The nature of procedural memory deficits in specific language impairment: An investigation using the serial reaction time task

by

Gillian Maree Clark
BSc, GDip(Psych)

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Abstract

This thesis examined the nature of procedural learning problems in specific language impairment (SLI). The ‘Procedural Deficit Hypothesis’ (PDH) has claimed that abnormalities in the cortico-striatal networks that support the procedural memory system underlie the core language deficits in SLI. Consistent with this position, a growing number of studies have demonstrated poor procedural memory in SLI. However, less studied aspects of the PDH are claims that poor procedural memory not only impacts on learning and using grammar, but also leads to deficits in other areas such as motor and reading skills.

Study 1 examined whether a common procedural memory task – the serial reaction time task (SRTT) – is a valid measure of procedural memory system functioning. This study was a meta-analysis of SRTT performance in individuals with neurodegeneration of neural structures that underpin the procedural system. Results confirmed that the task relies on the integrity of the procedural memory system. Studies 2 and 5 examined whether poor procedural memory was associated with deficits in grammar, reading, and motor skills. In Study 2 a second-order meta-analysis was conducted that compared procedural memory problems, assessed by the SRTT, in SLI and disorders of reading (dyslexia) and motor skills (developmental coordination disorder). Study 5 examined the relationship between grammar, reading, and motor problems within a sample of children with and without SLI. Collectively the results of Study 2 and Study 5 indicate that procedural memory is associated with a wide range of problems. However, in SLI there is no clear association between procedural memory and grammar, reading, or motor skills.

Another aspect of the PDH investigated in this thesis concerns the specificity of the procedural learning problems. In the SLI literature, procedural memory has been most widely examined using the SRTT, which involves the implicit learning of a visuomotor
sequence. To date, children with SLI have been tested on their ability to implicitly learn first-order conditional (FOC) and second-order conditional (SOC) sequences. FOC sequences are thought to rely heavily on cortico-striatal networks, while SOC sequences are thought to rely on neural regions outside these networks. Study 3 examined whether children with SLI are poorer learning both types of sequence. Study 4 elucidated the neural mechanisms that underpin FOC and SOC implicit sequence learning using transcranial magnetic stimulation. The results of these studies revealed that in SLI, it is the implicit learning of FOC sequences that is primarily affected. In Study 4, it was demonstrated that the implicit learning of FOC sequences predominantly relies on structures of the brain that underpin the procedural memory system.

Overall, the research presented in this thesis indicates that SLI is associated with an implicit sequence learning deficit that is primarily associated with parts of the brain that comprise the procedural memory system. That is, the basal ganglia and cortico-striatal networks. However, the way in which the procedural memory problems relate to the language and co-occurring deficits in SLI remains to be revealed.
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Chapter 1

General Introduction

Specific language impairment (SLI) is a developmental disorder characterised by difficulties in understanding and using language (Bishop, 2014; Leonard, 2014). The language problems occur in the absence of hearing problems, clear neurological damage, environmental deprivation, or intellectual impairments (American Psychiatric Association [APA] 2013). SLI is a common disorder estimated to affect approximately 7% of children (Tomblin et al., 1997). Children with SLI are late to begin talking, usually uttering their first words up to a year later than typically developing children (e.g., Trauner, Wulfeck, Tallal, & Hesselink, 2000). While some late-talkers show no signs of language difficulties by the time they are of school-age, children with SLI continue to lag behind their peers (Roos & Ellis Weismer, 2008; Whitehurst & Fischel, 1994). The difficulty these children have with producing and understanding language can lead to enduring academic and social problems (St Clair, Pickles, Durkin, & Conti-Ramsden, 2011; Tornqvist, Thulin, Segnestam, & Horowitz, 2008; Wadman, Durkin, & Conti-Ramsden, 2011).

While the language problems are the core deficit in SLI, affected children commonly present with a range of cognitive deficits. Children with SLI have been found to have poorer working-memory (Vugs, Cuperus, Hendriks, & Verhoeven, 2013), social cognition (Botting & Conti-Ramsden, 2008), attention skills (Ebert & Kohnert, 2011), and slower processing speeds (Kail, 1994) when compared to children without language impairments. Children with SLI can also present with comorbid disorders. Approximately half of children diagnosed with SLI also meet criteria for dyslexia (McArthur, Hogben, Edwards, Heath, & Mengler, 2000). Over a third of children with SLI also have motor deficits that allow diagnosis of developmental coordination disorder (Flapper & Schoemaker, 2013). Finally,
rates of autism spectrum disorder in groups with SLI are ten times higher than in the general population (Conti-Ramsden, Simkin, & Botting, 2006).

Two main classes of theories have been proposed to account for SLI; domain-specific and domain-general. Domain-specific theories have focused on the linguistic deficits, and claim that the language problems stem from dysfunction of a particular grammar module (Rice, Wexler, & Cleave, 1995; van der Lely, Rosen, & McClelland, 1998). Domain-general theories claim that the language, motor, and cognitive deficits in SLI arise from problems in one or more systems used for processing, learning, or storing any type of information (Baddeley, Gathercole, & Papagno, 1998; Gathercole & Baddeley, 1990; Kail, 1994; Tallal, 2004; Tallal, Stark, & Mellits, 1985). One domain general theory, which is the focus of this thesis, is the Procedural Deficit Hypothesis (PDH; Ullman & Pierpont, 2005). The PDH proposes that the underlying cause of SLI is an abnormality of the neural structures which underpin the procedural memory system. An impairment to this memory system is hypothesised not only to lead to language problems, but also problems in other abilities and skills that rely on the same structures.

**Research Aims**

Since the PDH was proposed, a substantial number of studies have investigated procedural memory in SLI (Lum, Conti-Ramsden, Morgan, & Ullman, 2014; Obeid, Brooks, Powers, Gillespie-Lynch, & Lum, 2016). Overall, groups with SLI have been shown to have poorer procedural memory than non-language impaired groups (Obeid et al., 2016). However, there is substantial variability in individual study findings, with some reports of intact procedural memory in SLI (e.g., Desmottes, Maillart, & Meulemans, 2017a; Desmottes, Maillart, & Meulemans, 2017b; Gabriel, Stefaniak, Maillart, Schmitz, & Meulemans, 2012; Hsu & Bishop, 2014; Lukacs & Kemeny, 2014). Furthermore, it is not
clear whether the procedural memory problems relate specifically to the language problems, or to co-occurring reading, motor, or social skills deficits. One suggestion forwarded to account for discrepancies in study findings is that the deficit is specific to tasks that assess sequence learning (Hsu & Bishop, 2014). One aim of this thesis is to investigate whether the deficit is even more specific to sequences of a particular structure. The second aim of this thesis is to investigate the extent to which procedural memory deficits in SLI relate to the language problems.

**Thesis Overview**

This thesis is presented in nine chapters. Chapters 2 to 4 comprise a literature review. In Chapter 2, the linguistic problems in SLI are described. This is followed in Chapter 3 by an outline of the comorbid conditions. In Chapter 4, the PDH is detailed, and evidence for the PDH of SLI is discussed. It is argued that while there is evidence for procedural problems in SLI, it is not yet clear how specific these problems are, nor whether these problems are causally related to the language impairments. Chapter 5 (Study 2) presents a second-order meta-analysis that compares procedural memory problems across a range of disorders using the serial reaction time task (SRTT). Chapter 6 (Study 3) investigated sequence learning in SLI. Chapter 7 (Study 4), used transcranial magnetic stimulation to investigate the neural regions responsible for learning different types of sequence. The final study (Study 5), presented in Chapter 8, investigated the relationship between procedural memory, grammar, reading, and motor skills in children with and without SLI. Finally, Chapter 9 consists of a general discussion of the overall thesis findings.
Chapter 2

The Language Problems in Specific Language Impairment

Individuals with specific language impairment (SLI) have an uneven profile of language ability, with grammatical skills being poorer than lexical skills (Leonard, 2014). This chapter summarises research that has examined the linguistic profile in SLI. While SLI is present across languages (Leonard, 2014), this chapter will focus on English.

2.1 Expressive and Receptive Grammatical Deficits in SLI

The defining feature of SLI appears to be problems using and understanding grammar (Rice, 2000). Grammar refers to the rules or conventions (depending on one's theoretical orientation; Chomsky, 1981; MacWhinney & Bates, 1989) in a language that exist for combining words and parts of words, such as prefixes and suffixes, to create sentences that can be understood by all speakers of the language (Baker & Hengeveld, 2012). Substantial evidence has accumulated that demonstrates children with SLI have difficulties with grammar in the expressive and receptive domain.

2.1.1 Expressive language in SLI. Expressive language refers to the ability to orally create a sentence or phrase that can be understood by others (Hoff-Ginsberg, 2005). Research has shown that the sentences and phrases spoken by children with SLI are shorter and contain more grammatical errors in comparison to non-language impaired children of the same age (Conti-Ramsden, Botting, & Faragher, 2001; Fletcher, 2009; Norbury & Bishop, 2003; Rice et al., 2010). This has often been demonstrated by examining the mean length of utterance (MLU) of children with specific language impairment. A child’s MLU is obtained by recording their spoken language for at least 10 minutes and dividing the total number of morphemes into the total number of sentences or utterances spoken (Miller & Chapman, 1981). Morphemes are the smallest unit of meaning in a language (Baker & Hengeveld,
For example, the word ‘play’ is a single morpheme, and the words ‘played’ or ‘playing’ comprise two morphemes. This is because the suffixes ‘-ed’ and ‘-ing’ both convey meaning. These two suffixes indicate whether an event has occurred in the past or is currently ongoing. Children proficient in the use of grammar typically have a higher MLU (Miller & Chapman, 1981; Rice, Redmond, & Hoffman, 2006). The relationship between MLU and grammar is demonstrated when considering the two utterances: “Tammy put food” which contains three morphemes, and “Tammy putting food floor” which contains five morphemes (Leonard, 2014). The shorter utterance shows a poorer understanding of the arguments requirements for the verb ‘put’ than the longer utterance. Due to the relationship between MLU and grammatical complexity, MLU is often taken as an estimate of general grammatical proficiency or developmental language level, particularly for children in the early stages of language development (Blake, Quartaro, & Onorati, 2008; Rice et al., 2006).

It has been repeatedly found that children with SLI have lower MLU in comparison to typically developing (TD) children of the same age (Bishop & Adams, 1990; Hewitt, Hammer, Yont, & Tomblin, 2005; Rice et al., 2010; Rice, Wexler, Marquis, & Hershberger, 2000). For example, Hewitt et al. (2005) examined MLU in a group of 27 children with SLI and 27 TD children. The mean age for each group was 6;0 (years; months). Utterances were elicited by reading the child a story and asking the child to re-tell it. A mean of 98 utterances were recorded from the SLI group, and 105 from the TD group. The MLU of the SLI group was found to be significantly lower than that of the TD group. Specifically, the SLI group produced utterances that comprised an average of 5.82 morphemes, while the TD group produced an average of 6.86 morphemes per utterance. The MLU of children with SLI is typically found to be comparable to that of TD children approximately two years younger (Rice et al., 2010). Indeed, it has been repeatedly found that children with SLI aged approximately 5-years-old have a MLU that is comparable to TD children aged
approximately 3-years-old (Krantz & Leonard, 2007; Leonard, Caselli, Bortolini, McGregor, & Sabbadini, 1992; Moore & Johnston, 1993; Oetting & Horohov, 1997; Rice et al., 1995; Riches, Tomasello, & Conti-Ramsden, 2005; Watkins, Kelly, Harbers, & Hollis, 1995).

In addition to using shorter, less complex sentences, it has also been repeatedly found that children with SLI make more grammatical errors in their speech than would be expected given their age (e.g., Bedore & Leonard, 1998; Conti-Ramsden, Botting, & Faragher, 2001; Fletcher, 2009; Lum & Bleses, 2012; Norbury, Bishop, & Briscoe, 2001; Oetting & McDonald, 2001; Rice & Wexler, 1996; Schuele & Tolbert, 2001). Errors typically take the form of omitting function words or grammatical morphemes in obligatory contexts. Function words that are commonly omitted include forms of ‘be’ and ‘do’ such as ‘is’, ‘are’, ‘am’, ‘was’, ‘were’, ‘did’ (e.g., “She is/was walking”; “He does/did not run”), and the word ‘that’ in sentences such as “I was scared of the dog that chased us” (Hadley & Rice, 1996; Leonard, Eyer, Bedore, & Grela, 1997; Owen & Leonard, 2006; Rice & Wexler, 1996; Schuele & Tolbert, 2001). For children with SLI speaking Germanic languages, the most common grammatical errors made are the omission of past-tense ‘-ed’, and third-person singular ‘-s’ (i.e., “Jack plays piano”) (Conti-Ramsden, Botting, & Faragher, 2001; Krok & Leonard, 2015; Rice & Wexler, 1996).

There are two common methods of assessing the omission rates of specific grammatical morphemes in SLI. One method involves analysing samples of spontaneous speech (Leonard et al., 1997; Rice & Wexler, 1996). In this type of task, children are encouraged to converse with an experimenter. The experimenter presents toys or asks conversational questions to facilitate dialogue with the child. The child’s speech is recorded for later analysis. The variable of interest is the number of times the grammatical morpheme of interest is produced as a proportion of times its use was obligatory. For example, if
examining the use of past tense ‘-ed’, a score of 60% might indicate that a child produced 10 utterances in which this tense marker was necessary, but only produced it in six of them. The second method commonly used to assess omission rates in SLI is using specific probing sentences (Marchman, Wulfeck, & Ellis Weismer, 1999; Rice et al., 1995). To probe production of past tense ‘-ed’ children are shown a picture, along with a spoken sentence such as “This boy is walking. He walks every day. Yesterday he….” (Marchman et al., 1999). Similarly, to probe use of third-person singular ‘-s’, a picture is shown along with a spoken sentence such as “This is a fire fighter. If I’m a teacher and I teach, he’s a fire fighter so he…” (Rice et al., 1995). The dependent variable for this method is the percentage of correct responses. For example, if 10 probing sentences are presented and a child produces the correctly inflected verb in eight out of 10 occasions, the score would be 80%.

Children with SLI have been shown to perform more poorly than age-matched TD children on both spontaneous speech and sentence probe tasks. On spontaneous speech elicitation tasks, children with SLI more frequently omit third person singular ‘-s’ and past tense ‘-ed’ compared to TD children of the same age (Eadie, Fey, Douglas, & Parsons, 2002; Leonard et al., 1992; Leonard et al., 1997; Norbury et al., 2001; Redmond, 2003; Rice & Wexler, 1996). For example, Rice and Wexler (1996) examined spontaneous speech samples of 37 children with SLI (mean age 4;10) and 45 TD children matched on age (mean age 5;0). The speech samples of each child contained at least 200 utterances. Spontaneous use of both third-person singular ‘-s’ and past tense ‘-ed’ were recorded. Scores were given as the percentage of times a correctly inflected verb was produced as a total of all obligatory contexts. The SLI group correctly produced each inflection significantly less consistently than the TD group. Specifically, the SLI group correctly produced the third-person singular ‘-s’ inflection in 36% of utterances that required it, while the TD group did so for 88% of
required cases. Similarly, past tense ‘-ed’ was produced by the SLI group in 22%, and the TD group 92%, of obligatory occasions.

When production of third person singular ‘-s’ and past tense ‘-ed’ are measured via sentence probe tasks, children with SLI also perform more poorly than age-matched TD children (Conti-Ramsden, 2003; Hoover, Storkel, & Rice, 2012; Leonard et al., 2003; Leonard et al., 1997; Marchman, 2004; Marchman et al., 1999; Moore & Johnston, 1993; Redmond, 2003, 2005; Rice & Wexler, 1996). This has been shown across ages ranging from 4;10 (Rice & Wexler, 1996) to 8;10 (Marchman, 2004). While the consistent finding is that the SLI group performs more poorly than the TD group, there are differences between studies in the extent of this deficit. The study by Rice and Wexler (described above) examined the grammatical skills of 37 5-year-old children with SLI and 45 age-matched TD children. In that study, the SLI group correctly produced the ‘-ed’ inflected verb in response to the probing sentence for 27% of sentences, whereas the TD group did so for 92% of sentences. Marchman (2004) also found significantly poorer performance in SLI, though the size of the difference between the two groups was smaller. In that study, 27 children with SLI were compared to 27 age-matched TD children. The mean age of the children with SLI was 8;10, and the TD group’s 7;6. In the study, the SLI group correctly produced an inflected verb on around 70% of trials and the TD group did so for approximately 85% of trials.

The omission of inflectional morphemes in SLI continues into late childhood (Conti-Ramsden, Botting, & Faragher, 2001). Conti-Ramsden, Botting, and Faragher (2001) examined inflectional morphology use in 160 children with SLI and an age-matched control group of TD children. The mean age of the children in the study was 10;9 years. Sentence probe tasks assessing production of ‘-ed’ and third-person singular ‘-s’ inflections were both
administered. In this study, Conti-Ramsden, Botting, and Faragher (2001) analysed whether omission rates of each inflection could accurately distinguish between SLI and TD groups. Omission of the third-person singular ‘-s’ inflection was found to distinguish between groups with an overall accuracy of 74%. Omission of the ‘-ed’ inflection was found to distinguish between children with and without SLI with 80% accuracy. This study indicates that even in late childhood, the omission of verb-related grammatical morphemes can be indicative of specific language impairment.

Children with SLI omit obligatory grammatical markers not only more often than TD children of the same age, but also younger children matched on MLU (e.g., Eadie et al., 2002; Redmond, 2003; Rice & Wexler, 1996). When examining the language skills of children with SLI, studies have compared the language impaired children to two control groups (e.g., Montgomery, 2004; Rice & Wexler, 1996; Watkins et al., 1995). One control group comprises TD children who are matched to the SLI group on the basis of chronological age. The other control group comprises TD children who are matched to the SLI group on the basis of general language skills using a score from a standardised language test (e.g., Montgomery, 2000, 2004; Norbury, Bishop, & Briscoe, 2002) or MLU (e.g., Redmond, 2003; Rice & Wexler, 1996; Watkins et al., 1995). Using these two control groups the following inferences are made depending on the pattern of differences. If performance is poorer than age-matched TD children, but equivalent to MLU-matched children, it indicates that performance can be attributed to delayed grammatical development. However, if performance by the SLI group is poorer than both control groups, it indicates that children with SLI are performing even lower than expected by their general grammatical proficiency.

While dual comparison groups are used regularly in SLI research, Plante, Swisher, Kiernan, and Restrepo (1993) noted that there are limitations to this approach. One limitation
relates to the potential for age to confound interpretation of findings. In comparing a group with SLI to a younger group matched on language, results are generally attributed entirely to language variables. However, this disregards that the two groups also differ on age-related variables including cognitive, social, and physical experiences, which may also contribute to task performance (Plante et al., 1993). A second limitation relates to the variability of language skills within and between individuals. Some studies match groups on a composite score reflecting averaged performance on a range of language abilities. Matching in such a way overlooks possible differences in the pattern of strengths and weaknesses, which may also contribute to differences in performance on the measure of interest (Plante et al., 1993). A third limitation relates specifically to the use of MLU as the matching variable. While MLU is often taken as a measure of general language or grammatical proficiency, this index does not provide information about the proportion of grammatical morphemes versus content words within the utterances. Thus, groups might match on MLU, though differ in the types of words or morphemes that contribute to the utterances. Alternatively, if the utterances of both groups contain predominantly content words without grammatical morphemes, the two groups may match on expressive vocabulary rather than language proficiency more broadly. Due to these limitations, the findings presented in this section must be interpreted with caution.

Children with SLI omit grammatical morphemes more frequently than non-language impaired children of comparable MLU. This has been shown repeatedly using spontaneous speech (Eadie et al., 2002; Leonard et al., 1992; Redmond, 2003; Rice & Wexler, 1996) and probe tasks (Leonard et al., 2003; Leonard et al., 1997; Moore & Johnston, 1993; Redmond, 2003; Rice & Wexler, 1996). In the study by Rice and Wexler (1996) the grammatical skills of the children with SLI were also compared to an MLU-matched control group comprising 40 children (mean age 3;0). When the production of inflectional morphology was assessed
using spontaneous speech samples, the SLI group produced the third-person singular ‘-s’ inflection 36% of the time in obligatory contexts. This was significantly less than the MLU-matched group, who produced the third-person singular ‘-s’ in 61% of obligatory contexts. Similarly, for the past tense inflection, the SLI group produced this 22% of the time in obligatory context which was significantly less than the MLU group’s 48%. Results from the sentence probe tasks were similar. For the third-person singular ‘-s’ inflection, the SLI group produced this correctly in 23% of trials, while the MLU-matched group did so for 44% of trials. Finally, for the ‘-ed’ probing sentences, the SLI group correctly responded in 27% of trials which was significantly less consistent than the MLU-matched group’s 44%. These findings further show that the grammatical skills of children with SLI are lower than expected given their overall language skills. This indicates that there is something about grammar that children with SLI struggle to use.

It should be noted that not all grammatical morphemes are equally affected in SLI (e.g., Rice & Wexler, 1996). For instance, it has been shown that use of progressive ‘-ing’ as in ‘The man is walking’ is relatively less problematic for children with SLI (Eadie et al., 2002; Leonard et al., 2003; Rice & Wexler, 1996). Studies investigating use of ‘-ing’ in 5-year-old children with SLI have found correct use in approximately 90% of obligatory contexts, whether measured via spontaneous speech (Eadie et al., 2002; Rice & Wexler, 1996) or sentence probe (Leonard et al., 2003) tasks. The consistency children with SLI use the progressive grammatical morpheme is at a level that is comparable to non-language impaired children of comparable age (Leonard et al., 2003; Rice & Wexler, 1996) and MLU (Eadie et al., 2002; Leonard et al., 2003; Rice & Wexler, 1996). Thus it is not the case the use of all morphological inflections are impaired in SLI.
2.1.1.1 Development of expressive language. While children with SLI regularly omit some grammatical morphemes in speech, the error rate does decrease (Rice et al., 2010; Rice, Wexler, & Hershberger, 1998). That is, their expressive language skills with respect to grammar certainly improve over time. This can be seen in a longitudinal study by Rice et al. (2010). This study examined MLU in 170 children with SLI and 136 age-matched TD children. At the first round of testing the mean age of the children was 2;6. At the final round of testing children were aged 9;0 years. MLU was measured at 6-month intervals, and was acquired by recording the spontaneous speech of children for around 20-30 minutes at each time point. As shown in Figure 2.1, MLU for the SLI group increased in a linear manner over time. At the first time point the mean MLU of the SLI group was 2.59, and this increased to 4.97 at the final round of testing. The study also showed that the MLU of the children with SLI still lagged behind those of the TD at all rounds of testing. Thus over the age ranges studied, while the SLI group still improved, they did not catch up to the TD group.

