give us a more precise understanding of the nature of the procedural learning deficit in DD.

**Scientific Background**

***1.1 Developmental Dyslexia.*** Developmental dyslexia (DD), one of the most common neurodevelopmental disorders, is characterized by a selective impairment in reading skill acquisition despite conventional instruction, normal intelligence, and typical sociocultural opportunities. DD is accompanied by a myriad of negative emotional and social consequences, including socioeconomic problems such as decreased labor force participation, greater reliance on public assistance, and lower civic involvement [[3](#_ENREF_3)]. Typical symptoms of DD include impaired phonological processing, slow lexical retrieval and verbal short-term memory impairments [[4](#_ENREF_4)]. However impairments are not limited to the linguistic domain [[for a review see 5](#_ENREF_5)]. The diverse range of impairments and suggested deficits in DD has initiated a shift toward a multiple deficit view [[6](#_ENREF_6)], according to which reading problems are the result of individually-based combinations of language-specific and domain-general deficits.

***1.2 The Procedural Deficit Hypothesis.*** One such deficit that may contribute to phonological and reading impairments in DD relates to procedural learning (learning that emerges by repeating a complex, multifaceted activity to the point that it is performed automatically without the need for conscious control or directed attention). The procedural memory system has been mainly associated with the learning and formation of motor procedures [[7](#_ENREF_7), [8](#_ENREF_8)]. However, an accumulating body of evidence implicates it in the computation of perceptual sequences [[9](#_ENREF_9)], the extraction of environmental regularities [[10](#_ENREF_10)], and non-motor probabilistic category learning [[11](#_ENREF_11)]. According to the Procedural Deficit Hypothesis, a selective disruption to the procedural memory system in DD can cause problems in the acquisition and automaticity of reading, spelling and writing skills [[12-16](#_ENREF_12)].

***1.3 Inconsistent Procedural Learning Profiles Among People with DD.*** Consistent with a broad role for procedural learning in cognition and perception, children and adults with DD are impaired at a variety of tasks believed to be sub-served by the procedural memory system [e.g., [17](#_ENREF_17), [18-28](#_ENREF_18)]. Furthermore, neuroimaging studies indicate impairment of procedural learning systems among individuals with DD [[29-31](#_ENREF_29)]. However, despite this evidence, results are not always consistent and there are several demonstrations of preserved procedural learning in DD [e.g., [32](#_ENREF_32), [33](#_ENREF_33), [34](#_ENREF_34)]. Conclusions from meta-analyses diverge as well [[22](#_ENREF_22), [35](#_ENREF_35)], and the relationship between procedural learning impairments and the severity of language impairments in DD remains unclear [[35](#_ENREF_35)].

One of the reasons for these inconsistencies is that procedural learning tasks *vary* considerably across multiple task dimensions (e.g., domain, sensory modality, feedback) and it is not clear whether they all tap into a common unified procedural memory mechanism even in neurotypicals. If procedural memory represents a componential [[36-38](#_ENREF_36)], rather than a unified, ability then it is possible that procedural functions in dyslexia are limited to certain facets of procedural memory. However, the lack of a comprehensive examination of multiple tasks within the same individuals limits our ability to discover which procedural learning patterns are associated with dyslexia severity. Adding to the complexity of the problem is the technical challenge of recruiting special populations. Sample sizes in the research field of dyslexia tend to be small and recruitment is mostly limited to a specific population (e.g., college students) or a specific clinical center, so samples may not be representative of the general population. Here we suggest joining forces to establish a novel online psychological testing platform for testing people with dyslexia to address the research challenges detailed above.

***1.4 Procedural Learning Tasks Vary Considerably Across Multiple Dimensions.*** Procedural learning is studied in the lab using a diverse range of tasks across different domains (e.g., cognitive, motor) [[9](#_ENREF_9), [39](#_ENREF_39)] and different sensory modalities [[40](#_ENREF_40)]. It is unclear, however, whether these tasks tap into a common unified procedural memory system [[38](#_ENREF_38)]. Although procedural learning is observed across domains and sensory modalities, this does not necessarily imply that this is a single, domain-general system. It is also probable that there are multiple procedural learning subsystems that share similar computational principles, but that only some of them are involved in specific task and input demands [[41-43](#_ENREF_41)]. For example, a typical taxonomy divides procedural memory into the acquisition of *motor/perceptual-motor*, *perceptual,* and *cognitive* skills [[44](#_ENREF_44), [45](#_ENREF_45)]. Perceptual-motor procedural learning refers to learned movement patterns guided by sensory input whereas cognitive procedural learning refers to skills that require problem-solving or the application of strategies [[46](#_ENREF_46)]. Although real-life procedural learning is likely to involve several domains, research conducted in the lab supports this taxonomy by revealing intact procedural learning in one domain alongside intact skill learning in another domain among patients' populations [[36](#_ENREF_36), [37](#_ENREF_37), [47](#_ENREF_47)]. These studies have led to the suggestion that some forms of procedural learning depend upon separable brain regions [[36](#_ENREF_36), [47](#_ENREF_47), [48](#_ENREF_48)]. Adding to this complexity is the observation that even within the same domain, procedural learning tasks can be dissociated depending on the type of *processes* involved [[8](#_ENREF_8), [44](#_ENREF_44)] and that procedural learning may be influenced by the sensory demands of a given *modality* [[43](#_ENREF_43)]. Finally, procedural learning tasks vary considerably with regard to task demands with some tasks involve intentional training conditions, whereas others have incidental training conditions; tasks can also vary with respect to whether *feedback* is provided or not. For example, the term implicit learning is usually used interchangeably with the term procedural memory and, although skill learning can sometimes occur incidentally (such as in the Serial Reaction Time Task), other well-known procedural learning tasks involve explicit instructions [[49](#_ENREF_49)]. Feedback also plays a significant role in the formation of procedural memory. This is supported by the observations that patients with Parkinson’s disease exhibit impairments in feedback-based procedural learning tasks [[50](#_ENREF_50)] but learning is sparse in similar tasks devoid of feedback [[51](#_ENREF_51)].