![Figure 2.1. Mean length of utterance (MLU) in children with and without SLI. Adapted from Rice et al. (2010).](image)
Children with SLI also make gains over time with respect to the production of specific grammatical morphemes. Rice et al. (1998) examined regular past tense and third person singular use in children with SLI. The SLI group comprised 21 children and their production of the inflections were studied longitudinally from the age of 5;0 to 8;0 at six month intervals. Data from this study are re-produced in Figure 2.2. On the spontaneous speech task, correct use of third person singular ‘-s’ increased from about 35% at age 5;0, to about 90% at age 8;0. For past tense ‘-ed’ correct use increased from 20% at age 5;0 to about 80% at age 8;0. The errors children with SLI make with respect to the studied grammatical morphemes decreased over time. A similar result was shown when performance was measured via

![Figure 2.2 Longitudinal data of performance on spontaneous speech tasks for third-person singular ‘-s’ (Panel A) and past tense ‘-ed’ (Panel B). Bottom row shows performance on sentence probe tasks for third person singular ‘-s’ (Panel C), and past tense ‘-ed’ (Panel D).]
sentence probe tasks. Correct use of the third person singular inflection increased from 20% at age 5;0 to above 90% at age 8;0. Correct use of regular past tense increased from around 30% at age 5;0 to approximately 85% at age 8;0. However, as shown in Figure 2.2, at all time points, the accuracy of the children with SLI producing the target grammatical morphemes was lower than the age-matched control group. The consistency with which inflections were produced in the TD group approached 100% between 5 and 6 years of age. In the SLI group, comparable levels of consistent production were not reached even in the final round of testing in which the children were 8;0 years of age.

2.1.2 Receptive language in SLI. Children with SLI also demonstrate problems with comprehending or understanding spoken sentences (e.g., Bishop & Adams, 1992; Montgomery, 1995; Montgomery & Evans, 2009; van der Lely & Stollwerck, 1997). Grammar is needed to understand phrases and sentences. For example, consider the sentence “The girl chased the boy”. This sentence follows a subject-verb-object structure which is highly frequent in the English language. Comprehension of this sentence requires understanding that the subject, which is the first noun phrase of the sentence (i.e., the girl), affected or acted on the object which is the second noun phrase (i.e., the boy) of the sentence. An understanding that the verb ‘chased’ specifies what activity was done, and that the ‘-ed’ indicates that this occurred in the past is also required. Comprehending sentences spoken in real time requires an understanding of grammar, in order to correctly follow how the different elements in a sentence relate to each other (Bishop, 2014). Leonard (e.g., Leonard et al., 1992; Leonard et al., 1997) further highlights that comprehending language must be done quickly. According to Leonard, comprehending speech in real time depends on the quick execution of a number of processes. For example, comprehending the regular past tense inflection affixed to a verb requires detect the inflection and processing the verb. This analysis must occur fast enough to allow further processing of forthcoming words.
Oral language comprehension in SLI has been assessed using sentence-picture matching tasks (Bishop, 2003; van der Lely & Harris, 1990; Waters, Caplan, & Rochon, 1995). In these tasks, children hear a sentence and view two to four pictures. The child is tasked with pointing to the picture that matches the sentence. One picture matches the sentence, while the remaining pictures are foils. For example, for the stimulus sentence “The girl is pushing the boy”, the foil pictures might include a picture of a boy pushing a girl, a picture of a girl pushing a cow, and a picture of a cow pushing a boy. In order to point to the correct picture, children require not only an understanding of the words ‘girl’, ‘boy’, and ‘push’, but also how these words or concepts relate to each other based on the grammatical structure of the sentence (Bishop, 2014). The dependent variable for these tasks is the total or percentage of correct responses.

Using the aforementioned task, sentence comprehension in SLI has been found to be poorer when compared to TD children of comparable age (e.g., Bishop, 1979; Montgomery, 2000; van der Lely, 1996). This is especially the case for relatively long (e.g., Montgomery, 2000, 2004), or passive (e.g., Marinis & Saddy, 2013; van der Lely, 1996) sentences. In relation to sentence length, Montgomery investigated comprehension of short and long active sentences in a series of studies (Montgomery, 1995, 2000, 2004). In this work sentences such as “The girl smiling is pushing the boy”, and long sentences such as “The girl who is smiling is pushing the boy” were presented to children with and without SLI. The number of participants in each of the three studies were similar (12 to 14 per group), and the SLI group were of similar age (mean age between 8;2 and 8;9). In addition to the SLI and age-matched groups, Montgomery (2000) and Montgomery (2004) included groups of 12 children matched on receptive language measures (mean age 6;8 or 6;10). The SLI group correctly comprehended a high number of the short sentences with accuracy between 83 and 93%. This performance was generally lower than the age-matched group, and generally comparable
to the younger language-matched groups. However, for the long sentences, the SLI group accurately comprehended significantly fewer sentences compared to both age- and language-matched groups. In the three studies, accuracy for the SLI group ranged from 71 to 73%, while the age- and language-matched groups’ accuracy ranged between 88 and 95%.

Children with SLI have been shown to have particularly poor comprehension of specific sentence structures such as passives (e.g., Norbury et al., 2002; van der Lely, 1996). It has been shown that children with SLI struggle to comprehend passives sentences between the ages of 7;4 to 11;3 (Bishop, Bright, James, Bishop, & van der Lely, 2000; Marinis & Saddy, 2013; Norbury et al., 2002; van der Lely, 1996). Evidence also indicates that children with SLI perform more poorly than non-language impaired children matched on a measure of language. Norbury et al. (2002) compared the performance of 14 children with SLI (mean age 8;9) to control groups matched on age and receptive vocabulary. Across all 48 sentences in the task (of which 36 were passives), mean correct response rate for the SLI group was 75%. This was significantly lower than the age- and receptive vocabulary-matched groups, who correctly responded to 94% and 91% of sentences, respectively.

Children with SLI have also been found to perform more poorly on omnibus tests of sentence comprehension such as the Test for Receptive Grammar (TROG; Bishop, 1989; Bishop, 2003). This is a commonly used, standardised test that comprises 80 sentences, divided into 20 blocks of four trials each. Each block assesses a different sentence structure, and sentences become progressively more complicated. For example, an early block comprises simple sentences such as “The sheep is running”, while the final block of trials comprises difficult sentences such as “The man the elephant sees is eating”. Raw scores on the TROG are given as the number of blocks ‘passed’. To pass a block of trials, the child must correctly respond to at least three out of four sentences.
In an early study using the first version of the TROG, Bishop (1979) compared performance of 73 children with SLI (age range 6;3 – 13;1) to 281 TD children (age range 3;9 – 13;2). A subset of the TD children were also matched to the SLI group on a test of receptive vocabulary. It was found that across all sentence types, children with SLI performed significantly more poorly than TD children matched on age. However, when compared to younger children matched on a measure of receptive vocabulary, children with SLI only performed more poorly on one type of sentence (reversible passive sentences).

More recent studies have also reported that children with SLI perform significantly more poorly on the TROG compared to age-matched control groups (Badcock, Bishop, Hardiman, Barry, & Watkins, 2012; Lum, Conti-Ramsden, Page, & Ullman, 2012; Montgomery, 2000; Norbury et al., 2002). For example, Lum et al. (2012) administered the TROG-2 to 51 children with SLI (mean age 9;9) and 51 age-matched TD children (mean age 9;10). The dependent measure was the number of blocks successfully passed. The SLI group passed on average 11.8 blocks of trials, while the TD group passed an average of 16.5 blocks of trials. The TROG assesses a wide range of syntactic structures. The finding that children with SLI perform more poorly on this test is consistent with the suggestion that SLI is associated with a deficit with grammar. Specifically, it seems that children with SLI struggle to comprehend any sentence structure which places demands on grammatical skills.

2.1.2.1 Development of receptive language. As with expressive grammatical skills, it seems that in SLI, these children also make advances in receptive grammatical skills over time. A large longitudinal study of receptive language in SLI was undertaken by Conti-Ramsden, St Clair, Pickles, and Durkin (2012). In this study the TROG-2 (Bishop, 2003) was administered to 242 children with SLI at age 7, and was readministered at ages 8 and 11. It was shown that the standard scores across this time period consistently remained at about
85, approximately one standard deviation below the normative mean. After converting to number of blocks passed, this indicates development across this period. At age 7, children passed around 10 blocks of trials. Performance increased to about 12 blocks at age 8, and further to about 14 blocks at age 11. This indicates that receptive language skills do improve with age in SLI. However even with this improvement receptive language remains below that of TD children of the same age.

2.1.3 Concluding remarks on grammar. The grammatical deficits in SLI are an area of substantial difficulty for affected children. In the expressive domain, children with SLI commonly produce short sentences that contain grammatical errors. The grammatical errors, particularly omission of the regular past tense inflection, occur more frequently than non-language impaired children of the same age and general language proficiency. In the receptive domain, children with SLI show deficits in comprehending a wide range of sentences. The expressive and receptive grammatical skills of children with SLI are consistently poorer than those of their non-language impaired peers (Conti-Ramsden et al., 2012; Rice et al., 2010; Rice et al., 1998). However, children with SLI do make advances in this area. The evidence suggests that with age, their spoken sentences become longer and more complex, and contain fewer grammatical errors (Rice et al., 2010; Rice et al., 1998). Similarly, fewer comprehension errors are made as the children grow older (Conti-Ramsden et al., 2012). One challenge for theories of SLI is to account for the deficits and at the same time, explain why these children do make advances in their ability to use and understand grammar.

2.2 Expressive and Receptive Vocabulary in Specific Language Impairment

Not all aspects of language appear to be equally impaired in SLI. Evidence suggests that lexical skills are less impaired relative to grammatical skills (Leonard, 2014). The
lexical skills in SLI have been measured in several ways. One approach has been to assess the number of words children know in the expressive (e.g., Thordardottir & Ellis Weismer, 2001; Watkins et al., 1995) or receptive domain at a particular point in development (e.g., Gray, 2006; Rice et al., 2010). Another approach has been to examine the ability of children with SLI to learn new words (e.g., Alt & Plante, 2006; Skipp, Windfuhr, & Conti-Ramsden, 2002).

2.2.1 Expressive vocabulary. Research investigating the number of words children with SLI know in the expressive domain, have typically found this area of language to be poorer compared to TD children of comparable age (e.g., Goffman & Leonard, 2000; Hewitt et al., 2005) but equivalent to children of comparable MLU (e.g., Thordardottir & Ellis Weismer, 2001; Watkins et al., 1995). One method used to investigate the number of words children with SLI know has been to measure the number of different words used in spontaneous speech (Goffman & Leonard, 2000; Owen & Leonard, 2002; Thordardottir & Ellis Weismer, 2001; Watkins et al., 1995). In spontaneous speech samples, it has been found that children with SLI produce fewer different words than TD children of comparable age (Goffman & Leonard, 2000; Hewitt et al., 2005; Leonard, Miller, & Gerber, 1999; Owen & Leonard, 2002; Watkins et al., 1995). Hewitt et al. (2005) compared 27 children with SLI (mean age 6;0) to 27 TD children matched on age (mean age 6;0). Spontaneous speech samples were acquired by asking children to re-tell a story. It was found that within the first 50 utterances, the SLI group produced 123 different word stems, while the TD group produced 138.

One study found poorer lexical diversity in SLI (Thordardottir & Ellis Weismer, 2001). That study found that a group of 25 children with SLI (mean age 7;10) produced a comparable number of different words to 25 age-matched TD children (mean age 7;9). The
measure of lexical diversity was obtained from spontaneous speech. It was found that the SLI group produced an average of 133 different words within this sample, and the TD group produced an average of 135. Interestingly, the SLI group took longer to reach 133 different words than the TD group. That is, the group with SLI reached 133 different words after producing an average of 53 utterances, whereas the TD group reached 135 different words after producing an average of 40 utterances.

Results have been more consistent when comparing children with SLI to younger children matched on MLU. It has been repeatedly found that children with SLI produce at least the same number of different words as MLU-matched children (Goffman & Leonard, 2000; Owen & Leonard, 2002; Thordardottir & Ellis Weismer, 2001; Watkins et al., 1995). For example, Watkins et al. (1995) showed that during a 100-utterance sample, 5-year-old children with SLI and 3-year-old TD children (matched on MLU) produced 111 and 112 different words, respectively. The age-matched TD children produced 160 different words. Thus, it appears that children with SLI have expressive vocabulary skills similar to younger children of comparable language proficiency.

2.2.2 Receptive vocabulary. Receptive vocabulary tasks aim to estimate the number of words a child understands. In SLI, receptive vocabulary has primarily been investigated using word-picture pointing tasks (e.g., Bishop & Hsu, 2015; Gray, 2006; Lum et al., 2012; Montgomery & Evans, 2009; Rice et al., 2010). Similar to the picture pointing task for sentence comprehension described earlier, these involve children hearing a word and pointing to one of four presented pictures that matches the word. Three common versions of word-picture pointing tasks that have been most widely used to investigate vocabulary in SLI are the Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 2007), the British Picture Vocabulary Test (BPVS; Dunn, Dunn, Whetton, & Burley, 1997), and the Receptive One
Word Picture Vocabulary Test (ROWPVT; Brownell, 2000). Each of these tests measures performance based on the number of correct responses, and each has been standardised to a mean of 100 and standard deviation of 15. Thus, a standard score of 85 indicates that performance is one standard deviation below the normative mean.

Studies that have assessed receptive vocabulary in children with SLI using one of the aforementioned tests have found their performance is poorer than age-matched control groups (Alt, 2011; Gray, 2006; Jackson, Leitao, & Claessen, 2016; Lum et al., 2012; Marchman, 2004). This has been found for children with SLI from the ages of 3;6 Gray (2006) to 9;9 (Lum et al., 2012). However, the available evidence indicates that children with SLI have a receptive vocabulary that is comparable to language matched control groups (Bishop & Hsu, 2015; Montgomery & Evans, 2009; Riches, 2012; Riches et al., 2005). Riches (2005) found that receptive vocabulary in 23 children with SLI (mean age 5;6) was comparable to that of 22 younger MLU-matched children (mean age 3;5). In this study the BPVS (Dunn et al., 1997) was administered. The children with SLI correctly responded to 41 words, and the MLU-matched group correctly responded to 37. In some cases the receptive vocabulary skills of children with SLI have been found to be superior to language-matched controls. Montgomery and Evans (2009) matched a group of children with SLI to a non-language impaired group using a standardised test of receptive language. In that study the children with SLI scored significantly higher on the PPVT (Dunn & Dunn, 2007) than the language-matched control group. The raw scores for the SLI and language-matched groups were 114 and 102, respectively. Taken together, these results indicate that receptive vocabulary in SLI is at least comparable to, or perhaps better than, receptive vocabulary of TD children with comparable language skills.
2.2.3 Word-learning. The ability for children with SLI to learn new words has also been examined (e.g., Eyer et al., 2002; Kiernan & Gray, 1998; Skipp et al., 2002). In this literature, the lexical learning in children with SLI have been found to be poorer than age-matched controls, but comparable to language-matched controls (Kan & Windsor, 2010). The typical paradigm used to assess word learning skills in SLI involves the children being auditorily presented with a novel word along with a made-up referent. For example, the experimenter might move a doll’s arm in a propeller motion, accompanied with “Look, it’s koobing” (e.g., Eyer et al., 2002). Depending on the study, the child may be asked to immediately reproduce the word (e.g., “Can you say koob?”) (e.g., Kiernan & Gray, 1998), or play may continue without such a request (Skipp et al., 2002). A second method is for the child to watch a cartoon, during which a novel or unfamiliar word such as “crustacean”, or “excavate” are presented within the narration (e.g., Rice, Oetting, Marquis, Bode, & Pae, 1994). Word learning is assessed using recognition and recall tasks.

A meta-analysis by Kan and Windsor (2010) summarised the word learning literature in SLI. They synthesised results from 28 studies, representing data from 582 children with SLI, and from age-matched (n = 497) and language-matched (n = 307) control groups. The mean age of SLI and age-matched groups found in this literature ranged from 4;2 to 12;3, and the language-matched groups from 2;4 to 7;4. The language-matched groups were matched on different measures of receptive and/or expressive language, depending on the study. The dependent variable extracted from each study was the ability to recall or recognise the novel words. Kan and Windsor found that the SLI groups performed significantly more poorly than age matched control groups. The effect size for this comparison was moderate-to-large (g = 0.6, p < .001). The comparison between SLI and language-matched groups was not significant (g = .001, p = .97). The literature shows that children with SLI are poorer at word
learning than TD children of the same age, but perform similarly to younger children with comparable general language skills.

### 2.2.4 Development of lexical skills.

To the author’s knowledge the only large-scale longitudinal study investigating development of lexical skills in SLI examined receptive vocabulary. Rice et al. (2010) assessed receptive vocabulary of 170 children with SLI, and 136 age-matched TD children, from the ages of 2;6 to 8;11. Receptive vocabulary was assessed using the PPVT. The PPVT was administered to children every six months. Children with SLI achieved a standard score of approximately 85 (one standard deviation below the normative mean) at each assessment period. To maintain this standard score the children would have had an increase in the raw scores across the period. This indicates that the number of correct responses provided on the task increased at each assessment point.

To the author’s knowledge there are no longitudinal studies of word-learning in SLI. However, in Kan and Windsor’s (2010) meta-analysis, they investigated whether age moderated performance on the task. That is, whether the difference between children with and without SLI on the word learning task changed at different ages. The results of this analysis found that the size of the difference in performance between SLI and TD groups was significantly larger in studies involving younger children ($g = 0.67$) than older children ($g = 0.49$). This result potentially suggests that the word-learning skills of children with SLI improve at a faster rate than those of TD children.

### 2.2.5 Summary of vocabulary in SLI.

Children with SLI produce a smaller range of words, and recognise fewer words than TD children of the same age. However, their overall lexical skills appear to be in line with their general language proficiency. In some cases receptive vocabulary and lexical learning might even be superior to language matched children. This hints at the possibility that the lexical skills of children with SLI might be
superior given their general language competence. As with grammar, the lexical skills of children with SLI are not stagnant; they develop over time, though it seems they still lag behind age-matched controls.

2.3 Are Grammatical and Lexical skills Equally Affected in SLI?

It has been suggested that in SLI grammar is more affected compared to lexical skills (Leonard, 2014). One common trend to emerge from the literature reviewed is that on measures of expressive or receptive grammatical skills children with SLI perform more poorly than both age-matched and language-matched groups (Leonard et al., 2003; Montgomery & Evans, 2009; Redmond, 2003; Rice & Wexler, 1996). In contrast, in studies examining lexical skills we find that while children with SLI may perform poorer than age-matched children, the difference between the SLI and language-matched groups are often not significant (Kan & Windsor, 2010; Riches et al., 2005; Watkins et al., 1995). This pattern of results suggests that after controlling for general language skills, lexical but not grammatical skills in children with SLI are comparable to non-language impaired children.

Further evidence that grammatical skills are especially affected in SLI relative to vocabulary, comes from a study investigating the diagnostic accuracy of grammar and vocabulary tests. Spaulding, Plante, and Farinella (2006) reviewed the diagnostic accuracy of a range of standardised language tests, including both grammar- and vocabulary-specific tests. Both sensitivity and specificity of the tasks were assessed. Diagnostic sensitivity refers to the percentage of children with SLI who are correctly diagnosed as SLI by the test. Diagnostic specificity refers to the percentage of children with typical language skills who are correctly identified as typical. It has been recommended that for a test to be considered useful in diagnosing SLI, sensitivity and specificity levels should both be at least 80% (Plante & Vance, 1994). Spaulding et al.’s (2006) review showed that tasks designed to measure
receptive or expressive vocabulary skills were not good predictors of whether an individual was language-impaired or not. Sensitivity and specificity of vocabulary measures ranged from 70 to 75%. In contrast, sensitivity and specificity ratings of tasks measuring grammatical skills ranged from 81 to 95%, depending on the test (Spaulding et al., 2006). These diagnostic accuracy levels reveal that for vocabulary, it is not uncommon to find children with SLI who have good vocabulary and TD children with poor vocabulary. However, for grammar, nearly all children with SLI perform poorer on tests that assess this aspect of language.

2.4 Conclusions
This chapter has outlined the language problems in SLI. Children with SLI demonstrate problems in the consistent use of grammatical morphemes, and in comprehending long or complex sentences. While deficits in vocabulary are also present in this group, these problems are not as severe as the grammatical deficits. Overall, the linguistic deficits in SLI result in difficulties in clearly expressing complex thoughts, as well as comprehending phrases spoken by others. However, in SLI skills develop over time in both the grammatical and lexical domains.
Chapter 3

Comorbid Problems in Specific Language Impairment

In addition to the language deficits outlined in the previous chapter, individuals with SLI often have co-occurring difficulties (e.g., Hill, 2001; Leyfer, Tager-Flusberg, Dowd, Tomblin, & Folstein, 2008; McArthur et al., 2000). Three of the most commonly reported co-occurring problems in SLI are deficits in reading, motor coordination, and social skills. This chapter reviews the evidence of these three problems.

3.1 Reading Difficulties and Dyslexia.

Children with SLI commonly demonstrate problems with reading (e.g., Botting, Simkin, & Conti-Ramsden, 2006; Kelso, Fletcher, & Lee, 2007). This includes single word reading (Catts, Fey, Tomblin, & Zhang, 2002; Snowling, Bishop, & Stothard, 2000) and sentence comprehension (Bishop & Adams, 1990; Conti-Ramsden, Botting, Simkin, & Knox, 2001; Kelso et al., 2007). In SLI it is perhaps not surprising to find that children with SLI have difficulty with reading comprehension at the sentence level. Comprehending the written language at the sentence level requires use of grammar. As outlined in the previous chapter this is an area of difficulty for this group. However, it has repeatedly been found that children with SLI also have reading difficulties at the single word level. In tasks that require children to read aloud a list of words or nonwords, those with SLI read significantly fewer than TD children of the same age (Alt, 2011; Badcock et al., 2012; Botting et al., 2006; Catts et al., 2002; Finlay & McPhillips, 2013; Hill, Hogben, & Bishop, 2005; Snowling et al., 2000). The reading problems in some children with SLI are severe enough to meet the criteria for dyslexia. In one study 52 children with SLI out of 102 met the criteria for dyslexia (McArthur et al., 2000). In another study 85 children with SLI out of 164 met the
criteria for dyslexia (Tomblin, Zhang, Buckwalter, & Catts, 2000). Thus, it appears that on average around 50% of children with SLI also have clinically significant reading problems.

3.2 Motor Difficulties and Developmental Coordination Disorder.

Children with SLI present with motor coordination problems as well (e.g., Hill, 2001; Rechetnikov & Maitra, 2009; Webster, Majnemer, Platt, & Shevell, 2005). The motor problems include both gross and fine motor skill deficits (Hill, 2001; Webster et al., 2005). Studies assessing gross motor skills have found that children with SLI perform more poorly than TD children of the same age on tasks such as balancing (e.g., standing on one leg), or the ability to accurately throw and catch (DiDonato Brumbach & Goffman, 2014; Finlay & McPhillips, 2013; Hill, 1998; Vukovic, Vukovic, & Stojanovik, 2010; Zelaznik & Goffman, 2010). Fine motor skills are another area of difficulty for children with SLI. It has been found that language impaired children perform more poorly than age-matched peers on peg moving tasks, stringing beads, and fastening buttons (Bishop, 2002; Brookman, McDonald, McDonald, & Bishop, 2013; DiDonato Brumbach & Goffman, 2014; Owen & McKinlay, 1997; Powell & Bishop, 1992; Zelaznik & Goffman, 2010). Deficits in fine motor skills are particularly salient in tasks that emphasise speed (Brookman et al., 2013; Hill, 2001). One such task is the peg-moving task (Tiffin, 1968). This requires children to place as many small pegs as possible into holes on a board, within a limited timeframe (e.g., 30-seconds). It has repeatedly been found that children with SLI place fewer pegs than non-language impaired children of the same age (Bishop, 2002; Bishop & Edmundson, 1987; Brookman et al., 2013; Powell & Bishop, 1992).

For some children with SLI, the motor problems are severe enough to meet the diagnostic criteria for developmental coordination disorder (DCD). DCD is characterised by difficulties in learning and carrying out coordinated motor skills, in the absence of medical conditions such as cerebral palsy or muscular dystrophy (APA, 2013). Research suggests
that approximately 30% of children with SLI also meet the diagnostic criteria for DCD (Flapper & Schoemaker, 2013).

3.3 Social Skills and Autism Spectrum Disorder.

Individuals with SLI also commonly have problems in the social domain. Research suggests individuals with SLI have difficulty making friends, socialising with peers, and initiating interaction with others (Conti-Ramsden & Botting, 2004; Fujiki, Brinton, & Todd, 1996; St Clair et al., 2011). Social skills deficits in SLI are also commonly reported. Social skills refer to a collection of abilities and behaviours that promote positive social interactions (Gresham & Elliott, 1984). In terms of specific abilities, children with SLI have been found to show lower levels of empathy and perspective taking than TD children (Botting & Conti-Ramsden, 2008; Nilsson & de Lopez, 2016). Children with SLI also have difficulty interpreting facial expressions. It has been shown that children with SLI perform more poorly than age-matched TD children at identifying emotions based on images of facial expressions (Ford & Milosky, 2003; Taylor, Maybery, Grayndler, & Whitehouse, 2015).

Some of the social skill deficits found in SLI overlap with symptoms of autism spectrum disorder (ASD). ASD is a developmental disorder defined by social communication and interaction deficits, and restricted, repetitive behaviours or interests (APA, 2013). The prevalence of children with SLI meeting the criteria for ASD is higher compared to the general population. Conti-Ramsden et al. (2006) reported that in a sample of 76 adolescents with SLI, the prevalence of ASD was 3.9%. In the general population the prevalence of ASD is less than 1% (Fombonne, 2003). Thus within the SLI population, the prevalence of ASD is approximately 10 times higher compared to the general population. Furthermore, across different studies, about 25% (Conti-Ramsden et al., 2006), or up to 40%
(Leyfer et al., 2008), of children with SLI have been found to display at least some of the social and communication deficits that are typical of ASD.

### 3.4 Conclusions

SLI is primarily diagnosed on the basis of language dysfunction. In this chapter it was shown that the problems found in this group extend to other areas. Specifically, common problems in SLI include reading, motor, and social communication deficits. However, it is certainly not the case that all children with SLI have one or all of the aforementioned co-morbid conditions. The range of linguistic and non-linguistic deficits in SLI represent a challenge for any theory that aims to explain the cause of the disorder. Specifically, at a minimum the goal would be to explain the seemingly very specific deficits in language, whereby grammar is discretionally affected compared to vocabulary. Yet, theories that focus exclusively on the language problems may struggle to account for the similarities and differences in comorbid conditions. That is, how does one explain the combinations of reading, motor, and social skills problems that are present in some, but not all, of those with language impairments? One theory that does aim to explain both the linguistic and non-linguistic impairments in SLI is the procedural deficit hypothesis (Ullman & Pierpont, 2005). The next chapter reviews the procedural deficit hypothesis.
Chapter 4

The Procedural Deficit Hypothesis (PDH)

A number of theories have been presented that aim to explain the cause of SLI. These can be classified as either domain-specific or domain-general theories. Domain-specific theories suggest that the grammatical difficulties in SLI are caused by dysfunction to an innate grammar-specific module in the brain (Gopnik, 1997; Rice et al., 1995; van der Lely, 2005). According to domain-specific theories, the grammar problems in SLI are independent of comorbid cognitive and motor difficulties. In contrast, domain-general theories suggest that language emerges from general cognitive processes. These theories purport that problems in functions such as working-memory (Baddeley et al., 1998; Gathercole & Baddeley, 1990) or auditory processing (Tallal, 2004; Tallal & Piercy, 1973; Tallal et al., 1985) directly cause the grammar problems in SLI, as well as comorbid problems with skills such as reading. One domain-general theory, which is the focus of this thesis, is Ullman and Pierpont’s (2005) Procedural Deficit Hypothesis (PDH).

The PDH is based on a more general model of language functioning which argues that the declarative and procedural memory systems play different roles in language (Ullman, 2001, 2004). This model of language is referred to as the declarative/procedural model. According to Ullman, in typical development the declarative memory system is required for learning and using individual words. The procedural memory system is necessary for learning and using grammar. The PDH proposes that the range of language and non-linguistic deficits in SLI is caused by dysfunction of the procedural memory system (Ullman & Pierpont, 2005). Furthermore, it is proposed that the declarative memory system remains intact, and compensates for some of the impairments arising from poor procedural memory. This chapter first describes the two memory systems and then explains how they relate to language and SLI. It is argued that while procedural memory appears to be impaired in SLI,
differences in study findings might be related to specific task characteristics. Following this discussion, different models are considered regarding how procedural memory dysfunction could lead to comorbid problems with reading, motor, and social skills in SLI.

4.1 The Declarative Memory System

4.1.1 Cognitive description of the declarative system. The declarative memory system underlies the encoding, retention, and retrieval of knowledge about personal events and experiences, referred to as episodic knowledge, and general facts about the world, referred to as semantic knowledge (Eichenbaum, 2004; Squire, 2004). An example of episodic memory is knowing particular events that occurred at a dinner party. An example of semantic knowledge is knowing that Tokyo is the capital city of Japan, or that the word ‘dog’ refers to the object or concept of a dog. There is some debate regarding whether episodic versus semantic memories require discrete processes (e.g., Burianova, McIntosh, & Grady, 2010; Moscovitch et al., 2005). For the purposes of this thesis, the umbrella term “declarative memory” is used to refer to both episodic and semantic memory.

The declarative system encodes information by associating or binding together arbitrary pieces of information (Cohen, Poldrack, & Eichenbaum, 1997; Mayes, Montaldi, & Migo, 2007), and associating stimuli across time (Poldrack & Rodriguez, 2003; Staresina & Davachi, 2009). Learning by this system can occur following a single exposure. However, through repeated exposures, the probability of the information being available for retrieval at a later period in time increases (Alvarez & Squire, 1994). The information processed by the declarative memory system is often described as being supported by explicit processes. This is because in many situations, encoding and retrieval via declarative memory involves conscious effort (e.g., Gabrieli, 1998). However, as described below, awareness is not a necessary requirement for declarative memory.
The encoding and retrieval of information by the declarative memory system can be explicit or implicit. One common task that involves explicit awareness is the word-pairs task (Cohen, 1997; Wechsler, 1997). In the encoding phase of this task, participants are presented with pairs of unrelated words (e.g., rice – chair). Participants are instructed to attend to and remember the word pairs. Retrieval is tested via recall and/or recognition. In cued-recall trials, participants are presented with one item from the pair, and are required to recall the missing word. Uncued recall trials require the participant to recall both words from all pairs. In recognition tasks, participants select which word pairs were shown in the encoding phase, from a list that also includes distractor word pairs.

Declarative tasks in which learning and/or retrieval of information is implicit can also be found (Chun & Phelps, 1999; Duss et al., 2014; Henke, Mondadori, et al., 2003; Henke, Treyer, et al., 2003). One type of task is the implicit association task (Henke, Mondadori, et al., 2003; Henke, Treyer, et al., 2003). This paradigm begins with an implicit encoding phase. During this phase, participants are presented with a target stimulus, which is a pair of items, on a computer screen. Each pair comprises stimuli from two different categories, such as a picture of a face along with a written word depicting an occupation. Presentation is very brief, and is immediately followed by a visual masking stimulus (such as: ‘######’). The effect of the brief presentation and masking stimulus is that participants are unable to report noticing the target stimulus. During the retrieval phase, participants are presented with one of the items in a pair, and are required to recall the second item. That is, participants might be presented with a picture of a face, and are asked to recall or guess the occupational category associated with each face. Participants remain unaware that they were presented with the face-occupation pairs during the encoding phase, yet retrieval accuracy in such tasks is above chance, indicating that some implicit learning has taken place (e.g., Duss et al., 2014).
4.1.2 Language and the declarative memory system. According to the declarative/procedural model, the declarative system supports learning and use of individual words (Ullman, 2001, 2004). Ullman (2004) claims that declarative memory is ideally suited for word learning since this system is adept at being able to encode and bind a particular speech sound (i.e., word) to its referent (e.g., binding the sound of the word ‘chair’ to the object chair). An additional role of the declarative memory system outlined by Ullman is to learn and store irregular verbs and nouns as well as other parts of speech that cannot be induced via a rule. For example, the irregular verb ‘caught’ is proposed to be learnt and stored by the declarative memory system. This is because ‘caught’ is an unpredictable form of the word ‘catch’, and so the two words must be encoded and stored as a bound pair or unit.

4.1.3 Neurological correlates of the declarative system. The declarative system primarily relies on the hippocampus and surrounding areas in the medial temporal lobes (MTL) (Eichenbaum, 2004; Squire, 2004; Squire & Zola, 1996). The hippocampus comprises the cornu ammonis fields, the dentate gyrus, and the subiculum. The surrounding parahippocampal gyrus, which largely serves as an interface between the hippocampus and the cortex, comprises the perirhinal, entorhinal, and parahippocampal cortices (see Figure 4.1 for a diagram of the MTL). Anterior and posterior regions of the parahippocampal gyrus predominately project information to and from anterior and posterior parts of the cortex, respectively (Libby, Ekstrom, Ragland, & Ranganath, 2012).

Different regions within the MTL are thought to make distinct contributions to the encoding, storage, and retrieval of information from declarative memory (e.g., Davachi, 2006; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001). One view is that the perirhinal cortex is important for encoding information about the physical characteristics of an object, whereas the parahippocampus encodes context and spatial information.
For example, when looking at a picture of a blue abstract shape, the perirhinal cortex encodes the item’s shape, and the parahippocampus encodes the context-related aspects such as the colour and location. Irrespective of the type of information being processed the hippocampus binds together the information, to encode the memory for the particular object within the particular context (Cohen et al., 1999; Eichenbaum et al., 2012; Slotnick, 2010; Yonelinas et al., 2001). The hippocampus is also required for connecting the object with its context during retrieval of newly acquired information (Alvarez & Squire, 1994; Diana et al., 2009). Similarly, when recalling a specific experience, the hippocampus is necessary for associating information from separate sensory inputs such as visual and auditory information (Eichenbaum, 2000; Eichenbaum et al., 2012; Squire & Zola, 1996; Treves & Rolls, 1994).

The structures that comprise the MTL play a role in early learning by declarative memory (Alvarez & Squire, 1994; Manns, Hopkins, & Squire, 2003). New declarative memories require the hippocampus for encoding, storage, and retrieval. However, after
consolidation occurs the information becomes independent of the hippocampus and represented in the neocortex (Alvarez & Squire, 1994; Manns et al., 2003; Smith & Squire, 2009). Different neocortical areas underlie different types of knowledge. For example, visual information relies on visual cortices (e.g., regions of posterior temporal and occipital lobes), whereas auditory memories rely on auditory cortices (Buckner & Wheeler, 2001; Martin & Chao, 2001).

Areas of the prefrontal cortex (shown in Figure 4.2) are also important for the encoding and retrieval of declarative memory (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005; Blumenfeld & Ranganath, 2007; Buckner, 1996; Fletcher, Shallice, & Dolan, 2000; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998). The prefrontal cortex is involved particularly when encoding or retrieval demands are high. For instance, prefrontal cortex is engaged in situations that involve multiple pieces of information competing for processing, or when information must be recalled rather than recognised (Blumenfeld & Ranganath, 2007; Buckner & Wheeler, 2001; Rugg, Fletcher, Chua, & Dolan, 1999). The ventrolateral prefrontal cortex aids encoding and retrieval by influencing attention and selection processes (Blumenfeld & Ranganath, 2007; Simons & Spiers, 2003). During encoding, ventrolateral prefrontal cortex directs attention to task- or goal-relevant stimuli or features, and disengages attention from irrelevant features (Blumenfeld & Ranganath, 2007; Fletcher et al., 2000; Thompson-Schill, D’Esposito, & Kan, 1999). Similarly, during retrieval the role of the ventrolateral prefrontal cortex appears to be in selecting the relevant information from memory (Badre & Wagner, 2004, 2007; Dobbins & Wagner, 2005). For example, if asked to recall an item’s colour, this region is involved in selecting the recollection specific to colour, from a range of competing information such as shape, location, and context.
The dorsolateral prefrontal cortex is also involved in encoding and retrieval of declarative information, though particularly when multiple items are to be remembered (e.g., Blumenfeld & Ranganath, 2006; Fletcher, Shallice, Frith, et al., 1998). Dorsolateral prefrontal cortex assists in encoding information by organising or grouping information (Blumenfeld, Parks, Yonelinas, & Ranganath, 2011; Blumenfeld & Ranganath, 2006; Long, Oztekin, & Badre, 2010). For example, if tasked with encoding a list of words, the dorsolateral prefrontal cortex is involved in re-organising the list by grouping together words that share meaning or perceptual features. The role of this region during retrieval appears to be in monitoring or checking the accuracy of retrieved information (Fletcher, Shallice, Frith, et al., 1998; Henson, Shallice, & Dolan, 1999; Rugg et al., 1999).

### 4.1.4 Declarative memory in specific language impairment.

According to the PDH (Ullman & Pierpont, 2005), declarative memory is unaffected in SLI. This section reviews findings from studies investigating verbal and non-verbal declarative memory in SLI. It will be argued that poor performance on verbal declarative memory tasks in SLI can be explained...
by working memory deficits and that non-verbal declarative memory is intact. Thus it is argued that in line with Ullman’s proposal, declarative memory is relatively unaffected in SLI.

4.1.4.1 Verbal declarative memory in specific language impairment. Verbal declarative memory in SLI has commonly been tested using word list learning tasks (e.g., Baird, Dworzynski, Slonims, & Simonoff, 2010; Dewey & Wall, 1997; Records, Tomblin, & Buckwalter, 1995). During the encoding phase, participants are auditorily presented with a list of unrelated words. After the list has been presented, participants are required to recall as many words from the list as possible. The list is then presented again, usually three or four more times, and the participant recalls as many words as possible after each trial. The retrieval phase of these tasks can involve both recall and recognition phases. Delayed recall and recognition trials occur after a delay of around 30 minutes. After the delay, participants are asked to again recall all items from the word list (delayed recall), or to select the previously presented words from a list which also includes distractor items (delayed recognition).

Word list learning tasks have been shown to rely on the structures of the declarative memory system, including MTL (e.g., Gleissner, Helmstaedter, Schramm, & Elger; Strange, Otten, Josephs, Rugg, & Dolan, 2002) as well as prefrontal cortex (Fletcher, Shallice, & Dolan, 1998). Prefrontal cortex involvement is thought to reflect strategies including grouping words of similar categories (Fletcher, Shallice, & Dolan, 1998). In terms of MTL involvement, neuroimaging studies have shown that both encoding and retrieval phases of word list tasks activate the MTL, including the hippocampus (Fernandez, Klaver, Fell, Grunwald, & Elger, 2002; Strange et al., 2002). Further evidence for the necessity of MTL in learning word lists comes from studies showing that performance is impaired in individuals with left medial temporal lobe damage (Gleissner et al.; Jones-Gotman et al., 1997). While
these groups do show learning, evidenced by recalling more words in each trial across the encoding phase, the total number of words recalled is significantly fewer than neurologically healthy controls (Jones-Gotman et al., 1997).

Word list learning tasks have frequently been administered to assess verbal declarative memory in SLI (e.g., Baird et al., 2010; Dewey & Wall, 1997; Records et al., 1995). It has been repeatedly found that individuals with SLI recall significantly fewer words than age-matched TD individuals across the encoding phase (e.g., Baird et al., 2010; Dewey & Wall, 1997; Duinmeijer, de Jong, & Scheper, 2012; Records et al., 1995; Riccio, Cash, & Cohen, 2007). Lum and Conti-Ramsden (2013) used meta-analysis to synthesise the findings of nine word list studies. It was shown that across the encoding phase, individuals with SLI performed on average .899 standard deviations more poorly than TD groups. This finding indicates that encoding verbal information into declarative memory is reliably impaired in SLI.

Performance on the retrieval phases of word list tasks has also been investigated. The results are less consistent than for the encoding phase data. Groups with SLI have been shown to recall significantly fewer words than TD groups after both short (Lum et al., 2012; Nichols, 2004) or long (Lum et al., 2012; Nichols, 2004; Shear, Tallal, & Delis, 1992) delays. However, other studies have found non-significant differences between groups in recall phases (Baird et al., 2010; Records et al., 1995; Riccio et al., 2007; Shear et al., 1992). Performance on a delayed recognition trial has consistently been found to be poorer in SLI (Lum et al., 2012; Nichols, 2004; Riccio et al., 2007). Lum and Conti-Ramsden (2013) also submitted data from word list retrieval phases to meta-analysis. Results from six studies were included, and data from immediate and delayed recognition and recall were averaged. It was argued that averaging in such a way was appropriate, because it has been found that
retrieval in each of these conditions is highly correlated. The meta-analysis showed that across the six studies, groups with SLI retrieved significantly fewer words than TD groups. Performance was .497 standard deviations poorer in SLI. Thus, retrieval of verbal declarative memory also appears to be poor in SLI.

While performance on verbal declarative memory tasks is poor in SLI, this may not indicate a compromised declarative memory system in this group. It is possible that working memory problems may explain the difficulties individuals with SLI have encoding information into declarative memory (Lum et al., 2012; Lum, Ullman, & Conti-Ramsden, 2015). That is, the fundamental associative learning mechanism is intact in SLI, but poor working memory skills impact on these processes. Working memory refers to the short term storage and manipulation of information (Baddeley, 2003). Typically, verbal working memory is poor in SLI (Alloway, Rajendran, & Archibald, 2009; Archibald & Gathercole, 2006; Ellis Weismer, Evans, & Hesketh, 1999; Gathercole & Baddeley, 1990; Montgomery, 2000). There is some evidence to implicate verbal working memory in word list learning tasks. Lum et al. (2012) found that after statistically controlling for verbal working memory, differences between SLI and TD groups on list learning performance were not significant. This was found for encoding, recall, and recognition phases of the task. In a follow up study, Lum et al. (2015) grouped children with SLI based on their working memory skills. One group comprised children with average working memory, and a second group comprised children with poor working memory. A control group with average working memory skills was also included. It was shown that the SLI group with poor working memory skills performed significantly more poorly than both the TD group and the SLI group with average working memory. There was no difference in performance between the SLI group with average working memory and the TD group. These findings indicate that children with SLI
have comparable declarative memory to TD children, once verbal working memory skills are taken into account.

4.1.4.2 Non-verbal declarative memory in specific language impairment. Commonly used non-verbal declarative memory tasks involve encoding and retrieving arrays of dots or abstract pictures (Cohen, 1997; McNealy, Mazziotta, & Dapretto, 2011; Scott-Van Zeeland et al., 2010). One example is the dots location task (Cohen, 1997), during which participants view a picture comprising a random array of dots. In the encoding phase, participants view the array for 10 seconds. The participant then attempts to re-create the array of dots by placing tokens on a grid. Three more trials follow, during which the participant views and attempts to re-create the same array. The retrieval phase follows after a delay. In the delayed recall condition, participants again recall the initial array of dots, after participating in other activities for around 30 minutes.