Given these complexities it is not surprising that individuals with DD perform poorly on some procedural learning tasks while having spared performance on other procedural learning tasks. Aside from methodological differences, it is possible that the multifaceted nature of procedural memory contributes to inconsistencies across studies [[38](#_ENREF_38)]. Just as important, the fact that sample sizes are relatively small, and that the reliability of some procedural learning tasks remains unclear, further complicates our ability to identify systematic aspects of procedural learning that are likely to be affected in DD.

***1.5 Defining Procedural Learning.*** Research examining multiple measures of procedural learning within the same individuals either in neurotypicals [[52-54](#_ENREF_52)] or people with DD is sparse [[32](#_ENREF_32), [33](#_ENREF_33)]. Even in studies examining multiple measures of procedural learning the examination is limited to 2-4 tasks [[52-55](#_ENREF_52)] and there is no systematic consideration of the possible different dimensions that may contribute to procedural learning performance.These factors are likely to contribute to inconsistencies across studies [[52](#_ENREF_52), [53](#_ENREF_53)] and limit our ability to understand procedural learning as a cognitive construct and to define what truly may underlie reported procedural learning deficits in DD. To account for the different aspects of procedural learning, we here define an initial mapping sentence in which we outline the dimensions of procedural learning performance. This method is based on Facet Theory, which provides a systematic approach to theory construction and data collection for complex multifaceted constructs [[56](#_ENREF_56)] and has been employed successfully in the fields of statistical learning [[57](#_ENREF_57)] and working memory [[58](#_ENREF_58)]. Based on a literature review our initial mapping sentence is:

"*Procedural learning refers to the acquisition of skills and habits that are learned through practice in different domains (motor/perceptual-motor, perceptual, cognitive) and sensory modalities (visual, auditory), under divergent task instructions (intentional, incidental) with or without external feedback".*

This initial mapping sentence allows us to outline a series of procedural learning tasks that cover the space defined by these four dimensions, and that are relevant to understanding procedural learning as a theoretical construct. These four dimensions—domain, modality, instructions, and feedback—have been well studied in the procedural memory literature. This does not exclude the possibility, however, that additional dimensions could be defined, tested, and explored, such as types of processes [[59](#_ENREF_59)] (e.g., conditional statistics, which is relevant to sequential learning tasks vs. distributional statistics, and which underlies category learning tasks) or different types of procedural memories [[60](#_ENREF_60)] such as skill learning (e.g., motor sequence learning, mirror tracing tasks) vs. habits (e.g. category learning and artificial grammar learning tasks).

Considering this initial mapping can help us reveal systematic challenges in procedural learning in those with DD. For example**,** procedural learning tasks that rely on trial-and-error explicit feedback are consistently disrupted in dyslexia [[17](#_ENREF_17), [20](#_ENREF_20), [61](#_ENREF_61)]. Furthermore, there is evidence that procedural learning in the auditory domain is consistently affected in dyslexia [[19](#_ENREF_19), [21](#_ENREF_21), [62](#_ENREF_62)]. Finally, cognitive procedural learning is affected in DD at least for tasks that rely on trial-and-error feedback [[17](#_ENREF_17), [20](#_ENREF_20)].Here we propose a large-scale online investigation consisting of multiple measures of procedural learning tested within the same individuals to identify latent dimensions of procedural learning affected in dyslexia.

***1.6 Identification of Dyslexia by Procedural Learning Profiles.*** Our proposed large-scale online study will provide sufficient data to allow the use of a Machine Learning (ML) algorithm to identify dyslexia based on procedural learning patterns. If a procedural learning deficit underlies dyslexia, then a diagnostic battery that measures procedural learning functions is likely to be successful in differentiating between DD and neurotypicals. The novelty of such a diagnostic battery lies in the combination of various measures of procedural learning and their analysis using a ML algorithm, making it possible to predict the probability that a given reader has DD. ML analysis has been gaining popularity in research in recent years. The added value of ML over classical statistics lies in its ability to detect complex non-linear high-dimensional interactions that may influence predictions, even in the presence of major instrumental and scoring noise.ML has been recently used for the identification of DD, but most studies are confined to a specific language [[63](#_ENREF_63)]. To the best of our knowledge, there are no studies that differentiate between DD and neurotypicals by using ML procedures to detect procedural learning patterns. As literacy assessments depend on reading in a specific language, adding this completely data-driven, non-linguistic tool as part of the diagnosis could assist in arriving at a differential diagnostic decision even before learning to read takes place and can also contribute to a general culture-independent understanding of the underlying mechanisms of DD.