Tasks that require encoding and retrieval of object-location relationships rely on the declarative memory system (e.g., McNealy, Mazziotta, & Dapretto, 2010; Milner, Johnsrude, & Crane, 1997). It has been shown that structures of the MTL, particularly the right parahippocampal region, are active during the task (Owen, Milner, Petrides, & Evans, 1996). This activity appears particularly important during retrieval phases in comparison to encoding (Milner et al., 1997; Owen et al., 1996). Furthermore, patients with damage to structures of the MTL have been shown to perform poorly on these tasks, especially in delayed recall phases (Gleissner et al.; McNealy et al., 2010; Milner et al., 1997; Stepankova, Fenton, Pastalkova, Kalina, & Bohbot, 2004).

Encoding and retrieval of non-verbal information has also been investigated in groups with SLI. Across encoding trials, it has repeatedly been shown that groups with SLI perform comparably to TD groups whether the stimuli are dots (Lum et al., 2012; Riccio et al., 2007)
or abstract pictures (Baird et al., 2010; Bavin, Wilson, Maruff, & Sleeman, 2005; Lum, Gelgic, & Conti-Ramsden, 2010). While the individual studies have all shown non-significant differences between groups, a meta-analysis of these five studies showed that on average, SLI groups performed significantly more poorly than TD groups (Lum & Conti-Ramsden, 2013). However, the size of the difference was found to be small ($d = .228$). Thus, encoding of non-verbal information does not appear to be substantially impaired in SLI.

Performance on retrieval phases has also been tested. Most studies have shown that recall of non-verbal information is comparable between SLI and TD groups across both short and long delays (Baird et al., 2010; Dewey & Wall, 1997; Riccio et al., 2007). One study found that recall for an array of dots was poorer in SLI than a TD group after a short delay, but comparable after a long delay (Lum et al., 2012). A meta-analysis of four studies showed that there was no significant difference between SLI and TD groups on retrieval phases of dots or abstract picture tasks (Lum & Conti-Ramsden, 2013). Taken together, encoding and retrieval of non-verbal information via the declarative memory system appears to be intact in SLI.

**4.1.4.3 Summary of declarative memory in specific language impairment.** Overall, declarative memory is relatively unaffected in SLI. Encoding and retrieval of non-verbal information is similar to that of age-matched peers. Encoding and retrieval of verbal information is poor in SLI, though this is likely due to interactions with verbal working memory. This supports the claim of the PDH that the declarative memory system is relatively unimpaired in SLI.
4.2 The Procedural Memory System

4.2.1 Cognitive description of the procedural system. The procedural memory system is one of several non-declarative systems (Squire, 2004). This memory system underlies the encoding, storage, and retrieval of cognitive and motor skills and habits (Gabrieli, 1998; Squire & Zola, 1996). This system appears to be particularly suited to encoding sequentially, probabilistically, or statistically structured information (Conway & Pisoni, 2008; Squire & Zola, 1996). In order for learning or information to be encoded into the procedural system, repeated exposure to the information or repetition of the skill (e.g., practice) is often required (Cohen et al., 1997; Seger & Spiering, 2011; Squire, 2004). Once knowledge has been acquired, however, the skills can be executed quickly (Poldrack et al., 2005; Squire, 2004). Procedural memory is often referred to as ‘implicit’ knowledge, because conscious awareness is not required for learning or retrieval to take place (e.g., Squire & Zola, 1996).

The perceptual and cognitive skills reliant on the procedural system include sequence learning (Fletcher et al., 2005; Willingham, Salidis, & Gabrieli, 2002), navigation that involves route- or response-learning (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Packard & McGaugh, 1996), and probabilistic classification (Knowlton, Mangels, & Squire, 1996; Poldrack et al., 2001; Seger & Cincotta, 2005). Each of these skills involves learning sequential or probabilistic regularities. Two experimental tasks that appear to be dependent on the procedural memory system are the Weather Prediction task (Knowlton, Squire, & Gluck, 1994), and the serial reaction time task (SRTT; Nissen & Bullemer, 1987).

The Weather Prediction task is a probabilistic classification learning task (Knowlton et al., 1994). Participants are presented with an image of a combination of one, two, or three of four cues (usually cards with different geometric shapes on them). Participants are
required to indicate whether they think the pattern predicts “sunshine” or “rain”. As soon as they respond, feedback is provided that indicates whether or not the answer was correct.

Each cue has its own predictive value. For example, it may be that Cue 1 predicts sunshine in 80% of all cases, Cue 2 in 60% of cases, Cue 3 in 40% of cases, and Cue 4 in 20% of cases. Because the associations are probabilistic, information from a single trial is not as reliable or useful as information accrued across many trials. As more trials are presented, participants gradually and implicitly learn the probabilistic regularities according to the entire pattern.

The SRTT is an implicit sequence-learning task (Nissen & Bullemer, 1987). In this task, participants view a visual stimulus that repeatedly appears in one of four locations on a computer screen. Participants are instructed to respond by pressing one of four buttons that corresponds to the location of the stimulus. Unknown to participants, on some trials the stimulus follows a predetermined sequence, while on other trials the location is random. Learning on this task is evidenced by faster reaction times to trials in which the stimulus follows the sequence compared to random trials.

4.2.2 Language and the procedural system. The declarative/procedural model (Ullman, 2001, 2004) proposes that the procedural system underlies the learning and use of grammar. That is, repeated exposure to language results in the gradual, implicit learning of consistent grammatical patterns. Grammar is acquired through learning the regularities one hears in the constant stream of language. General patterns relating to phonology (e.g., the sequencing of sounds), grammatical morphology (such as learning the regular past-tense convention of adding ‘-ed’ to a verb stem), and syntax (combining words to form complex, meaningful sentences) are all proposed to be reliant on this system (Ullman, 2004; Ullman & Pierpont, 2005).
4.2.3 Neurological correlates of the procedural system. The procedural memory system relies on both subcortical and cortical structures (Gabrieli, 1998; Graybiel, 1995). The main subcortical structure is the basal ganglia (Alexander, DeLong, & Strick, 1986; Squire & Zola, 1996), though the cerebellum has more recently been implicated in procedural memory as well (Doyon, Penhune, & Ungerleider, 2003; Molinari & Leggio, 2013). Substructures of the basal ganglia include the striatum, which in turn can be subdivided into the caudate and putamen. Other structures that comprise the basal ganglia include the globus pallidus, subthalamic nucleus, and substantia nigra. The cortical regions include motor cortex, dorsolateral prefrontal cortex, lateral orbitofrontal cortex, anterior cingulate, and frontal eye fields. Each of these five cortical regions transfers information to and from the basal ganglia. Information is transferred via parallel, closed loops (Alexander et al., 1986; Clark & Lum, 2017; Middleton & Strick, 2000b). These are referred to as cortico-striatal loops, circuits, or channels.

Figure 4.3 (next page) outlines the flow of information within the cortico-striatal loops (Alexander et al., 1986; Haber, Adler, & Bergman, 2012; Middleton & Strick, 2000b; Utter & Basso, 2008). As shown in Figure 4.3, the striatum receives information from the cortex (labelled route A). This information then travels through the basal ganglia structures via one of two pathways. In route B, also called the “direct pathway”, information is transferred from the striatum to the globus pallidus internal segment and substantia nigra. These two sub-structures comprise the primary output nuclei of the basal ganglia. Route C depicts the “indirect pathway”. In this pathway, information travels from the striatum to the globus pallidus external segment and subthalamic nucleus (route C1), before moving on to the output nuclei (route C2). From here, information is transferred to the thalamus (route D), where it is relayed back to the cortical region (route E). The direct and indirect pathways within the basal ganglia (route B and C) lead to an increase or decrease of thalamic activity,
respectively. Thus, the direct pathway leads to a reinforcement of cortical activity via increased thalamic firing. The indirect pathway leads to an inhibition of cortical activity via decreased thalamic firing.

The five cortical areas mentioned earlier correspond to the cortical area of five functionally and anatomically segregated loops (Alexander et al., 1986). Several highly connected cortical areas project into each loop. For example, the motor cortical areas that project to the striatum include primary motor cortex, somatosensory cortex, premotor cortex, and supplementary cortex (Alexander et al., 1986; Haber et al., 2012). Information from each of these areas projects to the striatum and through the basal ganglia and thalamus (as outlined Figure 4.3). The primary target of the motor loop after passing through the thalamus is the

![Figure 4.3. Schematic diagram of cortico-striatal loops. Red sections represent the basal ganglia.](image)

Note that the diagram presents a simple feedforward pathway, though feedback pathways and distinct inhibitory and excitatory paths through these structures are also known to exist. GPe = globus pallidus external segment, Gpi = globus pallidus internal segment, STh = subthalamic nucleus, SNr = substantia nigra.
supplementary motor area (Alexander et al., 1986; Haber et al., 2012). Thus information from the primary motor cortex might be sent through the basal ganglia via the “motor loop”, with the output of the loop at supplementary motor area. This information can then be sent from supplementary motor area to primary motor cortex (and other connected cortices). Each of the other five cortico-striatal loops operates in a comparable manner. That is, multiple highly connected cortical areas input information to their associated loop, with a single primary output area. Figure 4.4 shows the diverse cortical regions that are connected with the basal ganglia via closed loops.

Figure 4.4. Schematic diagram of the striatum is shown in (a). Illustrations of lateral (b) and medial (c) cortical areas and their connections to the striatum. The coloured section of the striatum represents the area of the striatum receiving projections from the cortical area of the same colour. dPFC = dorsolateral prefrontal cortex, IOFC = lateral orbitofrontal cortex, FEF = frontal eye field, MC = motor cortex, SSC = somatosensory cortex, PPC = posterior parietal cortex, SMA = supplementary motor area, AC = anterior cingulate cortex. Figure adapted from Utter and Basso (2008).
Each loop is thought to be involved in functions associated with the cortical area to which they project (Alexander et al., 1986; Middleton & Strick, 2000b). Thus, the loop involving frontal eye fields is involved in oculomotor functions, and the motor loop is involved in motor functions. The functions of the remaining loops are less well understood. However, both cognitive and emotion-related functions do appear to be processed via cortico-striatal loops (Arsalidou, Duerden, & Taylor, 2013; Haber et al., 2012). The terminal points of the loops in the striatum cluster into three rough sections, with motor-related functions, cognitive functions, and emotion-related functions each projecting to separate, but overlapping areas (Haber, 2003; Haber et al., 2012). Given that each loop follows a similar path through the same structures of the basal ganglia, it is generally considered that similar neuronal operations are performed at comparable stages of each circuit. That is, the basal ganglia appear to perform analogous computations that are applied to different sets of information from different domains (Alexander et al., 1986; Middleton & Strick, 2000a).

It is considered likely that there are more than five cortico-striatal loops (Alexander et al., 1986; Arsalidou et al., 2013). Ullman (Ullman, 2004; Ullman & Pierpont, 2005) suggests that there may be a cortico-striatal loop related to processing language. It was proposed that a cortico-striatal loop that projects to and from Broca’s area may exist (Ullman, 2006). In line with this proposal, one neuroimaging study has indicated that Broca’s area may be connected to the striatum via closed loops (Ford et al., 2013). Furthermore, a second study has suggested that connections between Broca’s area and the striatum relate to processing syntax (Teichmann et al., 2015). As noted above, the same computations would be undertaken in the basal ganglia for each domain (Alexander et al., 1986). That is, the sequential or probabilistic regularities are learnt for motor information through the motor loop, oculomotor information through the oculomotor loop, and according to Ullman
(Ullman, 2004; Ullman & Pierpont, 2005), possibly for language-based information through a Broca’s area loop.

As mentioned earlier, the cerebellum may also contribute to the procedural memory system (Doyon et al., 2003; Middleton & Strick, 2000a). Like the basal ganglia, the cerebellum has also been shown to have reciprocal connections with a range of cortical regions (Middleton & Strick, 2000a; Ramnani, 2006). Furthermore, the cerebellum is also connected with the basal ganglia (Hoshi, Tremblay, Feger, Carras, & Strick, 2005). The specific contributions of cortico-cerebellar circuits to procedural memory are not entirely clear. However, it has been suggested that the cerebellum is particularly important for processing information that involves continual adaptation to environmental changes (Doyon et al., 1997; Doyon et al., 2003; Gabrieli, 1998).

4.2.4 Procedural memory in specific language impairment. According to the PDH (Ullman & Pierpont, 2005), the grammatical problems in SLI are caused by an abnormality of the caudate and/or Broca’s area. This neurological deficit in turn is claimed to give rise to a procedural memory impairment. As a consequence, it is proposed that the acquisition and use of skills and abilities dependent on this memory system are subsequently affected. A crucial test of the PDH is whether in fact children with SLI have procedural memory impairments. Procedural memory in SLI has been assessed with a range of tasks (Desmottès et al., 2017b; Evans, Saffran, & Robe-Torres, 2009; Hsu & Bishop, 2014; Lum et al., 2010; Mayor-Dubois, Zesiger, Van der Linden, & Roulet-Perez, 2012). This section outlines performance of groups with SLI on two tasks that are commonly used to assess different aspects of procedural memory. These are probabilistic classification as assessed by the Weather Prediction task, and sequence learning assessed by the SRTT.
4.2.4.1 Probabilistic classification in specific language impairment. As described previously, probabilistic classification tasks, such as the Weather Prediction task, are a common measure of procedural learning (Knowlton, Mangels, et al., 1996; Knowlton et al., 1994). As a reminder, the Weather Prediction task involves predicting “sunshine” or “rain” based on cues that provide probabilistic feedback. Consistent with the claim that this task relies on procedural memory, neuroimaging studies have shown activation of the striatum during learning (Aron et al., 2004; Foerde, Knowlton, & Poldrack, 2006; Moody, Bookheimer, Vanek, & Knowlton, 2004; Poldrack, Prabhakaran, Seger, & Gabrieli, 1999; Seger & Cincotta, 2005). Performance of individuals with basal ganglia degeneration, such as individuals with Parkinson’s or Huntington’s disease, further indicate that the procedural memory network is required for learning. Significantly poorer learning by individuals with Parkinson’s or Huntington’s disease in comparison to controls has been found across the task (Holl, Wilkinson, Tabrizi, Painold, & Jahanshahi, 2012; Knowlton, Squire, et al., 1996; Shohamy et al., 2004; Witt, Nuhsman, & Deuschl, 2002), though this difference may be particularly pronounced in later trials (Knowlton, Mangels, et al., 1996; Shohamy et al., 2004).

Three studies have administered the Weather Prediction task to children with SLI (Kemeny & Lukacs, 2010; Lukacs & Kemeny, 2014; Mayor-Dubois et al., 2012). In one study, it was found that a group of children with SLI performed significantly more poorly that a group of age-matched TD children (Kemeny & Lukacs, 2010). In that study, while the classification accuracy of the SLI group did improve during the task, accuracy remained significantly below that of TD children. A further two Weather Prediction studies found different results (Lukacs & Kemeny, 2014; Mayor-Dubois et al., 2012). In these two studies, it was found that performance by the SLI group was comparable to that of an age-matched TD group. For example, Mayor-Dubois et al. (2012) found that the rate of improvement in
classification accuracy across the task was similar for children with and without language impairment. In the final block of trials, classification accuracy of the two groups was also comparable. Overall, it may be that probabilistic classification is generally unaffected in SLI. One suggestion to account for this finding is that procedural memory problems in SLI might be specific to the sequence learning functions of this system (Hsu & Bishop, 2014).

4.2.4.2 Auditory statistical learning in specific language impairment. The auditory statistical learning task (Saffran, Newport, Aslin, Tunick, & Barrueco, 1997) might also be considered as a measure of procedural memory. This task involves implicitly learning statistical regularities within a stream of speech. In the exposure phase of the task, participants hear a continuous stream of syllables. Embedded in the stream are three-syllable nonwords, (e.g., bupada). The only cues to the word boundaries are the transitional probabilities between pairs of syllables. The transitional probabilities are higher within nonwords than across nonword boundaries. After the exposure phase, participants are played two 3-syllable sequences. One of the sequences is a nonword that was present in the speech stream, and the other is made up of syllables from the stream, but in a sequence not played during the learning phase. Participants are required to indicate which of the two syllable sequences sounds more like those that were present in the speech stream. It has been shown that healthy adults and children both perform above chance on this task, indicating that learning has taken place (e.g., Karuza et al., 2013; Saffran, Newport, Aslin, Tunick, & Barrueco, 1997).

Like other procedural memory tasks, the auditory statistical learning task involves implicitly learning statistical regularities within a stream of information. However, neuroimaging evidence supporting the reliance of the task on the procedural memory system is mixed. There is some evidence consistent with procedural memory involvement in the
task. Specifically, in comparison to a rest, the exposure phase of the task has been shown to increase activation of the basal ganglia (McNealy et al., 2010, 2011), and prefrontal regions including Broca’s area (Cunillera et al., 2009; Karuza et al., 2013). However, the degree that this activation reflects learning rather than more general task demands is unclear. To address this limitation, some neuroimaging studies have included a control condition in which participants hear a second stream of randomly ordered syllables (McNealy, Mazziotta, & Dapretto, 2006; McNealy et al., 2010, 2011; Plante et al., 2015). The purpose of comparing neural activation during the stream that contains regularities to that during the random stream, is to determine regions that activate specifically to information that contains statistical regularities. These studies have not found activation of procedural memory regions that is specific to the stream containing regularities. Rather, more activation of temporal regions, particularly the left superior temporal gyrus, has been found during the exposure phase in comparison to a random syllable phase. Overall, the validity of statistical learning tasks as a measure of procedural memory performance is unclear.

To date, four studies have administered the auditory statistical learning task to children with SLI (Evans et al., 2009; Haebig, Saffran, & Ellis Weismer, 2017; Mainela-Arnold & Evans, 2013; Mayor-Dubois et al., 2012). In all four studies, it was found that children with SLI performed significantly more poorly than age-matched TD children. Specifically, in the recognition task each study found that the accuracy levels of the SLI group were significantly lower than those of the TD group. Furthermore, the SLI groups’ accuracy was not above chance levels. These results indicate that children with SLI are poor at implicitly learning statistical regularities within verbal information.

4.2.4.3 Serial reaction time task performance in specific language impairment. As mentioned, on the SRTT participants implicitly learn a visuomotor sequence. Note that
detailed descriptions of the SRTT are provided in each of Chapters 5-8, and so methodological details will be kept to a minimum in this section. Sequence learning as indexed by the SRTT relies on structures of the procedural memory system. Neuroimaging studies have repeatedly shown activation of the striatum during the task (e.g., Daselaar, Rombouts, Veltman, Raaijmakers, & Jonker, 2003; Grafton, Hazeltine, & Ivry, 1995; Hazeltine, Graffin, & Ivry, 1997; Reiss et al., 2005; Rieckmann, Fischer, & Backman, 2010; Rose, Haider, Salari, & Buchel, 2011; Thomas et al., 2004; Willingham et al., 2002). Engagement of cortical regions including motor and supplementary motor areas, as well as prefrontal regions have also been shown during learning (Daselaar et al., 2003; Grafton et al., 1995; Hazeltine et al., 1997; Willingham et al., 2002). Cerebellar activity is also commonly reported (Daselaar et al., 2003; Doyon, Owen, Petrides, Sziklas, & Evans, 1996; Rieckmann et al., 2010).

SRTT performance of individuals with Parkinson’s disease provides strong evidence about whether learning on the task relies on the structural integrity of the cortico-striatal networks. Parkinson’s disease is caused by the depletion of cells within the striatum (Lang & Lozano, 1998). The degeneration of the striatum should lead to poor performance on tasks that rely on this structure. The first study undertaken for this thesis was a meta-analysis investigating SRTT performance in Parkinson’s disease (the full publication of Study 1 is presented in Appendix A). It should be noted that the motor problems that characterise Parkinson’s disease are unable to account for poor performance on the SRTT. Groups with Parkinson’s disease are generally slower than healthy controls at pressing buttons in response to the visual stimuli (e.g., Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Smith & McDowall, 2004; Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998). However, groups with Parkinson’s disease typically show a decrease in reaction time across practice trials or sequence blocks of the task (e.g., Deroost, Kerckhofs, Coene, Wijnants, & Soetens,
2006; Jackson et al., 1995; Smith & McDowall, 2004; Werheid, Zysset, Müller, Reuter, & von Cramon, 2003), indicating intact ability to complete the movements required. Given that task performance is indexed as the difference in reaction time to sequence versus random blocks of trials, sequence learning can occur even by individuals with overall slow performance. The meta-analysis in Study 1 synthesised findings from 25 studies that compared SRTT performance of groups with Parkinson’s disease to groups of neurologically healthy controls of the same age. The forest plot depicting the results of the analysis is presented in Figure 4.5 (next page). This shows that after synthesising the results of all studies, groups with Parkinson’s disease were found to perform 0.531 standard deviations below that of controls. This indicates that sequence learning as indexed by the SRTT does depend on the structures of the procedural memory system. When the striatum is damaged, performance on the task decreases.