**2. Objectives and Significance of the Research**

Studies examining procedural learning in DD reveal inconsistent findings. Our ability to understand the nature of procedural learning in DD is limited because procedural learning is examined across a divergent range of tasks that are considered "procedural" but do not necessarily tap into a single common unified procedural memory system. Furthermore, studies are limited to small sample sizes which do not necessarily represent the whole population. Therefore, we propose a large-scale investigation of multiple procedural learning measures, tested within the same individuals, in order to truly comprehend the procedural learning functions of people with DD and the relationship of these functions to dyslexia severity. Our specific objectives are:

**Objective 1 is to determine whether procedural learning is a unified mechanism or a componential capacity, and whether procedural learning can be reliably measured.** Our first objective is to identify critical aspects of procedural learning in neurotypicals examined across a large battery of tests, and to assess whether procedural learning can be reliably measured. We will use confirmatory and exploratory factor analyses to identify shared and unique variances in procedural learning performance across tasks, and will assess the reliability of various procedural learning measures. As increasing evidence supports the role of procedural memory in language acquisition [[64](#_ENREF_64)] and developmental language disorders [[1](#_ENREF_1)], there is a need to refine and validate methods that tap into procedural memory. The current study will contribute to this effort, by providing a better understanding of procedural learning as a theoretical construct. Our online procedural learning battery once established, will be available to researchers and could contribute to open and reproducible research.

**Objective 2 is to determine whether there are systematic challenges to procedural learning functions in DD and their association with dyslexia severity.** Based on our working hypothesis that procedural learning systems are disrupted in DD, we expect people with DD to perform poorly on diverse measures of procedural learning that tap into a common underlying procedural memory system. Furthermore, we expect to observe a relationship between procedural learning performance and dyslexia severity. However, given the notion that there are multiple subsystems of procedural memory, it may also be the case that procedural learning for a specific level of a dimension (e.g., auditory learning, where the dimension is sensory modality) will be more affected in dyslexia than in other levels of that dimension (e.g., visual learning). Finally, it may also be possible that a specific level of a dimension that is impaired in DD is not distinct from other levels in neurotypicals. We will use confirmatory and exploratory factor analyses to identify critical dimensions of procedural learning that are mostly affected in dyslexia and that are best associated with dyslexia severity. The results of this study will allow us to refine models of procedural learning deficits in DD.

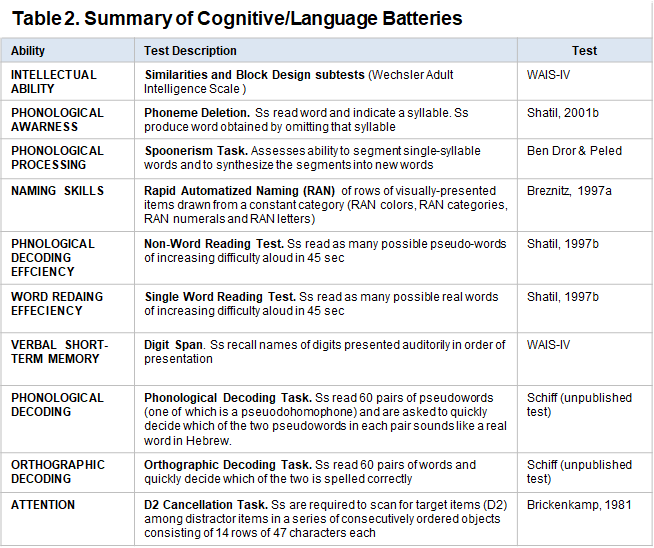
**Objective 3 is to develop a machine learning-based diagnosis support system for identifying developmental dyslexia.** We seek to determine whether dyslexia can be identified on the basis of procedural learning profiles. Here we will use a machine learning algorithm to determine whether DD can be detected based solely on various procedural learning measures. Meeting this objective means providing a cognitive battery that can be utilized as a support system for dyslexia diagnosis alongside standardized reading assessments. This battery could provide a profile of procedural learning inefficiencies that characterize an individual which, in turn, could enable more fine-tuned interventions.

**Methodology and Plan of Operation**

***3.1 Participants and Power Analysis****.* We aim to recruit 400 participants (200 in each group). A power analysis [[calculated using G\*Power software; 65](#_ENREF_65" \o "Faul, 2007 #1855)] indicates that in order to detect a small correlation (*r*=.2), a total sample of 193 participants is needed to obtain statistical power at a 0.80 level with an alpha of 0.05. This large-scale study should also provide sufficient power to conduct factor analyses. Calculating the necessary power a-priori is complicated [[66](#_ENREF_66)], however, our sample size exceeds those of past studies using factor analyses in similar [[52-54](#_ENREF_52)] and related research fields [[67](#_ENREF_67)].

***3.2 Establishing an Online Psychological Testing Platform.*** For conducting a large-scale investigation of procedural learning in people with DD and neurotypicals, we will develop a Platform for Online Psychological Testing of Dyslexia (POP-D) in which participants with DD and matched controls will a series of experimental tasks, as well as well as cognitive and literacy assessments, online. Developing such a platform will significantly facilitate the recruitment of special populations as online recruitment (as opposed to in-person testing) can be performed across the world and is not limited to the specific region in which a particular lab is located. We will recruit native Hebrew speakers with DD and neurotypicals. The Israeli research team has established a sample of approximately 100 participants with DD and 100 matched controls who have undergone in-person literacy and cognitive assessments in the lab and are available to participate in online studies. Furthermore, Co-PI Gabay developed connections with centers in Israel that will help to facilitate recruitment of additional participants with DD.

***3.3 Participant Recruitment:*** We will recruit additional participants across the country in the following ways: First, we will approach disability centers in universities and colleges and ask for their assistance with recruiting people who are diagnosed with dyslexia.After initiating contact with centers, we will ask them to advertise our study to people who have been diagnosed with, or identified as having, dyslexia by the centers by distributing advertisements in the centers or by sending emails to potential participants. In this method of recruitment, participants' details and diagnoses remain *confidential,* and are available only to the centers. People can then initiate contact with us only if they are interested in participating in our study. We have successfully recruited participants in exactly the same manner across several centers in both the United States and Israel. Since we aim to increase generalizability, we will not limit our recruitment to college students but recruit participants via social media networks. Participants who contact us will be invited to complete an online interview (in which the participant's history will be reviewed) and psychological testing. After completing this session, participants will receive a link to complete the procedural learning experiments across multiple sessions.

***3.4 Cognitive/Linguistic Batteries.***We will establish a protocol for online psychological testing of DD. Inspired by online medical and neuropsychological research [[68](#_ENREF_68)], we will create a battery of cognitive and literacy assessments that will be administered to people with DD during a live online session. These sessions will be supervised by a qualified team member using the screen-sharing feature in Zoom [[69](#_ENREF_69)], who will manage the whole assessment session. A team member, watching live through videoconference via participants using the screen sharing feature of their videoconference platform of choice, will manage the whole assessment session and supervise participants performance. For all participants, we will use a battery of tests to assess multiple indicators of oral and written language skills and general cognitive abilities (see **Table 2)**. These tests will be administered to participants using a zoom conference. Tests that require reading will be presented on the screen by the examiner, who will monitor the participants as they read. The research teams in both Haifa and Pittsburgh have substantial experience with recruiting and testing people with DD. Co-PI Holt has substantial experience with recruiting and testing participants with DD and neurotypicals via an online testing platform.

***3.5 Exclusion/Inclusion Criteria:*** All participants will be native Hebrew speakers with no reported signs of sensory or neurological deficits and will come from middle-to-high socioeconomic status (SES) families. Inclusion criteria for the DD group are: (1) having a non-verbal IQs >85 as verified with the Test of Nonverbal Intelligence (Raven, 1990, 1993). 2) normal or corrected-to-normal vision and hearing; (3) absence of neurological and/or psychiatric disorders; (4) absence of SLIs [[70](#_ENREF_70)]; (5) absence of attention deficit disorders with hyperactivity according to the American Psychiatric Association, 2013 and MOXO test [[71](#_ENREF_71)], and (6) A score of at least one standard deviation below the mean in a single-word reading test [[72](#_ENREF_72)] or non-word reading test [[73](#_ENREF_73)]. Notably, because there are no standardized reading tests for adults in Hebrew, selection will be based on local norms from an independent sample collected at the Yahel Learning Disabilities Center at the University of Haifa. One standard deviation is chosen following the standard practice in the Hebrew literature [[74](#_ENREF_74)]. The control group will consist of participants of the same age with no reading problems who will be matched to the DD group in terms of cognitive ability. Tests are listed in **Table 1**.

***3.6 Classification into subgroups of dyslexia.*** We will follow the procedure adapted by [Schiff and Raveh [75]](#_ENREF_75) to classify participants with DD into 2 subgroups: surface and phonological. The participants will perform two tests of word decoding skills (orthographic decoding test and phonological decoding test). Discrepancy scores between the standard scores of the orthographic and phonological decoding tests will be used as a classification criterion with a cut-off of one standard deviation from the mean. The surface subgroup will consist of participants with very low phonological skill relative to their orthographic decoding skill, and vice versa for the phonological subgroup. All others will be considered as mixed (poor in both orthographic and phonological decoding skills).

***3.7 Procedural Learning Measures:*** In order to compare our results with the findings from previous studies, we propose an examination of common procedural learning tasks (see Table 2). These tasks are regarded as involving procedural learning in the sense that performance on these tasks relies on common features that indicate the involvement of procedural learning (e.g., resistance to dual task interference, sensitivity to feedback delay) or that involve the procedural memory system based on neuroimaging and patient studies (e.g., patients who have a medial temporal lobe/procedural memory dysfunction).As procedural learning tasks involve a mixture of procedural and declarative processes, we have chosen versions of each task that are most likely to tap the procedural memory system (e.g., probabilistic sequences, immediate feedback, or tasks that penalize accuracy when explicit strategies are used). We also chose tasks that can be administered online. Each task will be completed in a separate one training online session completed via Gorilla [[76](#_ENREF_76)]. For all procedural learning tasks described here, a study team member, watching live via videoconference, will supervise participants' performance. For each of the tasks described above we will also obtain pilot data, collected in person from neurotypicals, that will be compared to the online data to ensure successful adaptation of the tasks to online testing settings. Co-PI Holt has accumulated ample experience in conducting experiments via online platforms.