The SRTT is the most common task used to assess procedural memory in children with SLI (Lum et al., 2014; Obeid et al., 2016). Some studies have found that children with SLI evidence poorer sequence learning to that of age-matched TD children (Hsu & Bishop, 2014; Lum et al., 2012; Lum et al., 2010). However, other studies have found comparable performance between SLI and TD groups (Gabriel, Maillart, Guillaume, Stefaniak, & Meulemans, 2011; Gabriel et al., 2012; Hedenius et al., 2011). Lum et al. (2014) undertook a meta-analysis of the eight SLI-SRTT studies that were available at the time. It was shown that on average, individuals with SLI performed 0.328 standard deviations below their peers of the same age. Most (Desmottes, Meulemans, & Maillart, 2015; Hsu & Bishop, 2014; Kuppuraj, Rao, & Bishop, 2016; Lukacs & Kemeny, 2014; Sengottuvel & Rao, 2013), but not all (Desmottes et al., 2017a; Mayor-Dubois et al., 2012), of the more recent studies that were not included in the meta-analysis have also found poorer sequence learning in SLI.
<table>
<thead>
<tr>
<th>Study</th>
<th>Cohen's d</th>
<th>Variance</th>
<th>95% C.I. Lower</th>
<th>95% C.I. Upper</th>
<th>p-value</th>
<th>Control group performs worse</th>
<th>PD group performs worse</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al. (2004)</td>
<td>-0.659a</td>
<td>0.192</td>
<td>-1.517</td>
<td>0.200</td>
<td>.132</td>
<td></td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Smith &amp; McDowall (2006)</td>
<td>-0.410</td>
<td>0.070</td>
<td>-0.928</td>
<td>0.108</td>
<td>.121</td>
<td></td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>Smith et al. (2001)</td>
<td>0.037</td>
<td>0.140</td>
<td>-0.695</td>
<td>0.769</td>
<td>.920</td>
<td></td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>Helmuth, Mayr, &amp; Daum (2000)</td>
<td>0.070</td>
<td>0.086</td>
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<td>.811</td>
<td></td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>Sommer et al. (1999)</td>
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<td>0.148</td>
<td>-0.596</td>
<td>0.913</td>
<td>.680</td>
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<td></td>
<td>3.6</td>
</tr>
<tr>
<td>Cameli (2006)</td>
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<td>0.202</td>
<td>-0.714</td>
<td>1.050</td>
<td>.709</td>
<td></td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Bondi (1991)</td>
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<td>0.101</td>
<td>-0.423</td>
<td>0.826</td>
<td>.527</td>
<td></td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>Selco (1998)</td>
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<td>0.172</td>
<td>-0.575</td>
<td>1.050</td>
<td>.566</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pascual-Leone et al. (1993)</td>
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<td>0.081</td>
<td>-0.293</td>
<td>0.826</td>
<td>.351</td>
<td></td>
<td></td>
<td>4.6</td>
</tr>
<tr>
<td>Brown et al. (2003)</td>
<td>0.288</td>
<td>0.186</td>
<td>-0.556</td>
<td>1.133</td>
<td>.503</td>
<td></td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Seidler et al. (2007)</td>
<td>0.347</td>
<td>0.260</td>
<td>-0.653</td>
<td>1.346</td>
<td>.487</td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Werheid, Zyssel, et al. (2003)</td>
<td>0.350</td>
<td>0.255</td>
<td>-0.639</td>
<td>1.340</td>
<td>.488</td>
<td></td>
<td></td>
<td>2.7</td>
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<tr>
<td>Deroost et al. (2006)</td>
<td>0.410c</td>
<td>0.124</td>
<td>-0.281</td>
<td>1.100</td>
<td>.245</td>
<td></td>
<td></td>
<td>3.9</td>
</tr>
<tr>
<td>Wang, Sun, &amp; Ding (2009)</td>
<td>0.418</td>
<td>0.098</td>
<td>-0.197</td>
<td>1.032</td>
<td>.183</td>
<td></td>
<td></td>
<td>4.3</td>
</tr>
<tr>
<td>Muslimovic et al. (2007)</td>
<td>0.454</td>
<td>0.034</td>
<td>0.095</td>
<td>0.814</td>
<td>.013*</td>
<td></td>
<td></td>
<td>5.6</td>
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<tr>
<td>Shin &amp; Ivry (2003)</td>
<td>0.692</td>
<td>0.195</td>
<td>-0.174</td>
<td>1.559</td>
<td>.117</td>
<td></td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Ferraro et al. (1993)</td>
<td>0.718</td>
<td>0.100</td>
<td>0.099</td>
<td>1.337</td>
<td>.023*</td>
<td></td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>Sarazin et al. (2001)</td>
<td>0.724</td>
<td>0.119</td>
<td>0.048</td>
<td>1.399</td>
<td>.036*</td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>van Tilborg &amp; Hulstijn (2010)</td>
<td>0.747</td>
<td>0.192</td>
<td>-0.113</td>
<td>1.607</td>
<td>.089</td>
<td></td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Smith &amp; McDowall (2004)</td>
<td>0.758c</td>
<td>0.125</td>
<td>0.065</td>
<td>1.451</td>
<td>.032*</td>
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<td>3.9</td>
</tr>
<tr>
<td>Gawryś et al. (2008)</td>
<td>0.821</td>
<td>0.117</td>
<td>0.151</td>
<td>1.491</td>
<td>.016*</td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>Westwater et al. (1998)</td>
<td>0.860</td>
<td>0.191</td>
<td>0.004</td>
<td>1.716</td>
<td>.049*</td>
<td></td>
<td></td>
<td>3.2</td>
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<tr>
<td>Werheid, Ziessler, et al. (2003)</td>
<td>0.926</td>
<td>0.188</td>
<td>0.076</td>
<td>1.775</td>
<td>.033*</td>
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<td>3.2</td>
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<tr>
<td>Stefanova et al. (2000)</td>
<td>1.295</td>
<td>0.069</td>
<td>0.781</td>
<td>1.808</td>
<td>&lt;.001**</td>
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<td>4.8</td>
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<tr>
<td>Gilbert (2004)</td>
<td>1.573</td>
<td>0.245</td>
<td>0.602</td>
<td>2.544</td>
<td>.002*</td>
<td></td>
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<td>2.8</td>
</tr>
<tr>
<td>Jackson et al. (1995)</td>
<td>1.639</td>
<td>0.240</td>
<td>0.679</td>
<td>2.599</td>
<td>&lt;.001**</td>
<td></td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td>Vandenbossche et al. (2013)</td>
<td>1.822d</td>
<td>0.150</td>
<td>1.063</td>
<td>2.581</td>
<td>&lt;.001**</td>
<td></td>
<td></td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>0.531</td>
<td>0.011</td>
<td>0.322</td>
<td>0.740</td>
<td>&lt;.001**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: *Effect size averages results from groups' performance on ambiguous and hybrid sequences; **Effect size averages results from groups' performance on SRT task using verbal and keypress response methods; ***Effect size averages results from groups' performance on FOC and SOC sequences;****Effect size average groups' performance on SRT task completed under single-task conditions and dual-task conditions.

*p < .05; **p < .001

Figure 4.5. Forest plot showing effect sizes of studies comparing SRTT performance of a group with Parkinson’s disease to a control group. Figure taken from Clark et al. (2014), which is presented in Appendix A.

The structure of the sequence may assist in explaining the discrepancies in study findings. There are two main types of sequence used in SRTTs. These are first-order conditional (FOC) and second-order conditional (SOC) sequences (Cohen, Ivry, & Keele, 1990). As described previously, the SRTT involves stimulus presentations in one of four locations on a computer screen, and participants press one of four corresponding buttons after each presentation. On most blocks of trials, the stimulus presentations follow a predetermined sequence. In FOC sequences, each element in the sequence can be predicted to some extent from the preceding element. An FOC sequence, where the numbers 1-4 represent each of the locations on screen, is 1-3-2-3-4-2-1-3-4-1-4-2. In this sequence, for
example, the case of a 3 being followed by a 4 occurs 66.6% of the time, the probability of a 3 being followed by a 2 is 33.3%, and a 3 is followed by a 1 in 0% of transitions. In contrast, for SOC sequences, the probability between transitions is equal. For example, in the sequence 4-2-1-3-2-4-1-2-3-1-4-3, there is a 33.3% probability that 3 will be followed by 1, 2, and 4, and this is the same for every transition. In these sequences, the occurrence of a single position does not give any indication as to what the next position will be. Instead, the position in which the stimulus appears can be predicted by the combination of the preceding two positions.

Learning SOC sequences may rely on different neural regions or networks than learning FOC sequences. One suggestion is that SOC sequence learning requires a network that includes structures of the MTL (Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003; Schendan, Searl, Melrose, & Stern, 2003). Because all transitions occur with equal probability in a SOC sequence, learning the sequence in this case must rely on representations that code one transition in context of the previous transition (Poldrack & Rodriguez, 2003; Schendan et al., 2003). As discussed, the hippocampus is required for binding arbitrary items to context, and so may play an important role in this situation. Evidence for this suggestion was provided in a neuroimaging study by Schendan et al. (2003). In that study, neural activity in healthy adults during SOC sequence learning was examined. It was found that learning, whether implicit or explicit, activated not only the striatum, but also the hippocampus and parahippocampal regions. Thus, it may be that a network that includes hippocampal regions can undertake sequence learning, but only for higher-order sequences.

The presence of multiple sequence learning networks may account for differences in SLI-SRTT findings. Specifically, if SOC sequence learning relies on networks or regions outside of the cortico-striatal system, SOC sequence learning may be intact in SLI. Learning
FOC sequences may present particular difficulty in SLI given that these sequences appear to rely on the cortico-striatal circuits of the procedural memory system. Supporting this proposal, some studies have presented a SOC sequence, and found intact learning in SLI (Desmottes et al., 2015; Mayor-Dubois et al., 2012). However, this has not always been the case, with other studies finding poor performance in SLI even when employing a SOC sequence structure (Gabriel et al., 2013; Lukacs & Kemeny, 2014). Further adding to the difficulty in interpreting differences between FOC and SOC sequence learning, other studies have administered sequences that do not clearly fall into either category (Gabriel et al., 2011; Gabriel, Meulemans, Parisse, & Maillart, 2014; Gabriel et al., 2012). To date, no study has compared FOC and SOC sequence learning in the same group of children with SLI.

4.2.4.3 Summary of procedural memory deficits in SLI. Overall, in support of the core claim of the PDH (Ullman & Pierpont, 2005), children with SLI demonstrate deficits in procedural memory. The procedural memory deficits are relatively small in comparison to the language problems. This questions whether the PDH can account for the substantial language problems in SLI. One suggestion is that a small procedural memory problem in SLI is compounded within the context of language-learning. Perhaps if very basic sequences or probabilities are not acquired in early language development, this leads to further difficulties in learning more complex relationships, and so on. The more pronounced deficit in sequence learning compared to other aspects of procedural memory, has led to the suggestion that the procedural memory problems in SLI are specific to sequence learning (Hsu & Bishop, 2014). Yet, within sequence learning studies, findings have not always been consistent. Using the SRTT, some studies have found that individuals with SLI perform comparably to age-matched peers (e.g., Gabriel et al., 2011; Gabriel et al., 2012), while others have found that performance in SLI is poor (e.g., Hsu & Bishop, 2014; Lum et al., 2012). One suggestion is that the structure of the sequence might influence learning. It may be that, rather than a
general problem with implicit sequence learning, this deficit is more specific to a sequence structure that relies more heavily on cortico-striatal networks. If this is the case, learning sequences of SOC structure may be intact in SLI, while FOC sequence learning may be poor. These issues were investigated in Studies 3 and 4.

4.3 The PDH and Comorbid Problems in Specific Language Impairment

As mentioned in Chapter 3, in addition to language problems, individuals with SLI often have difficulties with reading, motor, and social skills. According to the PDH, impairments of the procedural memory system explain comorbid problems in SLI. It is noted, however, that the PDH does not make specific claims regarding the exact site or extent of neurological abnormality in SLI. In proposing that “All non-linguistic functions that depend on the brain structures of the procedural system…should be problematic.” (Ullman & Pierpont, 2005, p. 425), it is implied that the whole caudate may be functioning abnormally. If this were the case, language, reading, motor, and social skills might all be equally affected. However, Ullman and Pierpont (2005) also state that “…we do not expect that all channels [i.e., cortico-striatal loops] have an equal probability of being affected in SLI. Rather certain channels should be more likely than others to be dysfunctional.” (p. 406). This statement opens the possibility for different types or degrees of comorbid conditions depending on which cortico-striatal loops are dysfunctional. The less ambiguous proposal of the PDH, however, is that a language-related cortico-striatal loop is impaired in SLI, and the subcortical site of this abnormality is likely the caudate. This section outlines three theoretical mechanisms whereby impairments to the procedural memory system may lead to language and additional comorbid problems in reading, motor, and social skills.
4.3.1 Mechanisms I: Comorbid problems occur in SLI because there is not a cortico-striatal loop that is specific to language. As mentioned, while several parallel cortico-striatal loops have thus far been identified, the precise behavioural functions are unknown (Arsalidou et al., 2013; Middleton & Strick, 2000b; Utter & Basso, 2008). Ullman and Pierpont (2005) emphasise that it is not yet known whether a language-specific cortico-striatal loop exists. It may be that comorbid problems occur in SLI because the cortico-striatal loop that is involved in language also processes other information. The same loop that is involved in procedural memory for grammatical regularities may also be involved in processing information needed for reading, motor coordination, or social skills. If this is the case, damage to a single loop could account for comorbid problems in SLI.

4.3.2 Mechanisms II: Comorbid problems occur in SLI because there is damage to multiple cortico-striatal loops of the procedural system. A damaged striatum may also cause comorbid problems in SLI if more than one cortico-striatal loop is impaired. That is, damage may not be exclusive to the cortico-striatal loop that is involved in learning grammar, but also to the loops that underlie skills such as motor coordination, reading, and social functions. As shown in Figure 4.6, it may be that the loops that pass near the same area as the language-related loop are most likely to be damaged. It has been shown that projections from the cortex cluster in three overlapping sections within the striatum (Draganski et al., 2008; Haber, 2003; Haber et al., 2012). These sections appear to be related to emotional functions, cognitive functions, and motor functions (Haber, 2003; Haber et al., 2012). For individuals with SLI who have comorbid motor problems, for instance, it may be that damage is focused on an area in the striatum that receives overlapping projections from cortical areas involved in cognitive and motor functions.
4.3.3 Mechanisms III: Comorbid problems occur in SLI because compromised information is shared between parallel loops. If damage is focused on a language-related loop, comorbid problems could be explained if this damage is passed from one loop to another. While the cortico-striatal loops are able to process information in parallel, evidence suggests that they must also share and integrate information (Draganski et al., 2008; Haber, 2003; Haber et al., 2012). One way that the information could be shared is via interneurons. It has been shown that the axons and dendrites of interneurons cross functional boundaries (Haber, 2003; Haber et al., 2012). Evidence also points to the existence of additional pathways that transfer information between functionally separate loops (Haber, 2003; Haber et al., 2012). Therefore, if one loop is damaged, it may pass faulty signals to other circuits, thereby interrupting the purity of their signals as well (see Figure 4.7). In this way, damage specific to a language-related cortico-striatal loop could flow on to cause problems within other loops that underlie functions such as reading, motor, or social skills.

In summary, deficits to the procedural system could theoretically account for both the language problems and comorbid problems present in SLI. However, neurological evidence is not available to support or refute the proposed mechanisms. The underlying proposal of
the PDH is that abnormalities to structures of the procedural memory system can lead to a range of comorbid problems in SLI. This implies that developmental disorders characterised by deficits in reading, motor skills, or social skills (i.e., dyslexia, DCD, or ASD) will also be associated with procedural memory impairments. This proposal was tested in Study 2. The following section outlines the evidence for procedural memory system deficits in dyslexia, DCD, and ASD.

4.3.4 Do the comorbid problems relate to procedural impairments?

4.3.4.1 Dyslexia. Procedural memory system dysfunction has been proposed to cause dyslexia (Nicolson & Fawcett, 2007; Nicolson, Fawcett, & Dean, 2001). Procedural memory has been suggested to play a role in the acquisition or manipulation of phonological information, and especially in the automatisation of processes that underlie fluent reading (Nicolson & Fawcett, 2007, 2011). Cortico-cerebellar circuitry has been particularly implicated in dyslexia, with impairments in these circuits considered to underpin deficits in automatic processing (Nicolson & Fawcett, 2007; Nicolson et al., 2001). According to this proposal, the reading problems in dyslexia are caused by difficulty in making skills automatic, so that they can be undertaken fluently and with little conscious effort (Nicolson, Fawcett, Brookes, & Needle, 2010; Nicolson et al., 2001). Neuroimaging studies support the
claim of cerebellar involvement in dyslexia, repeatedly showing that the cerebellum is abnormal in children and adults with dyslexia (Kronbichler et al., 2008; Linkersdorfer, Lonnemann, Lindberg, Hasselhorn, & Fiebach, 2012; Pernet, Poline, Demonet, & Rousselet, 2009).

Abnormalities have also been found in structures of the basal ganglia in dyslexia. For instance, abnormalities have been found in the striatum (Brown et al., 2001; Georgiewa et al., 2002; Hoeft et al., 2007; Jednorog, Gawron, Marchewka, Heim, & Grabowska, 2013), and the basal ganglia more generally (Eckert et al., 2005; Pernet et al., 2009). One suggestion is that striatal dysfunction is related to problems learning phonological patterns that underlie language and reading processes (Jednorog et al., 2013). Alternatively, the cortico-cerebellar dysfunction may relate to reading problems, while the apparent cortico-striatal deficits may reflect comorbid language impairment (Nicolson & Fawcett, 2007).

Support for procedural system impairments in dyslexia also comes from performance on procedural memory tasks. Lum, Ullman, and Conti-Ramsden (2013) conducted a meta-analysis of 13 studies that investigated SRTT performance in individuals with dyslexia. It was found that on average, those with dyslexia performed significantly more poorly on the SRTT than their TD peers of comparable age. Thus, both behavioural and neurological evidence supports the proposal that reading problems are associated with procedural memory system impairments.

4.3.4.2 Developmental Coordination Disorder. Few studies have investigated the neurological correlates of DCD. However, it has been suggested that structures of the procedural system including the basal ganglia and/or cerebellum are likely to be dysfunctional (Nicolson & Fawcett, 2007; Zwicker, Missiuna, & Boyd, 2009). One neuroimaging study has provided evidence for atypical cerebellar functioning in DCD.
In that study, it was found that during a fine motor task, cerebellar activity in a group of children with DCD was lower than that of age-matched TD children. Studies that have administered behavioural tasks have also suggested that the cerebellum is implicated in the disorder. The cerebellum is important for postural control and for sensorimotor adaptation (Bernard & Seidler, 2013; Doyon et al., 2003; Imamizu et al., 2000), both of which may be poor in DCD. For children with DCD, altered postural muscle activity takes the form of delayed anticipatory activation, which leads to poor stability (Geuze, 2005; Owen & Leonard, 2006). Sensorimotor adaptation may also be poor in DCD. Sensorimotor adaptation tasks require participants to perform a motor task such as throwing or drawing, while adapting to distorted visual feedback (Kagerer, Bo, Contreras-Vidal, & Clark, 2004). The performance of children with DCD on these tasks is poor (Cantin, Polatajko, Thach, & Jaglal, 2007; Kagerer et al., 2004; Seger & Spiering, 2011; Stark & Okado, 2003). The pattern of errors made by children with DCD resembles that of individuals with cerebellar degeneration (Bo, Block, Clark, & Bastian, 2008; Lang & Bastian, 2002; Morton & Bastian, 2004). The similarity in performance between the two groups has been taken as evidence that cerebellar functioning might be affected in DCD (Bo & Lee, 2013; Kagerer et al., 2004).

The basal ganglia and cortico-striatal loops have also been suggested as sites of abnormality in DCD (Bo & Lee, 2013; Nicolson & Fawcett, 2007). Supporting this proposal, one neuroimaging study found reduced connectivity between the striatum and parietal cortex in children with DCD (Querne et al., 2008), and a second study found reduced connectivity between the striatum and primary motor cortex (McLeod, Langevin, Goodyear, & Dewey, 2014). Additionally, behavioural tasks have been administered to assess procedural memory functioning in DCD, though these studies are also scarce. Three studies have administered the SRTT to children with DCD (Gheysen, Van Waelvelde, & Fias, 2011; Lejeune, Catale,
Willems, & Meulemans, 2013; Wilson, Maruff, & Lum, 2003). In all three studies, children with DCD performed more poorly than TD children on the task. However, this difference only reached statistical significance in one study (Gheysen et al., 2011). Overall, there have been very few studies that have investigated procedural memory system functionality in DCD. The available evidence suggests that procedural memory may be impaired in this group.

4.3.4.3 Autism Spectrum Disorder. ASD has also been associated with atypical procedural memory system structures. Both the cerebellum (Fatemi et al., 2012; Nayate, Bradshaw, & Rinehart, 2005), as well as connectivity within several cortico-striatal loops (Delmonte, Gallagher, O’Hanlon, McGrath, & Balsters, 2013; Langen et al., 2012) have been implicated. Abnormalities of the cerebellum have been repeatedly found in both children and adults with ASD (Bailey et al., 1998; Courchesne et al., 1994; Fatemi et al., 2012; Nayate et al., 2005). The cerebellar deficits are considered to contribute to the problems with posture, balance, and coordination that many individuals with ASD experience (Fatemi et al., 2012; Nayate et al., 2005).

Aberrant cortico-striatal connectivity has also been found in groups with ASD (Delmonte et al., 2013; Ecker et al., 2012; Kohls et al., 2012; Langen et al., 2012). It appears that ASD is related to functional hyperactivity, rather than hypoactivity, of procedural memory system circuitry (e.g., Delmonte et al., 2013; Picci, Gotts, & Scherf, 2016). Several cortico-striatal loops have been implicated in ASD, including the loops that involve dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex (Delmonte et al., 2013; Langen et al., 2012). As discussed, the specific role of each circuit is not clear, though emotion- and cognition-related functions, along with motor functions, have been broadly proposed (Arsalidou et al., 2013; Haber et al., 2012). In ASD, it has been shown that
hyperconnectivity within the loop that includes dorsolateral prefrontal cortex, correlates with the degree of restricted repetitive behaviours (Delmonte et al., 2013; Ecker et al., 2012). Social motivation deficits in ASD may be related to abnormalities within the orbitofrontal-striatal loop (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Kohls et al., 2012). In one study, it was found that increased hyperconnectivity within this circuit related to increased social motivation in ASD groups, possibly reflecting compensatory processes in some individuals (Delmonte et al., 2013).

Hyperactivity of the procedural memory system may explain the performance of individuals with ASD on behavioural measures of procedural memory. A common finding is that groups with ASD demonstrate intact performance on procedural memory tasks (e.g., Brown, Aczel, Jiménez, Kaufman, & Grant, 2010; Travers, Klinger, Mussey, & Klinger, 2010). A meta-analysis summarised results of 11 studies investigating procedural memory task performance in ASD (Obeid et al., 2016). It was found that on average, groups with ASD performed comparably to TD groups. Thus, although structures of the procedural memory system may be abnormal in ASD, this does not appear to lead to procedural memory difficulties for this group. This result may provide difficulties for the PDH in explaining comorbidity between ASD and SLI. The PDH proposes that comorbid conditions in SLI, such as social skill deficits, arise from shared procedural memory problems. It seems, however, that procedural memory impairments are not common in all conditions that are comorbid with SLI.