**Table 2- procedural learning measures**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Tasks** | **Domain** | **Modality** | **External Feedback** | **Modes of instruction** | **Indicators of procedural learning** | **Online testing (Y/N)** |
| Motor Sequence Tapping | Motor | Visual | No | Intentional | Imaging [[77](#_ENREF_77)], patients [[78](#_ENREF_78)]. | Y [[79](#_ENREF_79)] |
| Visuomotor Adaptation Task | Perceptual motor | Visual | No | Incidental | Behavior [[80](#_ENREF_80)], imaging [[77](#_ENREF_77)], patients [[81](#_ENREF_81)] | Y [[82](#_ENREF_82)] |
| Alternating Serial Reaction Time Task | Perceptual motor | Visual | No | Incidental | Behavior [[80](#_ENREF_80)], imaging[[83](#_ENREF_83)], patients [[81](#_ENREF_81)] | Y [[54](#_ENREF_54)] |
| Mirror Tracing Task | Perceptual motor | Visual | No | Intentional | Behavior [[80](#_ENREF_80)], patients [[81](#_ENREF_81)] | Y [[84](#_ENREF_84)] |
| Statistical Learning Task | Perceptual | Auditory | No | Incidental | Imaging [[85](#_ENREF_85), [86](#_ENREF_86)] | Y [[87](#_ENREF_87)] |
| Artificial Grammar Learning Task | Perceptual  cognitive | Auditory | No | Incidental | Behavior [[80](#_ENREF_80)], imaging, patients [[81](#_ENREF_81)] | N |
| II Category Learning Task | Cognitive | Auditory | Yes | Intentional | Behavior [[88](#_ENREF_88)], imaging, [[89](#_ENREF_89)] | Y [[90](#_ENREF_90)] |
| Weather Prediction Task | Cognitive | Visual | Yes | Intentional | Behavior [[91](#_ENREF_91)], imaging [[92](#_ENREF_92)], patients [[93](#_ENREF_93)] | N |

***Motor Sequence Tapping Task* –** The task and stimuli will be similar to that used in prior online research [[79](#_ENREF_79)]. Participants will be required to press four numeric keys on a standard computer keyboard with the fingers of their non-dominant hand (left hand), repeating the five-element sequence 4-1-3-2-4 as quickly and accurately as possible for a period of 30s.Throughout the finger-tapping trials, the numeric sequence will be displayed at the top of the screen. The session will consist of twelve trials of 30s, with 30s rest periods between trials.Learning will be calculated by the percent increase in correct sequences typed from the first trial to the average of the last three trials as in prior research [[78](#_ENREF_78), [94](#_ENREF_94)]. In addition, learning will be also measured by the tapping speed (keypresses) for correctly performed sequences [[95](#_ENREF_95)].

***Visuomotor Adaptation Task*** –Task and stimuli will be similar to that used in prior online research [[96](#_ENREF_96)]. Participants will be required to reach a visual target and will receive cursor feedback that follows a trajectory defined relative to the target and, importantly, will be not contingent on the position/trajectory of the participant’s actual movement. This task involves explicit and implicit processes. However, we will use a version that is more likely to tap implicit adaptation processes following prior research [[96; Experiment 1](#_ENREF_96)]. The session will include 230 trials (first 10 trials as baseline) with non-contingent feedback in which the angular offset of the feedback cursor from the target varies from trial to trial, both in direction (clockwise - or counterclockwise +) and magnitude (3°, 10°, 30°, 45°). The measure of adaptation is the change in hand angle on trial n + 1 as a function of the clamped rotation size on trial n as a function of rotation magnitude.

***Alternating Serial Reaction Time Task* –** The procedure will be similar to that employed in our prior research [[97](#_ENREF_97), [98](#_ENREF_98)]. Participants will be required to respond to a visual target presented in one of four possible locations by pressing a corresponding key. We will use probabilistic sequences following a study by [Howard [99]](#_ENREF_99" \o "Howard Jr, 2006 #71). The stimulus presentation will follow an eight-element sequence where the four odd-numbered elements follow a fixed sequence, and the even-numbered elements are selected at random (1r2r3r4r). The eight-element sequence will be repeated 10 times for each block. Participants will be presented with 21 blocks of 90 trials. Each of these blocks will begin with 10 random trials. Sequence learning will be calculated by comparing responses to high versus low-frequency triplets, over epochs, reflecting increasing sensitivity to the statistical structure of the sequence [[100](#_ENREF_100)]. To account for RT differences, we will also examine normalized RT differences between high and low-frequency triplets. We will assess the development of explicit knowledge as in prior research.

***Mirror Tracing Task*** *-* An online mirror-tracing task will be employed as in prior research [[84](#_ENREF_84)]. The display will have two rectangular canvases—the top canvas will be the ‘mirror’ and the bottom canvas will be the ‘drawing pad’. When the participants move the cursor within the drawing pad, it produces an inverted trail on the mirror but leaves no marks on the canvas. In each trial, the mirror presents a different complex line drawing, and the participant’s goal is to trace the drawing as precisely as possible within a 2-minute/trial time limit. Participants will complete a series of 6 consecutive mirror-tracing tasks. The score for each trial will be determined as the percentage of each trail within the target outline.

***Auditory Statistical Learning Task***– Task and stimuli will be similar to that used in our prior research [[62](#_ENREF_62)]. Participants will be exposed to a continuous auditory input of tones that will follow a predetermined sequential structure. A detection task will be employed (detecting repeating stimuli during familiarization) to make sure that participants are attending the task during the familiarization phase. Participants will be subsequently tested for recognition of novel short sequences that adhere to this statistical pattern. Learning will be measured by calculating the percentage of trials in which the structured sequence is identified, as in our prior research [[62](#_ENREF_62)]. Notably, a probabilistic structure that reduces the involvement of chunking, which relates to declarative processing, will be used. Furthermore, data collected in our lab (*N*=20) indicates that performance on this task is correlated with perceptual procedural learning performance (*r*=.45), but not with motor procedural learning or declarative learning performance. This provides evidence that the version that we will use overlaps with procedural learning mechanisms.