4.3.4.4 The relationship between comorbid disorders. Dyslexia, DCD, and ASD often co-occur with each other and with SLI (Conti-Ramsden et al., 2006; Dyck, Piek, Hay, & Hallmayer, 2007; Flapper & Schoemaker, 2013; Kaplan, Wilson, Dewey, & Crawford, 1998; McArthur et al., 2000), and it is possible that the procedural impairments do not relate
to each disorder to the same degree. It may be that children with SLI often have procedural system impairments, but that these impairments are related to comorbid problems, and not related directly to the language impairments themselves (e.g., Mayor-Dubois et al., 2012).

Many studies investigating dyslexia, DCD, or ASD do not assess the language skills of their participants, making inferences about which skills are related to procedural learning difficult. It is necessary for future studies to directly examine procedural learning along with reading, motor, and social skills in a group with SLI to clarify these relationships. This issue will be addressed in Chapters 5 and 8 of this thesis.

4.4 Declarative Memory Compensation

A further claim made by the PDH is that the declarative memory system compensates for the impaired procedural memory system (Ullman & Pierpont, 2005; Ullman & Pullman, 2015). The proposal is that the encoding, storage, and retrieved of information and skills typically undertaken by the procedural memory system, are instead undertaken by the declarative memory system. In the case of SLI, it is proposed that the learning and use of grammar is supported by the declarative memory system. How might the declarative memory system learn and use grammar? Ullman suggests that the declarative system might be able to learn grammar via some associative rule. For example, to learn the past tense inflection via the declarative memory system might require each regular past tense inflection and regular verb to be learnt item-by-item. This type of learning might explain why grammatical development is slower in SLI. As reviewed in Chapter 2, it is not the case that SLI is associated with an absence of grammatical development. As shown in Figure 2.2, from the ages of 3 to 9 years children with SLI produce fewer grammatical errors. Presumably, under the PDH, this protracted period of grammatical development occurs as each past tense inflection is learnt one verb at a time.
There is currently very little direct evidence for declarative memory based compensation in SLI. One study (Lum et al., 2012) examined compensation in a group of 51 children with SLI (mean age 9;10), and 51 TD children (mean age 9;10). Tests of procedural memory (the SRTT) and declarative memory, along with measures of expressive and receptive grammar and vocabulary skills were administered. As predicted by the PDH, the group with SLI performed significantly more poorly on the SRTT than their TD peers. It was found that for both SLI and TD groups, vocabulary skills correlated with the test of verbal declarative memory. This is in line with the suggestion that individual words are encoded and retrieved by the declarative system. Grammatical skills correlated with the procedural task in the TD group, but with the verbal declarative task in the SLI group. This finding is in line with Ullman and Pierpont’s (2005) claim that declarative memory compensates for procedural memory system problems in SLI. Children with SLI who had better declarative memory demonstrated better grammatical skills.

Not all studies provide support for the claim that declarative memory compensates for procedural memory in SLI. Poll, Miller, and van Hell (2015) investigated compensation in groups of young adults with and without language impairment. Declarative memory compensation might be expected to be clearer for adults than children. Regions of the MTL that underpin the declarative memory system mature in late adolescence (Giedd et al., 1999; Gogtay et al., 2004). Thus declarative memory functioning is also expected to develop beyond childhood. Participants in this study were 21 adults with language impairment (mean age 22;3) and 21 age-matched controls (mean age 21;6). Tests of procedural memory (the Weather Prediction task), along with a measure of non-verbal declarative memory, and measures of grammar were administered. Based on the compensation aspect of the PDH, it was expected that for the language impaired group, grammar would correlate with declarative memory. For non-language impaired adults, grammar was expected to correlate with the
procedural memory. Results of this study did not support the compensation hypothesis. First, in contrast to the proposal that declarative memory is unaffected in SLI, the language impaired group performed significantly more poorly than the control group on the declarative memory task. The language impaired group also performed significantly more poorly than controls on the procedural memory task, as expected by the PDH. In the key test of compensation, grammar skills did not significantly correlate with performance on the declarative memory task for the language impaired group. For both groups of participants, grammar did not correlate with either the declarative memory or procedural memory tasks. These findings are difficult to reconcile not only with the proposal of declarative memory compensation, but also with the proposal that grammar is typically undertaken by the procedural memory system. Overall, it is not clear whether declarative memory does compensate for procedural memory impairments in SLI.

5. Overall Summary and Thesis Aims

In summary, research investigating the PDH indicates that procedural memory is impaired in SLI. Evidence suggests that the procedural learning deficits appear to be most strongly related to implicit sequence-learning. However, not all studies have shown impaired implicit sequence learning in SLI. It may be that implicit sequence learning is not all undertaken by the procedural memory system. Specifically, it has been suggested that while FOC sequences likely rely on cortico-striatal networks, SOC sequences may be learnt via a different network. This raises the possibility that in SLI, it is only learning sequences of a FOC structure that is problematic. However, research to date has not compared FOC and SOC sequence learning in SLI.

A second issue that has not been investigated is whether procedural memory impairments are directly related to the grammar difficulties in SLI, or are more related to
reading, motor, or social problems. The PDH claims that the range of problems in SLI all stem from dysfunction of procedural memory system circuitry, and that declarative memory compensates for these problems. First, this suggests that if procedural memory impairments cause the reading, motor, and social skill deficits in SLI, it might underpin the same deficits in other disorders. Thus, it would be expected that along with SLI, dyslexia, DCD, and ASD are each associated with procedural memory deficits. Indeed, this claim has been made by a number of researchers (e.g., Mayor-Dubois et al., 2012; Mostofsky, Goldberg, Landa, & Denckla, 2000; Nicolson & Fawcett, 2007; Ullman & Pierpont, 2005; Vicari et al., 2005).

Second, the claims of the PDH imply that in SLI, language, reading, motor, and social skills would be correlated. That is, if the declarative memory system is responsible for learning each skill, proficiency of each skill will be determined by declarative memory abilities. This thesis investigated these research questions. Specifically, the following two questions were posed:

1. Are the implicit sequence learning problems specific to FOC sequences? If so, this might mean there are different neural mechanisms that underpin implicit sequence learning. This question is addressed in Chapters 6 and 7. Chapter 6 presents a study in which children with and without SLI completed both a FOC and SOC sequence learning task. Chapter 7 used transcranial magnetic stimulation to investigate the neural networks responsible for learning each type of sequence.

2. Are the implicit sequence learning deficits in SLI related to the language problems, or to comorbid problems? This question is addressed in Chapters 5 and 8. Chapter 5 uses second-order meta-analysis to compare SRTT performance across different disorders. Chapter 8 presents a study which investigated the relationship between implicit sequence
learning, language, reading, and motor skills in a group of SLI children and a group of TD children.
Chapter 5

Study 2: Is Poor Procedural Memory Only Associated with Grammatical Impairment?

As reviewed in Chapter 4, according to the PDH (Ullman & Pierpont, 2005), dysfunction associated with the cortico-striatal circuitry of the procedural memory system in SLI is hypothesised not only to lead to grammatical impairment, but also may explain why affected children present with co-morbid problems. An assumption of this claim is that poor procedural memory can lead to a range of different types of problems. The study presented in this chapter tested this claim using a second order meta-analysis of serial reaction time task (SRTT) studies.

In Chapter 4 it was argued that the SRTT can be considered to provide a measure of the procedural memory system, as it is sensitive to cortico-striatal functioning (Jackson et al., 1995; Westwater et al., 1998). To date, the SRTT has been commonly used to test the procedural memory system in SLI (Lum et al., 2012; Tomblin, Mainela-Arnold, & Zhang, 2007) and other disorders as well. This includes dyslexia (Russeler, Gerth, & Munte, 2006; Vicari et al., 2005), autism spectrum disorder (Gordon & Stark, 2007; Mostofsky et al., 2000), and disorders affecting motor functioning such as Parkinson’s disease (Deroost et al., 2006; Muslimović, Post, Speelman, & Schmand, 2007) and developmental coordination disorder (Gheysen et al., 2011; Wilson et al., 2003). The literature from each of the aforementioned disorders have now been summarised in separate meta-analyses (Clark et al., 2014; Lum et al., 2013; Obeid et al., 2016; Wilson & McKenzie, 1998). If poor procedural memory can result in a range of different problems (e.g., problems with reading, motor, or social skills), the expectation is that disorders with quite different symptoms should also have poor procedural memory, at least measured using the SRTT. The second order meta-analysis (Clark & Lum, 2017) presented in this chapter tests this claim.
The manuscript presented in this chapter is the post-publication version, except that table, figure, and subheading numbers have been altered to improve flow within the thesis.

The final publication is available at Springer via http://dx.doi.org/10.1016/j.bandc.2017.07.004.
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<tr>
<td>Gillian Clark</td>
<td>School of Psychology</td>
<td><a href="mailto:gillian.clark@deakin.edu.au">gillian.clark@deakin.edu.au</a></td>
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Conceptualised the paper, completed the systematic search, data extraction and data analysis, drafted manuscript and revisions.

*I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.*

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<td>Thesis supervisor – involved in conceptualising the paper, analysing the data, drafting and revising of the manuscript.</td>
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Procedural learning in Parkinson’s disease, specific language impairment, dyslexia, schizophrenia, developmental coordination disorder, and autism spectrum disorders: A second-order meta-analysis

Gillian M. Clark and Jarrad A. G. Lum

Cognitive Neuroscience Unit, School of Psychology, Deakin University, Australia

Author Note

Gillian M. Clark, Cognitive Neuroscience Unit, School of Psychology, Deakin University; Jarrad A. G. Lum, Cognitive Neuroscience Unit, School of Psychology, Deakin University.

Correspondence concerning this article should be addressed to Gillian Clark, Cognitive Neuroscience Unit, School of Psychology, Deakin University, 221 Burwood Highway, Burwood, Victoria, Australia, 3121.

Email: gillian.clark@deakin.edu.au
Abstract

The serial reaction time task (SRTT) has been used to study procedural learning in clinical populations. In this report, second-order meta-analysis was used to investigate whether disorder type moderates performance on the SRTT. Using this approach to quantitatively summarise past research, it was tested whether autism spectrum disorder, developmental coordination disorder, dyslexia, Parkinson’s disease, schizophrenia, and specific language impairment differentially affect procedural learning on the SRTT. The main analysis revealed disorder type moderated SRTT performance ($p = .010$). However, in autism spectrum disorder procedural learning is intact. This report demonstrates comparable levels of procedural learning impairment in developmental coordination disorder, dyslexia, Parkinson’s disease, schizophrenia, and specific language. With respect to autism, procedural learning in this group is spared.

*Keywords:* Serial reaction time task; procedural learning; meta-analysis; neurodevelopmental disorders
5.1 Introduction

Nissen and Bullemer’s (1987) Serial Reaction Time Task (SRTT) is commonly used to examine procedural learning (e.g., Gordon & Stark, 2007; Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Knopman & Nissen, 1991; Tomblin, Mainela-Arnold, & Zhang, 2007). In broad terms, procedural learning describes knowledge that is acquired incrementally, often implicitly, through repeated exposures to stimuli or training (Squire & Zola, 1996). A substantial number of studies have used the SRTT to examine whether procedural learning is impaired in a wide range of neurodegenerative and neurodevelopmental disorders (e.g., Deroost et al., 2010; Gordon & Stark, 2007; Knopman & Nissen, 1991; Lum, Conti-Ramsden, Page, & Ullman, 2012; Wilson, Maruff, & Lum, 2003). The SRTT literature from a number of disorders has now been summarised using meta-analysis (e.g., Lum, Ullman, & Conti-Ramsden, 2013; Siegert, Weatherall, & Bell, 2008). The existence of multiple meta-analyses that examine SRTT performance provides a unique opportunity to compare the status of procedural learning impairments across multiple disorders using second order meta-analysis. In second order meta-analysis, results of multiple meta-analyses are combined. While second order meta-analysis has been used in the field of organisational psychology widely (e.g., Archer et al., 2014; Barrick, Mount, & Judge, 2001; Peterson, 2001; Tamim, Bernard, Borokhovski, Abrami, & Schmid, 2011), to our knowledge this is the first report to apply this technique to summarising research in the field of neuropsychology.

5.1.1 The Serial Reaction Time Task

On the SRTT a visual stimulus repeatedly appears in one of four spatial locations on a computer display. Participants aim to press a button on a response pad that corresponds to the location of the stimulus. A schematic overview of the task is presented in Figure 5.1. In
the standard version of the task, stimulus presentations are grouped into blocks of trials. Unknown to participants, on most blocks the presentation of the stimulus follows a pre-determined sequence. After several blocks in which the stimulus repeatedly follows the sequence, a block of trials is presented in which the stimulus appears in random order. Reaction times that measure the time taken to press the correct button after stimulus presentation are recorded throughout the task. If the sequence is learnt, reaction times across sequence blocks become faster, and then slow down for the random block (Nissen & Bullemer, 1987). This result has been observed in both children and adults (e.g., Cohen, Ivry, & Keele, 1990; Thomas & Nelson, 2001). Figure 5.1 (see right panel, solid line) depicts hypothetical data when the sequence has been learnt. The increase in reaction times from sequence to random blocks likely occurs because the sequence has been learnt, but on the random trials knowledge about the sequence cannot be used to anticipate the stimulus’ location and responses needs to be adjusted (Robertson, 2007). When the sequence has not been learnt, the presence or absence of the sequence does not influence reaction times and a reliable difference between these two blocks does not occur. Hypothetical data when the sequence has not been learnt is also presented in Figure 5.1 (see right panel, broken line). This result has been observed in several neurodegenerative (e.g., Ferraro, Balota, & Connor, 1993; Knopman & Nissen, 1991) and neurodevelopmental disorders (e.g., Gheysen, Van Waelvelde, & Fias, 2011; Lum et al., 2012; Vicari et al., 2005).

Much is known about the neurological structures activated when participants complete the SRTT. Neuroimaging studies have shown that the basal ganglia, particularly the striatum, are engaged during learning on the task (Daselaar, Rombouts, Veltman, Raaijmakers, & Jonker, 2003; Grafton, Hazeltine, & Ivry, 1995; Rauch, Whalen, et al., 1997; Reiss et al., 2005; Willingham, Salidis, & Gabrieli, 2002), and that the degree of striatal activation positively correlates with task performance (Rauch, Whalen, et al., 1997; Reiss et
Figure 5.1. Left panel shows a schematic overview of the serial reaction time task depicting a single trial. Right panel shows hypothetical data when the sequence has been learnt (solid line), or has not been learnt (broken line). When the size of the difference in reaction times between the final sequence block and the random block is smaller for a disordered group in comparison to a control group, it is taken as evidence for a procedural learning deficit in the disorder.

The cerebellum also appears to play a role on the SRTT. Individuals with cerebellar dysfunction demonstrate poorer learning on the SRTT (Pascual-Leone et al., 1993; Torriero, Oliveri, Koch, Caltagirone, & Petrosini, 2004). Neocortical structures associated with the task are primary and supplementary motor regions and prefrontal regions (Clerget, Poncin, Fadiga, & Olivier, 2011; Daselaar et al., 2003; Grafton et al., 1995; Pascual-Leone, Wassermann, Grafman, & Hallett, 1996; Wilkinson, Teo, Obeso, Rothwell, & Jahanshahi, 2009; Willingham et al., 2002). Thus, it appears that SRTT performance relies on the cortico-subcortical network of the procedural memory system.

5.1.2 Procedural Learning in Neurodegenerative and Neurodevelopmental Disorders

The SRTT has been used to investigate procedural learning in a range of clinical populations (e.g., Clark, Lum, & Ullman, 2014; Obeid, Brooks, Powers, Gillespie-Lynch, & Lum, 2016; Siegert et al., 2008). One of the first studied were conditions characterised by neurodegeneration of the basal ganglia, such as Parkinson’s and Huntington’s diseases (e.g.,
Ferraro et al., 1993; Knopman & Nissen, 1991; Pascual-Leone et al., 1993). Research undertaken with these groups showed poorer procedural learning on the SRTT compared to controls. Specifically, the difference in reaction times between the random and sequence blocks was smaller in groups comprising individuals with Parkinson’s or Huntington’s diseases compared to control groups (Clark et al., 2014; Knopman & Nissen, 1991; Willingham & Koroshetz, 1993).

In relatively more recent times, performance on the SRTT has been studied in neurodevelopmental disorders in order to test whether procedural learning is impaired. This includes autism spectrum disorder (ASD; e.g., Gordon & Stark, 2007), dyslexia (e.g., Vicari et al., 2005), specific language impairment (SLI; e.g., Lum et al., 2012), schizophrenia (e.g., Schwartz, Howard, Howard, Hovaguimian, & Deutsch, 2003), and developmental coordination disorder (DCD; e.g., Gheysen et al., 2011). Procedural learning problems in each of these disorders are proposed to stem from atypical development of cortico-subcortical networks. In SLI, a cortico-striatal network comprising the caudate and Broca’s area is implicated (Ullman & Pierpont, 2005). DCD has been associated with aberrant connectivity between the striatum and primary motor cortex (McLeod, Langevin, Goodyear, & Dewey, 2014), and between the cerebellum and parietal cortex (Zwicker, Missiuna, Harris, & Boyd, 2011). Dyslexia has been associated with abnormalities in cortico-cerebellar circuits, possibly involving bilateral inferior frontal gyrus (Nicolson & Fawcett, 2007; Nicolson, Fawcett, & Dean, 2001; Stanberry et al., 2006). Finally, in ASD and schizophrenia, cerebellar (Andreasen & Pierson, 2008; Fatemi et al., 2012; Nayate, Bradshaw, & Rinehart, 2005) and cortico-striatal connectivity abnormalities (Langen et al., 2012; Nayate et al., 2005; Robbins, 1990; Simpson, Kellendonk, & Kandel, 2010; Yoon, Minzenberg, Raouf, D'Esposito, & Carter, 2013) have been reported.
In all the aforementioned disorders one hypothesised endpoint is procedural learning problems and therefore poorer performance on the SRTT. Results from meta-analyses have found poor procedural learning in SLI (Lum, Conti-Ramsden, Morgan, & Ullman, 2014; Obeid et al., 2016), dyslexia (Lum et al., 2013), DCD (Wilson, Ruddock, Smits-Engelsman, Polatajko, & Blank, 2013), and schizophrenia (Siegert et al., 2008). Each of these meta-analyses have shown that on average, individuals with the disorder demonstrate a significantly smaller difference in reaction time between random and sequence trials than typically developing individuals. In contrast, meta-analyses have shown that individuals with ASD perform comparably to their peers on the SRTT (Foti, De Crescenzo, Vivanti, Menghini, & Vicari, 2015; Obeid et al., 2016). Results from these meta-analyses have been interpreted to suggest that procedural learning problems cause the language deficits in SLI (Lum et al., 2014), reading problems in dyslexia (Lum et al., 2013), and possibly the social cognition problems in schizophrenia (Siegert et al., 2008). Nicolson and Fawcett (2007) suggest that impairments to different parts of the procedural learning network lead to the different patterns of cognitive deficits across disorders.

5.1.3 Does ‘Disorder Type’ Moderate Performance on the SRTT?

It is not yet known whether there are differences in procedural learning problems between neurodegenerative disorders of the basal ganglia (Clark et al., 2014) and some neurodevelopmental disorders (Lum et al., 2013; Obeid et al., 2016; Siegert et al., 2008; Wilson et al., 2013). That is, whether the type of disorder asserts a differential influence on procedural learning. According to Nicolson and Fawcett’s (2007) model, the type of cognitive or behavioural problems observed in a neurodevelopmental disorder depends on the loci of the neurological problems within the network that supports procedural learning. This might lead to a situation where performance on the SRTT task is more affected in one
condition compared to another. For instance, Parkinson’s disease is characterised by neurodegeneration of the basal ganglia (Lang & Lozano, 1998). There is no neurodegeneration in SLI, dyslexia, or DCD. Given this, it could be that the procedural learning problems in Parkinson’s disease are more severe in comparison to neurodevelopmental conditions.

However, there is an alternative possibility. There are high rates of comorbidity between each of the developmental disorders (e.g., Flapper & Schoemaker, 2013; Kaplan, Wilson, Dewey, & Crawford, 1998; Leyfer, Tager-Flusberg, Dowd, Tomblin, & Folstein, 2008; McArthur, Hogben, Edwards, Heath, & Mengler, 2000). For example, Kaplan et al. (1998) found that over 50% of children with DCD also met criteria for dyslexia. Similarly, McArthur et al. (2000) reported an overlap of 50% between dyslexia and SLI. Furthermore, the core symptoms of one disorder are quite often the secondary symptoms of another disorder. Language, reading, and motor skill problems are common to SLI, dyslexia, DCD, schizophrenia, ASD, and Parkinson’s disease (Altmann & Troche, 2011; Archibald & Alloway, 2008; Condray, Steinhauer, van Kammen, & Kasparek, 2002; Fawcett & Nicolson, 1995; Hill, 2001; McArthur et al., 2000; Murray & Rutledge, 2014; Revheim et al., 2006; Walther & Strik, 2012). One possibility is that procedural learning problems are uniquely, or most strongly, related to one of these symptoms. For example, if procedural learning is uniquely or most strongly related to motor problems, one might expect that the procedural learning problems are most severe in conditions whose core deficit is characterised by motor dysfunction. Under this view one might expect DCD and Parkinson’s disease to have poorer procedural learning compared to other types of disorders.

5.1.4 Using Second-order Meta-analysis to Examine whether Disorder Type Moderates Performance on the SRTT
Second-order meta-analysis can be used to investigate the effect of disorder type on performance on the SRTT. In a first-order meta-analysis, study-level effect sizes are synthesised and an overall summary effect is computed (Borenstein, Hedges, Higgins, & Rothstein, 2011; Hunter & Schmidt, 2004). The advantage of this approach is that by pooling findings across studies, sampling error can be reduced in computing an effect size. In a second-order meta-analysis, differences between first-order effect sizes can be examined. The extent to which these differences reflect either meaningful/systematic influences (such as disorder type) or second-order sampling error can be quantified (Hunter & Schmidt, 2004; Tamim et al., 2011). Second-order sampling error occurs because the total number of studies included in first-order meta-analyses is not infinite, and it reflects random error that remains even after first-order sampling error is accounted for (Hunter & Schmidt, 2004).