***Auditory Artificial Grammar Learning Task***. The procedure will follow [Conway and Christiansen [43]](#_ENREF_43). Participants will be informed that they will hear pairs of sequences. For each pair they will be required to decide whether the two sequences are identical or not (by pressing yes/no button). Twelve pairs of sequences will be used, six of which consist of the same sequence presented twice whereas the other six pairs consist of two different sequences. Each pair will be presented six times in random order for a total of 72 exposures. Before the test phase, participants will be informed that the sequences they heard were generated by a computer program that determined the order of the stimuli by using a complex set of rules. During the test phase participants will be asked to classify 20 new sequences according to whether they thought each sequence was generated by the same rules. The dependent measure will be the sensitivity index ["d prime" [101](#_ENREF_101" \o "Macmillan, 2004 #2314)] derived from the standardized hit rate (correct endorsement rate of grammatical test items) and false alarm rate (incorrect endorsement rate of non-grammatical test items).

***Auditory Information Integration Category Learning Task*** – The stimuli and task will be identical to those used in our prior research [[102; under review](#_ENREF_102)]. Participants will be required to categorize complex auditory stimuli that adhere to an implicit non-verbalizable rule by receiving feedback. They will complete eight 50-trial training blocks followed by 100 trials of generalization in which no feedback will be provided. Accuracy-based analyses will be performed using ANOVA tests as in prior research [31]. In addition to traditional statistical models, we will apply decision-bound computational models to understand learners’ strategies (hypothesis-testing, procedural, and guessing models).

***Visual Weather Prediction Task*** - Participants will be presented with arrangements of one to four cards on the screen, each of which is associated with a particular weather outcome (rainy or fine) similar to the method described by [Gabay [20]](#_ENREF_20" \o "Gabay, 2015 #300). A percent accuracy of chosen optimal outcome will be calculated. In addition to traditional statistical models, we will fit models based on trial-by-trial data to understand learners’ strategies (one-cue, singleton, multi-cue) as in prior research [[53](#_ENREF_53)]. Optimal accuracy in the task can be achieved by using multi-cue strategies. However, in the original version simple declarative strategies can achieve almost optimal accuracy [[103](#_ENREF_103)]. To circumvent this difficulty we will use a variant of the task [[104](#_ENREF_104)] in which the best single-cue strategy yields an accuracy far below optimum by adjusting the probabilities associated with specific stimuli.

**3.7 Study 1: Establishing an Online Psychological Testing Platform for Examining People with DD and Neurotypicals Across Multiple Measures of Procedural Learning.**

***Research questions: Is procedural learning a unified mechanism or componential capacity? Can it be measured reliably? Are there systematic challenges to procedural learning abilities in dyslexia that are best associated with dyslexia severity?*** If procedural learning is a unified ability, we expect to observe high correlations between the various assessments of procedural learning. If, however, there are multiple procedural learning subsystems [[41](#_ENREF_41), [42](#_ENREF_42)], we expect to find strong positive correlations across different tasks at the same level of a dimension (e.g. positive correlations between motor procedural learning tasks) and weaker correlations across tasks between dimensions (e.g. motor and perceptual tasks). Confirmatory and exploratory analyses will be used to identify whether there are shared and unique variations in procedural learning performance across the different measures, based on our hypothesized dimensions. Reliability measures will determine whether procedural learning is reliable. The results will help to discover systematic challenges in procedural learning in our DD sample.

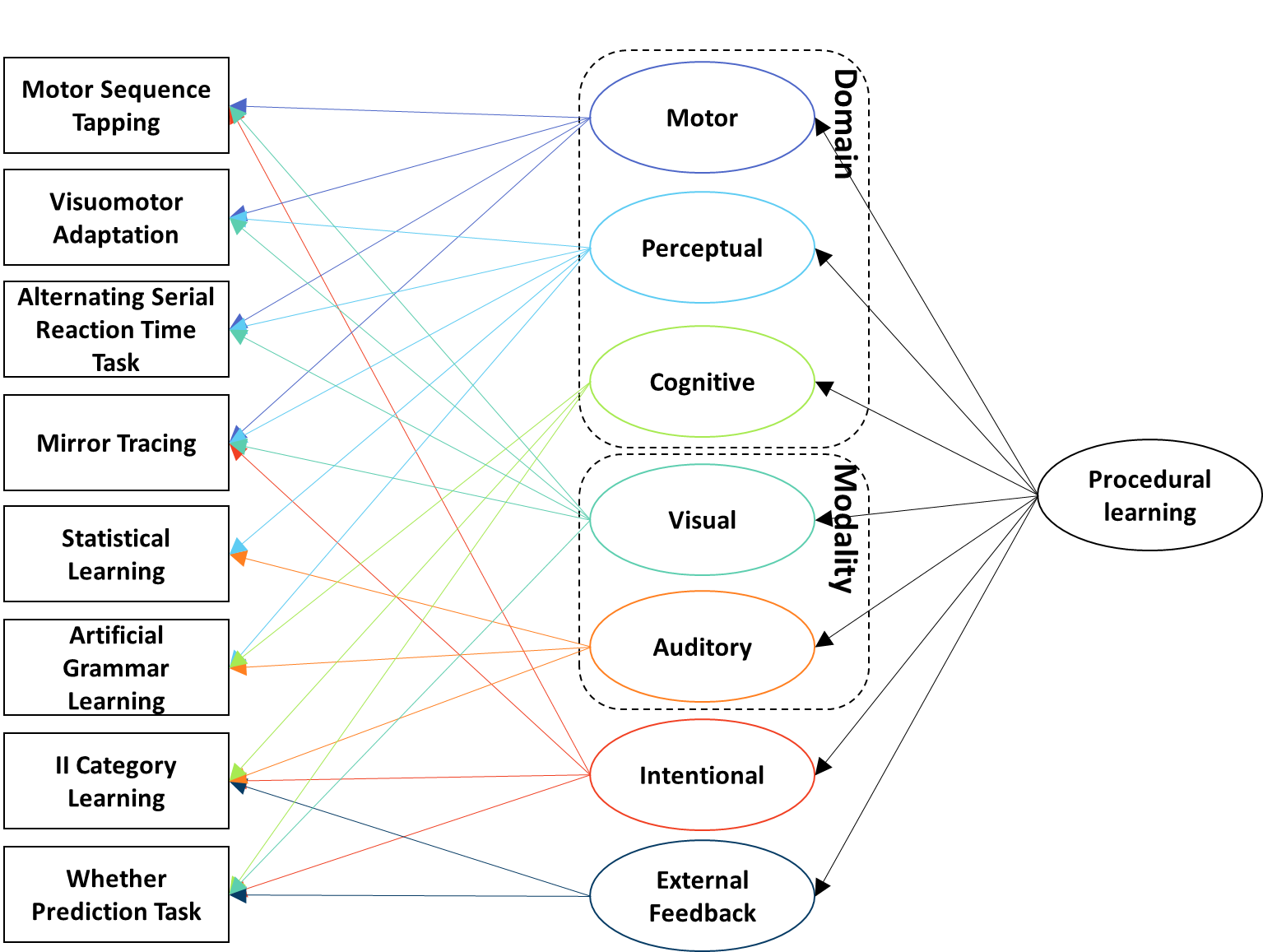
***3.7.1 Approach to Analyses.***

***Group Level Analyses***. We will examine whether there are differences across the DD and neurotypcials groups in all the procedural learning tasks described above using traditional statistical models (e.g., ANOVA tests or linear mixed-effect regression models). For some tasks, we will examine group differences in strategy use by applying decision-bound computational models.

***Reliability Assessments.*** We will first calculate reliability scores for each of our dependent measures separately for each group in order to examine whether it differs between the two groups. Reliability will be assessed by calculating the Spearman-Brown corrected split-half coefficient. A reliability coefficient at or above .70 will be considered an “acceptable” level of reliability [[105](#_ENREF_105)].

***Correlation Matrix.*** As a preliminary investigation we will use a correlation matrix for all procedural learning tasks to examine the simple Pearson correlations between tasks regardless of the facet of procedural learning performance. Bartlett’s test of sphericity will be used to test whether there exist substantial correlations between the measures to justify a factor analysis procedure.

***Confirmatory Factor Analysis***. Next, we will conduct a Confirmatory Factor Analysis (CFA) to examine our proposed multi-facet model (Domain, Type of Instructions, Feedback) of procedural learning (see **Figure 1**). Model fit will be assessed using CFI, TLI, GFI and RMSEA indices [[106](#_ENREF_106)]. will be done by comparing Bayesian Information Criterion (BIC), thus penalizing the greater model complexity (i.e., larger number of parameters) of the multi-faceted model. If procedural learning represents a unified ability then a model that contains a single procedural memory factor that encompasses all the procedural learning tasks will provide the best fit to the data. However, if procedural learning is a componential ability, then it is possible that a model containing all the different dimensions would provide the best fit to the data. Notably, we will also explore how specific facets are related to a second order latent factor (i.e., reflecting overall individuals’ differences in procedural learning ability across facets), to gain insights regarding the structure of procedural learning as a theoretical construct. Modification indices will be examined as needed, and theoretically sound covariances or loadings will be added if necessary. Assuming a good model fit, we will examine potential group differences in the structure and measurement of procedural learning by testing for a lack of measurement invariance between the groups. Lastly, we will compute factor scores for dyslexic and control participants. The factor scores will then be compared between the two groups and correlated with literacy scores.

***Exploratory Factor Analysis.*** Additionally, we will use exploratory factor analysis (EFA) to identify latent dimensions of procedural learning ability and to explore the possibility of shared and unshared variance across all the procedural learning tasks. The number of factors to be extracted will be selected according to the amount of variance explained, using the Keiser criterion a scree plot. The minimum loading of a factor will be 0.32 [[107](#_ENREF_107)]. Factor values that exceed 0.4 will be considered as having high uniqueness values [[108](#_ENREF_108)]. If there is a general shared process across the different procedural learning tasks, we expect to see that all procedural learning tasks load on the same factor. Alternatively, converging evidence could be found if the same dimension that was found as informative in the CFA is also found as a loading factor in the EFA. However, it is also possible that additional factors will emerge from the exploratory analysis, representing different important dimensions that differentiate the processes involved in various procedural learning tasks. Lastly, we will compute factor scores for dyslexic and control participants. The factor scores will then be compared between the two groups and correlated with literacy scores.

**Figure 1**: Proposed multi-faceted model of procedural learning, with a possible second order unifying latent factor.

**3.8 Study 2 -** **Developing A Machine Learning-Based Diagnosis Support System for Identifying Developmental Dyslexia**.

***Research question: Can dyslexia be identified on the basis of procedural learning functions*?** The large-scale online study we propose invites the possibility of examining whether DD can be identified based on performance on procedural learning measures. Here the data we collected in the first study will be analyzed according to machine learning algorithms.