Second-order meta-analysis can be used to statistically test whether disorder type influences effect sizes on the SRTT. As noted earlier, one possibility is that performance on the SRTT varies between different disorders. If this is the case, the expectation is that the second-order sampling error would be less than 100%. In this scenario disorder type would be considered to moderate the overall summary effect sizes between the first-order meta-analyses. Furthermore, there may be a reliable or significant difference in the average effect size computed from a meta-analysis undertaken with one disorder compared to another. These comparisons can be undertaken in the context of a second-order meta-analysis (Borenstein et al., 2011; Tamim et al., 2011). Another outcome is that disorder type does not moderate the overall summary effect sizes from first-order meta-analyses. If this is the case variability or differences between first-order effect sizes should reflect second-order sampling error. Second order meta-analyses permits one to test the influence of disorder type on procedural learning.
5.1.5 Aim of the Current Report

This report tested whether disorder type influences procedural learning. Specifically, we compared the average first-order effect sizes of meta-analyses investigating SRTT performance in individuals with Parkinson’s disease, SLI, dyslexia, ASD, DCD, and schizophrenia. The goal of this analysis was to examine the extent to which disorder type moderates performance on the SRTT. The hypothesis tested was that disorder type would be a moderator variable on the SRTT. This moderator effect would arise because Parkinson’s disease and DCD would be associated with a more severe deficits on the SRTT relative to the other studied disorders.

5.2 Method

5.2.1 Study Design

A search was undertaken using the electronic databases PsycInfo, MEDLINE, CINAHL, ERIC, and PubMed. Titles and abstracts were searched for keywords relating to the SRTT and to meta-analysis. Details of all keywords, Boolean operators, and syntax are presented in the Supplementary material. The search strategy was executed in August, 2016.

5.2.2 Inclusion Criteria

Articles were only included if they met the following two criteria. First, the article needed to present a meta-analysis that summarised studies that investigated performance on the SRTT. Second, the meta-analysis needed to compare performance of a clinical group to an age-matched control group. To ensure that each study was represented only once, articles that included data that were also reported in a larger meta-analysis were excluded (this included the omission of a meta-analysis by Foti et al. (2015), which did not measure SRTT performance using a comparable method to the other meta-analyses, and which included only
256 records identified through database searching.

126 duplicate records excluded.

130 records left after duplicates removed.

109 records excluded for not meeting eligibility criteria:
- Analyses did not involve a comparison between a disordered group and a control group (n = 9).
- Article did not involve meta-analysis (n = 16).
- The SRTT was not used (n = 84).

21 records left after screening abstracts for eligibility.

5 records (reporting 6 meta-analyses) used in quantitative review.

4 records excluded for being a duplicate analysis.

12 records excluded for not meeting eligibility criteria:
- Article did not use the SRTT (n = 10).
- Article was not a meta-analysis (n = 1).
- Analyses did not involve a comparison between a disordered group and a control group (n = 1).

Figure 5.2. PRISMA flowchart showing process of identifying articles for the second-order meta-analysis
5.2.3 Study Selection

After the removal of duplicates, the authors independently screened articles according to the eligibility criteria described above. There was 100% agreement on these articles. A total of five articles, corresponding to six meta-analyses, were included and their data extracted for second-order meta-analysis.

5.2.4 Data Extraction Procedures

The information extracted from each meta-analysis were the effect sizes, confidence intervals, and sample sizes for each study included in the meta-analysis. All these data were only collected from SRTT data. This resulted in excluding studies from three meta-analyses (the two meta-analyses in Obeid et al., 2016; one from Wilson et al., 2013). The overall summary effect size for each meta-analysis was recalculated, using a random-effects model. This method assumes that differences between effect sizes are due to a combination of both within-study error (sampling error) and between-study error (systematic influences). To facilitate comparability of the meta-analyses, all effect sizes were converted to Hedges’ $g$. This ensures that effect sizes can be compared directly, as they are all in the same metric. Converting from Cohen’s $d$ to Hedges’ $g$ involves multiplying $d$ by a correction factor (see Supplementary material). All calculations were undertaken using Comprehensive Meta-Analysis software (Borenstein, Hedges, Higgins, & Rothstein, 2005). A description of the data extracted from each meta-analysis along with final sample sizes is outlined in Table 5.1.

5.2.5 Meta-analytic Procedures

First, the proportion of variance between the first-order meta-analyses that was due to sampling error versus systematic influences was determined. Following the method used by Tamim et al. (2011), this was calculated using the $I^2$ statistic. In first-order meta-analysis, the
Table 5.1.

**Summary of Data Extracted from Meta-Analyses**

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Disorder</th>
<th>Data extracted</th>
<th>No. Studies</th>
<th>n (study group)</th>
<th>n (control group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark et al. (2014)</td>
<td>Parkinson's disease</td>
<td>Sample sizes extracted from Table 1, effect sizes and CIs extracted from Figure 3.</td>
<td>27</td>
<td>505</td>
<td>460</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample sizes extracted from Table 1, effect sizes and CIs from Figure 5. Overall summary effect size and CIs recalculated after excluding four studies that did not use the SRTT.</td>
<td>11</td>
<td>259</td>
<td>319</td>
</tr>
<tr>
<td>Lum et al. (2013)</td>
<td>Dyslexia</td>
<td>Sample sizes extracted from Table 1, effect sizes (Cohen's $d$) and CIs extracted from Figure 3. Converted from Cohen's $d$ to Hedges' $g$.</td>
<td>14</td>
<td>314</td>
<td>317</td>
</tr>
<tr>
<td>Siegert et al. (2008)</td>
<td>Schizophrenia</td>
<td>Sample sizes extracted from Table 1, effect sizes and CIs extracted from Table 2.</td>
<td>9</td>
<td>205</td>
<td>159</td>
</tr>
<tr>
<td>Wilson et al. (2013)</td>
<td>Developmental coordination disorder</td>
<td>Studies identified from Table S1. Effect sizes calculated from statistics provided in original studies.a</td>
<td>2</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Obeid et al. (2016)</td>
<td>Autism spectrum disorder</td>
<td>Sample sizes and task types extracted from Table 2, effect sizes and CIs from Figure 6. Overall summary effect size and CIs recalculated after excluding 11 studies that did not use the SRTT.</td>
<td>7</td>
<td>101</td>
<td>130</td>
</tr>
</tbody>
</table>

CIs = 95% Confidence Intervals.

aFor further details see Supplementary Materials

$I^2$ statistic quantifies the percentage of heterogeneity that is due to systematic influences. For example, an $I^2$ value of 100 would indicate 100% of the differences between study level effect sizes is due to one or more systematic influence. Alternatively, an $I^2$ value of zero would indicate differences between a set of study level effect sizes is solely due to sampling error. Applying this statistic to the average effect sizes from the first-order meta-analyses provides the percentage of heterogeneity between meta-analyses that is due to between-meta-analysis error or systematic influences. For example an $I^2$ value of zero would indicate that
variability between first order meta-analyses can be attributed to second-order sampling error. In the context of the current report, if the $I^2$ value was not significantly different from zero, this would indicate that disease/disorder type does not moderate performance on the SRTT.

The second set of analyses used in this report investigated whether disease/disorder type was related to effect sizes. Following the same approach as Tamim et al. (2011), the analysis used was mixed-effects subgroup analysis. Using the effect sizes for all individual studies, this analysis tested whether there were significant differences in the average effect size of each meta-analysis.

5.3 Results

5.3.1 SRTT Performance

A forest plot showing the recalculated summary effect sizes, along with 95% confidence intervals, is presented in Figure 5.3. As noted earlier, only data from SRTTs were summarised, and all effect sizes were converted to Hedges’ $g$. Positive values indicate that on average, the control group had a larger difference in reaction time between sequence and random conditions than the disorder group. That is, positive values indicate that the disorder group performed more poorly on the task than their respective control group. Figure 5.3 shows that only the ASD meta-analysis found that the disordered group did not perform significantly worse than their control group on the task.

5.3.2 Heterogeneity between First-Order Meta-Analyses

To investigate whether differences between the effect sizes shown in Figure 5.3 were due to second-order sampling error or to systematic influences, the $I^2$ statistic was calculated. Details of this calculation are presented in the Supplementary material. $I^2$ was found to be 66.86 and significantly different from zero ($Q (5) = 15.089, p = .010$). This indicates that
66.86% of the variability between first-order meta-analysis effect sizes is due to one or more systematic influences that likely includes disorder type. The remaining 33.14% of variability is thus attributed to second-order sampling error.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study group</th>
<th>Hedges' $g$</th>
<th>Variance</th>
<th>95% C.I.</th>
<th>$p$-value</th>
<th>Control group performs worse</th>
<th>Study group performs worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark et al. (2014)</td>
<td>Parkinson's</td>
<td>0.532</td>
<td>0.011</td>
<td>0.324 - 0.740</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obeid et al. (2016)</td>
<td>SLI</td>
<td>0.432</td>
<td>0.016</td>
<td>0.181 - 0.683</td>
<td>.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lum et al. (2013)</td>
<td>Dyslexia</td>
<td>0.440</td>
<td>0.015</td>
<td>0.199 - 0.681</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siegert et al. (2008)</td>
<td>Schizophrenia</td>
<td>0.523</td>
<td>0.012</td>
<td>0.311 - 0.735</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson et al. (2013)</td>
<td>DCD</td>
<td>0.891</td>
<td>0.072</td>
<td>0.365 - 1.418</td>
<td>.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obeid et al. (2016)</td>
<td>ASD</td>
<td>-0.159</td>
<td>0.033</td>
<td>-0.513 - 0.195</td>
<td>.379</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 5.3.* Forest plot depicting summary effect sizes of each first-order meta-analysis. Parkinson’s = Parkinson’s disease, SLI = specific language impairment, DCD = developmental coordination disorder, ASD = autism spectrum disorder.

Based on the data summarised in Figure 5.3, it seems likely that the elevated $I^2$ value can be attributed to the influence of ASD. This is because the average effect size from ASD falls outside the confidence intervals of the other disorder types. To investigate this further the $I^2$ statistic was recalculated after removing ASD. The ensuing value was found to be less than 1, and non-significant ($Q(4) = 2.755, p = .600$). That is, after removing the ASD meta-analysis, all variability between effect sizes from remaining meta-analyses can be explained with respect to second-order sampling error.

### 5.3.3 Mixed-effects Subgroup Analysis

To address the exploratory aim of this report, that is to determine whether disorder type moderated effect sizes, mixed-effects subgroup analysis was undertaken. This indicated a significant difference between effect sizes based on the type of disorder ($Q(5) = 15.119, p = .010$). To investigate this finding further, pairwise comparisons between each disorder were undertaken. To correct for multiple comparisons, $p$-values were adjusted using
Benjamini and Hochberg’s (1995) procedure that controls for the false discovery rate. The $Q$-values and associated $p$-values for each comparison are presented in Table 5.2. These analyses show that the ASD effect size was significantly different from each of the other disorders, and that there were no significant differences between any other pair of disorders.

Table 5.2

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Parkinson's (Clark et al., 2014)</td>
<td>—</td>
<td>0.365</td>
<td>0.324</td>
<td>1.547</td>
<td>0.004</td>
</tr>
<tr>
<td>2.</td>
<td>SLI (Obeid et al., 2016)</td>
<td>0.706</td>
<td>—</td>
<td>0.002</td>
<td>2.387</td>
<td>0.295</td>
</tr>
<tr>
<td>3.</td>
<td>Dyslexia (Lum et al., 2013)</td>
<td>0.706</td>
<td>0.963</td>
<td>—</td>
<td>2.338</td>
<td>0.257</td>
</tr>
<tr>
<td>4.</td>
<td>DCD (Wilson et al., 2013)</td>
<td>0.357</td>
<td>0.270</td>
<td>0.270</td>
<td>—</td>
<td>1.621</td>
</tr>
<tr>
<td>5.</td>
<td>Schizophrenia (Siegert et al., 2008)</td>
<td>0.963</td>
<td>0.706</td>
<td>0.706</td>
<td>0.357</td>
<td>—</td>
</tr>
<tr>
<td>6.</td>
<td>ASD (Obeid et al., 2016)</td>
<td>0.005*</td>
<td>0.024*</td>
<td>0.023*</td>
<td>0.005*</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

Note. $Q$-values are presented above the diagonal, and associated (corrected) $p$-values are presented below the diagonal. Significant $Q$-values are in bold. Parkinson's = Parkinson's disease, SLI = specific language impairment, DCD = developmental coordination disorder, ASD = autism spectrum disorder.

* $p < .05$

5.4 Discussion

This report used second-order meta-analysis to compare SRTT performance in Parkinson’s disease, SLI, DCD, ASD, schizophrenia, and dyslexia. The data presented summarised the results from six meta-analyses, representing data from 1412 individuals with a disease/disorder and 1415 age-matched controls. The hypothesis tested was that disorder type would be a moderator variable on SRTT task performance. This was forwarded under the assumption that poor procedural learning on the SRTT would be linked to motor problems. Results showed that, while disorder type did moderate effect sizes, this was attributable to ASD. Differences between Parkinson’s disease and DCD and the remaining neurodevelopmental disorders was due to second order sampling error (i.e., chance).
The second order meta-analysis showed that differences in average effect sizes computed from the SRTT between Parkinson’s disease, SLI, dyslexia, DCD, and schizophrenia can be attributed to second or sampling error. Nicolson and Fawcett’s (2007) model might explain this finding. According to their model dyslexia, SLI, and DCD arise from impairments to the procedural memory system. The extent to which problems with reading, language, or motor functioning arise depends on which network is affected. In this second order meta-analysis we demonstrate that if this is the case, the SRTT is sensitive to dysfunction or impairment to any part of the brain the supports procedural learning.

In this report, disorder type was found to moderate performance on the SRTT. Against expectation this moderator affect was attributable to ASD. Specifically, the second-order meta-analysis revealed that performance on the task in ASD was reliably better than Parkinson’s disease, SLI, dyslexia, DCD, and schizophrenia. At a conceptual level this result is unexpected given that ASD is associated with abnormalities to cerebellar and cortico-striatal regions that support SRTT performance (Fatemi et al., 2012; Langen et al., 2012; Nayate et al., 2005). One suggestion to account for this finding is that the abnormalities in ASD are related to over-activity of these circuits. While the neural abnormalities that characterise ASD are under debate (e.g., Hull, Jacokes, Torgerson, Irimia, & Van Horn, 2017; Picci, Gotts, & Scherf, 2016) there is evidence showing cortico-striatal hyperconnectivity in ASD (Picci et al., 2016). This has been linked to restricted interests and repetitive behaviours that are characteristic of the disorder (Delmonte, Gallagher, O’Hanlon, McGrath, & Balsters, 2013). The working hypothesis to emerge from this second order meta-analysis is that hyperconnectivity of cortico-striatal networks might lead to superior procedural learning on the SRTT compared to the other studied disorders. Thus neural dysfunction of procedural system networks might be operationalised as impaired and enhanced SRTT performance. In order to investigate this suggestion, one avenue for future
research may be to investigate procedural learning in disorders such as Tourette’s syndrome or obsessive compulsive disorder, which are also associated with cortico-striatal hyperconnectivity (Harrison et al., 2009; Worbe et al., 2015). Indeed, there is some evidence to suggest intact SRTT performance in both of these conditions (Channon, Pratt, & Robertson, 2003; Rauch, Savage, et al., 1997).

The finding that first-order effect sizes between Parkinson’s disease, SLI, dyslexia, DCD, and schizophrenia reflect second order sampling error has implications in understanding the neuropsychology of the SRTT. The result of the Parkinson’s disease meta-analysis indicate that neurodegeneration of the basal ganglia results in poor performance on the task (Clark et al., 2014; Siegert, Taylor, Weatherall, & Abernethy, 2006). However, it appears that this is not the only cause of poor procedural learning on the SRTT. Atypical neurological development of the kind present in DCD, SLI, dyslexia, and schizophrenia can also cause procedural learning problems. Future work is need to better specify the nature of neurological problems in these conditions to better understand the origin of procedural learning problems in these groups. However, given the types of neurological problems found in DCD, SLI, dyslexia, and schizophrenia differ (ref), it appears there is more than one ‘route’ to poor procedural learning.

The idea that dysfunction to multiple sites or networks results in poor procedural learning is consistent with data from brain stimulation studies (Clerget et al., 2011; Pascual-Leone et al., 1996; Torriero et al., 2004; Wilkinson et al., 2009). Several studies have administered transcranial magnetic stimulation to disrupt neural activity while participants undergo a SRTT. It has been found that inhibiting activity in primary motor cortex (Wilkinson et al., 2009), dorsolateral prefrontal cortex (Pascual-Leone et al., 1996), Broca’s area (Clerget et al., 2011), or the cerebellum (Torriero et al., 2004) all significantly disrupt
performance on the task. Overall, our results show that performance on the SRTT is sensitive to deficits to a wide range of cortical regions or cortico-subcortical networks. However, it is not the case that any type of neurodevelopmental problem will result in poor performance on the SRTT. In this report we found procedural learning to be significantly better in ASD compared to the other studied disorders. The implication of this finding is that the type of neurological problems present in ASD may be different to those in DCD, SLI, dyslexia, schizophrenia, and Parkinson’s disease.

The second order meta-analysis undertaken in this report highlights one important limitation in using the SRTT to make inferences about the underlying nature of neurological dysfunction in clinical populations. Based on the analyses presented in this report, performance on the SRTT can be disrupted by a number of different types of neurological insults either through the course of development or neurodegeneration. To identify brain networks responsible for procedural learning in disordered populations more neuroimaging studies will be required.

**Conclusion**

The initial study by Nissen and Bullemer (1987) that first described the SRTT has been cited more than 2000 times in research investigating procedural learning in clinical and non-clinical groups. For the first time, this report demonstrated equivalent performance deficits on the task across Parkinson’s disease, SLI, dyslexia, schizophrenia, and DCD. Thus it appears that these disorders can be characterised as having a procedural learning impairment. This report also provides new evidence that this type of impairment is not present in all neurodevelopmental disorders. Procedural learning in ASD appears to be superior to the other studied disorders. The findings highlight that abnormalities to different neural regions or networks can lead to comparable procedural learning deficits. This report
points to important limitations in the extent to which the SRTT can further our knowledge of procedural learning. Future research is required to more closely examine the processes that underlie procedural learning difficulties across disorders.
Conflict of Interest: The authors declare that they have no conflict of interest.

References


magnetic resonance imaging study. *Neuroreport, 16*(12), 1291-1295. doi:
10.1097/01.wnr.0000175615.93312.1a

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(2006). Reading impairment and visual processing deficits in schizophrenia.
*Schizophrenia Research, 87*(1), 238-245. doi: 10.1016/j.schres.2006.06.022


**Supplementary Material**

**Supplementary Material 1 - Search syntax.**

<p>| S1 | (TI Implicit Memory) OR (TI Implicit Learning) OR (TI serial reaction) OR (TI serial learn*) OR (TI sequence N5 learning) OR (TI implicit N5 sequence) OR (TI implicit learn*) OR (TI implicit N5 visuo-spatial) OR (TI implicit N5 visuospatial) OR (TI procedural learn*) OR (TI procedural mem*) OR (TI srt) OR (TI srtt) OR (TI motor skill learning) OR (TI statistical learning) OR (AB Implicit Memory) OR (AB Implicit Learning) OR (AB serial reaction) OR (AB serial learn*) OR (AB sequence N5 learning) OR (AB implicit N5 sequence) OR (AB implicit learn*) OR (AB implicit N5 visuo-spatial) OR (AB implicit N5 visuospatial) OR (AB procedural learn*) OR (AB procedural mem*) OR (AB srt) OR (AB srtt) OR (AB motor skill learning) OR (AB statistical learning) |
| S2 | (TI meta-analys*) OR (TI metaanalys*) OR (TI meta analys*) OR (TI quantitative review*) OR (TI systematic review*) OR (AB meta-analysis) OR (AB metaanalysis) OR (AB meta analysis) OR (AB quantitative review*) OR (AB systematic review*) |
| S3 | S1 AND S2 |</p>
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<tr>
<td>S2</td>
<td>(meta?analys*[TIAB]) OR (metaanalys*[TIAB]) OR (quantitative review*[TIAB]) OR (meta?analysis[TIAB]) OR (metaanalysis[TIAB]) OR (quantitative review*[TIAB]) OR (systematic?review*[TIAB])</td>
</tr>
<tr>
<td>S3</td>
<td>S1 AND S2</td>
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</table>
Supplementary Material - Calculations for first-order meta-analyses.

One meta-analysis (Wilson, Ruddock, Smits-Engelsman, Polatajko, & Blank, 2013) did not provide separate effect sizes and confidence intervals for each study. Thus, it was necessary to extract this data from the original studies and to perform the first-order meta-analysis.

Note that the procedures here are the same as used for every meta-analysis included in the second-order meta-analysis.

Two studies using the SRTT were identified from Wilson et al. (2013):

Wilson, Maruff, and Lum (2003)


The effect size for a Group (DCD, Control) X Block (reaction time for Random block, reaction time for preceding Sequence block) were calculated. Cohen’s $d$ was calculated and then converted to Hedges’ $g$. The general calculations for Cohen’s $d$ and its variance are below (all equations are taken from Borenstein, Hedges, Higgins, and Rothstein (2011):

$$d = \frac{\bar{x}_{control} - \bar{x}_{study}}{SD_{pooled\ within}}$$

$$Var(d) = \frac{n_{control} + n_{study}}{n_{control} \times n_{study}}$$

$$f = 1 - \frac{3}{4df - 1}$$

$$g = f \times d$$

$$Var(g) = f^2 \times Var(d)$$

Where:
\[ df = n_{control} + n_{study} - 2 \]

\( \bar{x} \) = Mean difference in reaction times between final random block and preceding sequence block

\( SD_{\text{pooled within}} \) = Within-group SD of the difference between the final random block and preceding sequence block, pooled across the study and control groups.