***3.8.1 Approach to Analyses:*** A Machine Learning algorithm based on bagged decision trees [[109](#_ENREF_109), [110](#_ENREF_110)] will be designed to be sensitive enough to detect a behavioral pattern for each group of participants and classify them into two groups (i.e., DD vs. neurotypcials). The use of bagged decision trees facilitates accurate classification in the presence of large variance in the measures within each group as these trees allow for a large number of repetitions of the classification process in different configurations of the input variables. Thus, even subtle trends will manifest themselves in the classification results. Once the classification rules are inferred, group membership for each new (unclassified) participant will be predicted according to his/her procedural learning task scores.

In the proposed study, different procedural learning measures (See Table 2) will be obtained for each participant. A binary classification (DD or neurotypical) will be assigned to each participant based on inclusion criteria described above (p.). The procedural learning measures will be used as input features to train the ML models to predict participants' classification. To infer the importance of each behavioral measure in the diagnosis, following training of the ML model, feature ranking will be performed [[111](#_ENREF_111)] where the contribution of each feature to the prediction is evaluated and ranked. Very low-ranking features will be excluded, and the ML model retrained. The resulting high-ranking features will be considered and assessed for their relation to DD and underlying mental processes. Model training will follow an N-fold Cross Validation protocol [[111](#_ENREF_111)] where the data samples are divided into N equal sized subsets. Each subset in turn is set aside and used for testing a model trained on the remaining samples. Statistics on the accuracy of the N folds provide the outcome of the ML modeling.

***3.8.2 Cluster Analysis.*** We acknowledge that DD is a heterogeneous phenomenon that might originate from different deficits and includes several subtypes [[112](#_ENREF_112), [113](#_ENREF_113)]. Phonological and surface DD are the main two subtypes that have been identified. In order to detect potential sub-groups within the DD participants, their behavioral patterns will be subjected to a hierarchical cluster analysis, based on a standardized Euclidian distance metric, using a centroid clustering approach such as K-means. Number of groups will be selected based on visual inspection of the resulting dendrogram.

4. **Respective roles of the Israeli and American principal investigators.** Our collaboration capitalizes on the complementary strengths of our research team. Dr. Holt’s expertise is in auditory cognitive neuroscience, with a focus on procedural learning in the auditory domain. Several of the proposed experiments are based on prior research conducted in her laboratory. Her ample experience in conducting experiments in both offline and online settings, with neurotypicals and individuals with DD, is vital for the successful implementation of the proposed research. Dr. Gabay is an educational psychologist with substantial experience in psychoeducational assessments. She will be contributing her substantial expertise in examining various procedural learning functions in neurotypicals and DD. Dr. Gabay and Prof. Holt have both been involved in the design of the study and in the preparation of this proposal, and will both be involved in project management, data analysis, interpretation of results, and the writing up and dissemination of the findings. This collaboration presents a unique opportunity to conduct a large-scale investigation by combining different basic science disciplines that will be united to inform the study of procedural learning in dyslexia and neurotypicals.

**5. Risk Analysis and Alternative Paths.** *Adapting tasks to online environments.*There is a risk of difficulty in adapting the tasks to an online testing platform. However, several of the tasks have already been successfully administered . Furthermore, we will conduct pilot studies to ensure the successful online implementation of tasks*. Participant Attrition.* The project is ambitious in that it involves common multiple assessments of learning across diverse participant groups. Mitigating this risk, each of the investigators has extensive experience in running multi-session experiments. We have structured our participants’ payments to encourage low dropout rates. *Participant Recruitment*. There is a risk that we will not be able to recruit a large sample of participants with DD. However, the online testing platform and our long experience with recruiting participants with DD mitigates this difficulty. Dr. Gabay has developed partnerships within and outside the university, enabling her to reach out to individuals with DD (see letters of support) and there is currently a sample of 100 DD and matched controls in Dr. Gabay's lab that is available to participate in online studies.

**6. Available U.S. and Israeli Resources.** Prof. Holt has laboratory space in Carnegie Mellon University’s Baker Hall with computer workstations available for stimulus analysis, editing, and synthesis. Prof. Holt will lead stimulus creation, task design, and pilot testing of the protocols. Dr. Gabay is an educational psychologist by training, with many years of clinical experience in conducting psychoeducational assessments in children and students with learning disabilities. At the University of Haifa, Dr. Gabay founded the Learning and Language Laboratory. Recruiting of participants with DD is a well-established routine in her lab, which currently has a large pool of participants with DD (N=100) and matched neurotypicals (N=100) who come to the lab to participate in different experiments across multiple sessions and will be available to participate in the online study. Dr. Gabay's partnership with Dr. Lerner, Mr. Dula, and Ms. Gorelick affords excellent access to additional participants with DD (see Letters of Support). Dr. Noam Siegelman and Prof. Hagit Hel-or will serve as consultants for the proposed research. Dr. Siegelman is a senior lecturer at the Hebrew University of Jerusalem in Israel. He is a leading expert in the fields of statistical learning and reading and has substantial experience in studying multifaceted phenomena using factor analytic approaches. Dr. Siegelman will provide theoretical and statistical guidance for study 1 (see Letter of Support). Prof. Hagit Hel-Or is a professor in the computer science department at the University of Haifa and head of the Computational Human Behavior lab. Prof Hel-Or has substantial experience with implementing ML algorithms to study various cognitive and motor aspects of human behavior. Prof. Hel-or will be available to provide theoretical and computational support for Study 2 (see Letter of Support).

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