The result of each study was depicted using one effect size, that quantified the comparison between study and control groups on the difference in reaction time between the random block and preceding sequence block.

For Wilson et al. (2003) the data extracted was the \( t \)-value (\( t = 1.780 \)) associated with an independent measures \( t \)-test (comparing the groups on the size of the response time difference between the Random and Sequence blocks). Sample sizes (DCD group = 10, control group = 10) were also extracted.

For Gheysen et al. (2011) the data extracted was the \( F \)-value (\( F = 9.210 \)) for the Group X Block interaction. Sample sizes (DCD group = 18, control group = 20) were also extracted.

Conversion to Hedges’ \( g \) was undertaken using Comprehensive Meta-Analysis Software (Borenstein, Hedges, Higgins, & Rothstein, 2005), according to the equations provided above.

The summary effect size (\( M^* \)) was calculated using a random effects model according to the equation below.

\[
M^* = \frac{\sum_{i=1}^{k} W_i^* Y_i}{\sum_{i=1}^{k} W_i^*}
\]

\[
W_i^* = \frac{1}{V_{Y_i}}
\]
\[ V_{Y_i}^* = V_{Y_i} + T^2 \]

\[ T^2 = \frac{Q - df}{C} \]

\[ Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left( \sum_{i=1}^{k} W_i Y_i \right)^2}{\sum_{i=1}^{k} W_i} \]

\( df = k - 1 \) (where \( k \) is number of studies)

\[ C = \sum W_i - \frac{\sum W_i^2}{\sum W_i} \]

\( Y \) is the notation given for the Hedges’ \( g \) value from above.

\( V_Y \) (i.e., without the asterisk) is the \( \text{Var}(g) \) from above.

Similarly, \( W \) (without the asterisk) is the inverse variance (\( 1/V_Y \))

The variance of the summary effect (\( M^* \)) is estimated as:

\[ V_{M^*} = \frac{1}{\sum_{i=1}^{k} W_i^*} \]

And the standard error of the summary effect is the square root of the variance.
Applying the equations to the DCD-SRTT studies results in the following:

<table>
<thead>
<tr>
<th></th>
<th>Y</th>
<th>V</th>
<th>W</th>
<th>C</th>
<th>Q</th>
<th>df</th>
<th>T^2</th>
<th>V*</th>
<th>W*</th>
<th>M*</th>
<th>V_M*</th>
<th>S_E_M*</th>
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<td>Wilson et al.</td>
<td>0.762</td>
<td>0.198</td>
<td>5.051</td>
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<td>5.051</td>
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<td>Gheysen et al.</td>
<td>0.965</td>
<td>0.113</td>
<td>8.850</td>
<td>0.113</td>
<td>8.850</td>
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<td></td>
<td></td>
<td>13.900</td>
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</tr>
</tbody>
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Note that \( T^2 \) is set to 0 when the value is less than 0 (as was the case here). The \( T^2 \) value is the between-studies variance.

Note that the value for \( M^* \) and its variance were then used in the second-order meta-analysis. It is these values that appear in the forest plot.

References


Supplementary Material - Details of calculations used to estimate second-order $I^2$

Equations taken from Borenstein, Hedges, Higgins, and Rothstein (2011), with adjustments made to apply to second-order meta-analysis. All calculations were undertaken using Comprehensive Meta-Analysis Software (Borenstein, Hedges, Higgins, & Rothstein, 2005).

$$I^2 = \left( \frac{Q - df}{Q} \right) \times 100$$

Where

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \left( \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i} \right)^2$$

$W =$ inverse of meta-analysis variance

$Y =$ meta-analysis summary effect

$df = k - 1$

$k =$ number of meta-analyses

The table below shows values used to calculate the $I^2$ statistic, when including all six meta-analyses.

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<th>Study</th>
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<th>Variance</th>
<th>W</th>
<th>WY²</th>
<th>WY</th>
<th>df</th>
<th>Q</th>
<th>$I^2$</th>
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<td>0.03</td>
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<td>-4.85</td>
<td>5.00</td>
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<tr>
<td>DCD (Wilson et al., 2013)</td>
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<td>10.97</td>
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<td>Schizophrenia (Siegert et al., 2008)</td>
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</table>

References


Chapter 6

Study 3: The Influence of Sequence Structure on SRTT Performance in SLI

The study presented in this chapter tested the hypothesis outlined in Chapter 4 that in SLI, implicit learning of first order conditional (FOC), but not higher order sequences, should be impaired. According to the PDH (Ullman & Pierpont, 2005), it is only the learning and memory of information for information that relies on cortico-striatal structures that should be impaired in SLI. In Chapter 4, it was suggested that learning FOC sequences most likely rely on this network and should therefore should be impaired in SLI. However, learning of higher order sequences (such as SOC sequences) appears to rely on other networks in the brain and should be intact or less affected in this SLI. This study tested this claim.

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<tr>
<td>Gillian Clark</td>
<td>School of Psychology, Deakin University</td>
<td><a href="mailto:gillian.clark@deakin.edu.au">gillian.clark@deakin.edu.au</a></td>
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| Conceptualised the study, designed the methodology, collected the data, ran the analyses, drafted the manuscript |

*I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.*

---

### 4. Description of all author contributions

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<tr>
<th>Name and affiliation of author</th>
<th>Contribution(s) (for example, conception of the project, design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)</th>
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<tr>
<td>Jarrad Lum, Deakin University</td>
<td>Thesis supervisor - Involved in study design and development, advised on recruitment methods, assisted with analyses, revised manuscript.</td>
</tr>
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</table>
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6. Other contributor declarations

I agree to be named as a non-author contributor to this work.

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* If an author or contributor is unavailable or otherwise unable to sign the statement of authorship, the Head of Academic Unit may sign on their behalf, noting the reason for their unavailability, provided there is no evidence to suggest that the person would object to being named as author

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First-order and higher-order sequence learning in specific language impairment

Gillian M. Clark and Jarrad A. G. Lum

Cognitive Neuroscience Unit, School of Psychology, Deakin University, Australia

Author Note

Gillian M. Clark, Cognitive Neuroscience Unit, School of Psychology, Deakin University; Jarrad A. G. Lum, Cognitive Neuroscience Unit, School of Psychology, Deakin University.

The authors thank Scott Ruddock for his assistance with data collection, and Gery Karantzas for his statistical advice.

Correspondence concerning this article should be addressed to Gillian Clark, Cognitive Neuroscience Unit, School of Psychology, Deakin University, 221 Burwood Highway, Burwood, Victoria, Australia, 3121.

Email: gillian.clark@deakin.edu.au
Abstract

Objective: A core claim of the Procedural Deficit Hypothesis of specific language impairment (SLI) is that the disorder is associated with poor implicit sequence learning. This study investigated whether implicit sequence learning problems in SLI are present for first-order conditional (FOC) and higher-order conditional (HOC) sequences. Method: Twenty-five children with SLI and 27 age-matched, non-language impaired children completed two serial reaction time tasks. On one version, the sequence to be implicitly learnt comprised a FOC sequence and on the other a HOC sequence. Results: Results showed that the SLI group learnt the HOC sequence (partial $\eta^2 = .285, p = .005$), but not FOC sequence (partial $\eta^2 = .099, p = .118$). The control group learned both sequences (FOC partial $\eta^2 = .497$, HOC partial $\eta^2 = .465$, ps < .001). Conclusions: The SLI group’s difficulty learning the FOC sequence is consistent with the Procedural Deficit Hypothesis. However, the study provides new evidence that multiple mechanisms may underpin the learning of FOC and HOC sequences.

Keywords: Specific language impairment; implicit sequence learning; serial reaction time task; procedural memory
First-order and higher-order sequence learning in specific language impairment

Specific language impairment (SLI) is a neurodevelopmental disorder characterized by varying degrees of difficulty associated with the production and comprehension of language (American Psychiatric Association [APA], 2013; World Health Organization, 1992). The language problems in this group occur even though there are no sensory or intellectual impairments, and the child’s environment is conducive to language development (APA, 2013; Leonard, 2014). In recent times studies have demonstrated implicit sequence learning deficits in SLI (e.g., Hsu & Bishop, 2014; Lukacs & Kemeny, 2014; Lum, Conti-Ramsden, Page, & Ullman, 2012), which may be related to the grammatical difficulties in this group (e.g., Lum et al., 2012; Tomblin, Mainela-Arnold, & Zhang, 2007).

Implicit Sequence Learning and the Procedural Deficit Hypothesis

The idea that implicit sequence learning problems might be present in SLI was proposed by Ullman and Pierpont (2005). The claim forwarded was that the language and non-linguistic problems, such as motor difficulties, were caused by cortico-striatal dysfunction arising from abnormalities of the basal ganglia and/or regions of the prefrontal cortex, especially Broca’s area. It was further hypothesized that not all neural networks are compromised in SLI. In particular, structures that comprise the medial temporal lobes such as the hippocampus and parahippocampal regions are argued to be spared. This profile is proposed to lead to a dissociation in memory functioning, whereby the basal ganglia supported procedural memory is impaired, and medial temporal lobe supported declarative memory is intact (Ullman & Pierpont, 2005; Ullman & Pullman, 2015).

Procedural memory underlies the acquisition, storage, and retrieval of motor and cognitive skills (Gabrieli, 1998). The system is suited to encoding information that is inherently statistical, sequential, or rule-like in structure (Packard & Knowlton, 2002; Squire & Zola, 1996). Learning via this system is usually gradual and requires repeated exposure to
information before storage occurs (Squire, 2004). Ullman and Pierpont (2005) proposed that in SLI, poor procedural memory leads to the difficulties with the learning and use of grammar. Also, other skills that rely on the procedural memory system, such as implicit sequence learning of non-verbal information (Grafton, Hazeltine, & Ivry, 1995) are also likely to be impaired.

The Serial Reaction Time Task

Implicit sequence learning in SLI has been tested using the Serial Reaction Time Task (SRTT; Nissen & Bullemer, 1987). There is particular interest in the performance of children with SLI on SRTTs. This is because the task has long been shown to be dependent on the procedural memory system (e.g., Nissen & Bullemer, 1987; Rauch et al., 1997; Reiss et al., 2005; Willingham, Nissen, & Bullemer, 1989). Additionally, lower levels of implicit sequence learning on the task is observed following striatal (Clark, Lum, & Ullman, 2014; Knopman & Nissen, 1991) or prefrontal (Pascual-Leone, Wassermann, Grafman, & Hallett, 1996; Siegert, Weatherall, & Bell, 2008) dysfunction. On the SRTT a visual stimulus repeatedly appears in one of four positions on a computer display. Participants are instructed to press one of four buttons on a response box that corresponds to the stimulus’ location on the display. Unknown to participants, on some blocks of trials the order in which the stimulus appears follows a predetermined sequence. However, on control blocks of trials the stimulus appears in random positions. Reaction times (RTs) that measure how long it takes the participant to press the button after stimulus onset are the main dependent variable of interest on the task.

In non-clinical paediatric and adult groups RTs decrease (i.e., become faster) across blocks comprising sequenced trial presentations. However, when the block of random trials is presented RTs increase (Nissen & Bullemer, 1987). This increase in RTs (i.e., responses become slower) is argued to occur because knowledge about the sequence has been obtained,
but can no longer used to anticipate the stimulus’ location (Robertson, 2007). Subsequently, responses need to be adjusted and more time is required to press the correct response button. For implicit versions of the SRTT, learning is incidental because no indication is given to participants that the location of the stimulus follows a sequence or pattern. Furthermore, even when participants are informed that there was a recurring sequence, they often cannot replicate or recognise it (Destrebecqz & Cleeremans, 2001). If no information about the sequence had been obtained, the expectation would be for RTs to continue to decrease or reach asymptote as participants become proficient pressing buttons in response to a visual stimulus. This result has been observed in individuals with basal ganglia pathology. In these groups little or no change in RT is observed between sequence and random trial presentations (Clark et al., 2014; Kim et al., 2004; Knopman & Nissen, 1991). These findings provide one line of evidence linking the basal ganglia to the learning and memory functions of the procedural memory system, and implicit sequence learning.

Because implicit sequence learning on the SRTT is supported by the basal ganglia and procedural memory system, Ullman and Pierpont (2005) predicted that children with SLI would perform more poorly on the task compared to non-language impaired controls. In some studies this has indeed been the case (e.g., Hsu & Bishop, 2014; Lukacs & Kemeny, 2014; Lum et al., 2012; Lum, Gelic, & Conti-Ramsden, 2010). For instance, Lum et al. (2012) administered the SRTT to children with and without SLI. In this study the RT increase from sequence to random blocks was significantly smaller in the SLI group compared to controls. More recently, a meta-analysis summarising the SRTT-SLI literature revealed that overall, individuals with SLI perform significantly more poorly on the SRTT than controls (Lum, Conti-Ramsden, Morgan, & Ullman, 2014). There is also evidence potentially indicating differences in the pattern of implicit learning on the SRTT between individuals with and without SLI. Tomblin et al. (2007) and Hsu and Bishop (2014) found
that the rate RTs decreased across the blocks comprising sequenced presentations was faster for the TD group than the SLI group. In accounting for this finding Tomblin et al. suggested that sequence learning might be slower in SLI.

However, poor implicit sequence learning in SLI has not been universally observed. Close inspection of Lum et al.’s (2014) meta-analysis reveals that six out of eight studies did not observe significant differences between SLI and control groups. A series of studies by Gabriel and colleagues (Gabriel, Maillart, Guillaume, Stefaniak, & Meulemans, 2011; Gabriel, Meulemans, Parisse, & Maillart, 2014; Gabriel, Stefaniak, Maillart, Schmitz, & Meulemans, 2012) found intact sequence learning in children with SLI. In these studies implicit sequence learning was investigated in both the visuo-spatial and auditory domains (Gabriel et al., 2014) and using a response method that places fewer demands on fine motor skills (Gabriel et al., 2012). In each of these studies the increase in RTs from sequence to random blocks was comparable between SLI and control groups. One suggestion forwarded by this group is that the complexity of the sequences may account for some discrepancies in findings (Gabriel et al., 2013).

**Implicit Learning of First and Higher Order Sequences**

One aspect of the SRTT that may lead to discrepant findings in the SLI literature is the statistical structure of the sequence presented to participants. Within the SRTT literature sequences have been classified as either first-order conditional (FOC), second or higher-order conditional (HOC) sequences (Cohen, Ivry, & Keele, 1990; Curran, 1997; Reed & Johnson, 1994). In a FOC sequence each element in the sequence predicts the following element with varying degrees of probability. For example, in the sequence 4-2-4-3-1-2-3-1-4-2, the occurrence of a 4 predicts a 2 (66% probability) or a 3 (33% probability) and never a 1 (0% probability). Similarly, the occurrence of a 3 predicts a 1 with 100% probability. In the case of second and higher-order conditional sequences, the probability of all pairwise or first-order
transitions is equal, and so all pairwise transitions can be considered ‘ambiguous’ (Cohen, Ivry, & Keele, 1990). That is, the occurrence of one position does not provide unique information about the subsequent position. For example, in the sequence 1-3-4-2-3-1-4-3-2-4-1-2, the occurrence of a 1 predicts a 2, 3, or 4 with equal probability (i.e., 33% probability each). In second- and higher-order conditional sequences each position in the sequence is predicted by at least two preceding positions.

While it is known that performance on the SRTT in general relies on the cortico-striatal system (Clark et al., 2014; Grafton et al., 1995; Rauch et al., 1997), it has been suggested that learning HOC sequences relies on different or additional cognitive processes and neurological structures compared to those required to process FOC sequences (Cohen et al., 1990; Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003; Poldrack & Rodriguez, 2003). Cohen et al. (1990) proposed that learning a FOC sequence requires a mechanism capable of learning relationships between adjacent items. The same mechanism would struggle to learn HOC sequences because pairwise transitions do not provide any unique information about the sequence. To learn HOC sequences the suggestion is that hierarchical encoding, involving short-term memory is required to represent local pairwise transitions in the context of a larger ‘set’.

Another proposal implicating distinct mechanisms in the processing of FOC and HOC sequences was forwarded by Keele et al. (2003). This model posits the existence of ‘unidimensional’ and ‘multidimensional’ sequence learning mechanisms. The basal ganglia contributes to sequence learning via either mechanism, but other structures differ depending on which mechanism is engaged. The unidimensional mechanism is claimed to be supported by structures comprising a dorsal pathway (including parietal cortex, supplementary motor cortex and primary motor cortex). In contrast, the multidimensional mechanism is supported
by a ventral pathway (including inferior and medial temporal cortices, prefrontal cortex, and lateral premotor cortex). The dorsal pathway is suited to learning simple, predictable series of events. The ventral pathway, but not the dorsal pathway, is able to learn associations that are ambiguous or temporally remote. Thus, while the dorsal pathway can learn FOC sequences, the ventral pathway is required to learn the associations of HOC sequences.

Another proposal is that the medial temporal lobes are required to learn HOC sequences (Poldrack & Rodriguez, 2003; Schendan, Searl, Melrose, & Stern, 2003). Similar to Keele et al. (2003), it is acknowledged that the medial temporal lobe activation for HOC sequences is in addition to the involvement of the basal ganglia. Poldrack and Rodriguez (2003) proposed that learning HOC sequences requires the associative learning mechanisms of the medial temporal lobes to associate one element in the sequence within the context of the previous two elements. The hippocampus is known to undertake contextual, associative learning (Eichenbaum, Sauvage, Fortin, Komorowski, & Lipton, 2012; Wallenstein, Eichenbaum, & Hasselmo, 1998) which might be necessary for learning statistical structures, especially the arbitrary pairwise transitions that are inherent to HOC sequences.

To our knowledge no neuroimaging studies have directly tested neurological networks involved in the learning of FOC and HOC sequences. However, at the behavioral level, research suggests there might be at least partially separate mechanisms involved in learning the two types of sequence. In non-clinical groups, the size of the RT difference between blocks of sequenced and random trials has been found to be larger for FOC than HOC sequences (Deroost, Kerckhofs, Coene, Wijnants, & Soetens, 2006; Deroost & Soetens, 2006; Kelly, Jahanshahi, & Dirnberger, 2004; Soetens, Melis, & Notebaert, 2004). Interestingly, evidence has been presented suggesting that individuals with Parkinson’s disease show the opposite pattern. These individuals appear to show better learning for HOC
compared to FOC sequences (Deroost et al., 2006; Smith & McDowall, 2004). Given that Parkinson’s disease is characterized by degeneration of the striatum and basal ganglia (Lang & Lozano, 1998), HOC sequences may rely on neural structures outside of the basal ganglia network. It should be noted, however, that general cognitive functioning may also play a role in whether individuals with Parkinson’s disease are able to learn either sequence (Deroost et al., 2006).

In summary, evidence has been presented showing implicit learning and memory for FOC sequences is supported by the procedural memory system (Clark et al., 2014; Hardwick, Rottschy, Miall, & Eickhoff, 2013). But it seems that processing of HOC sequences may require a different or additional network used to learn FOC sequences (Keele et al., 2003; Poldrack & Rodriguez, 2003; Schendan et al., 2003). In the case of SLI, the possibility that different networks are involved in the processing of FOC and HOC sequences, might mean implicit sequence learning is not universally impaired in this disorder. Poldrack and Rodriguez’ (2003) proposal that learning HOC sequences requires support from the hippocampal associative learning mechanisms is of particular relevance for understanding implicit sequence learning in SLI. Learning via the declarative memory system is intact in SLI, especially for non-verbal information (see Lum & Conti-Ramsden, 2013). For example, for tasks involving associating an abstract shape with a spatial location, it has been shown that groups with SLI perform equally as well as their TD peers (e.g., Bavin, Wilson, Maruff, & Sleeman, 2005). Thus it might be expected that children with SLI are more proficient at learning HOC sequences than FOC sequences.

**Aims and Hypothesis**

The aim of this study was to investigate the implicit learning of FOC and HOC sequences in children with SLI and a control group comprising typically developing non-language impaired (TD) children. In this study children were presented with two SRTTs. On
one task the sequence comprised a FOC sequence and in the other a HOC sequence. Two hypotheses were forwarded in this study on the basis that FOC sequences are processed by the basal ganglia supported procedural memory system and HOC rely on additional networks. First, the SLI group would show poorer implicit learning of a FOC sequence compared to a control group. Second, implicit learning of a HOC sequence would be comparable between SLI and TD groups.

Method

Participants

Twenty-seven children with SLI (16 males, 11 females), and 27 typically developing (TD) children (16 males, 11 females) participated in the study. However, two children with SLI failed to complete the assessment battery and their data was excluded from all analyses (see Summary of Dependent Variables section for details). The groups were matched on age (ages ranged from 7-12 years) and non-verbal reasoning skills (see below). Informed written consent was given by the children’s parents prior to participating in the study.

Identification of children with and without SLI. Language skills were assessed using the Core Language (CLS) subtests of the Clinical Evaluation of Language Fundamentals – Fourth Edition: Australian Standardisation (CELF-4: Australian; Semel, Wiig, & Secord, 2006). The CELF-4 is a standardized language test suitable for children aged between 5 and 16 years. The CLS summarizes performance across four subtests and provides an overall estimate of children’s expressive and receptive language skills. Performance on the CLS is described as a standardized score which has a mean of 100 and standard deviation of 15. A score of 85 or less (i.e., language skills 1SD or more below the normative mean) has been shown to have a high level of diagnostic accuracy in an Australian sample (sensitivity = .83, specificity = .90; Semel et al., 2006). All TD children obtained a CLS between 91 and 113. Thus their language scores were in the average range.
Non-verbal intelligence was assessed using either the Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) or the Raven’s Coloured Progressive Matrices (RCPM; Raven, 1998). Scores on both of these measures were transformed to standardized scores with a mean of 100 and standard deviation of 15. All children obtained a standardized non-verbal intelligence score between 94 and 122.

Table 6.1 presents summary statistics and results of analyses comparing the two groups on the CLS, non-verbal reasoning score, and age. Analyses reported in Table 6.1 show significant differences only on the language scores, but not on the non-verbal intelligence scores or age.

Table 1. Summary Statistics showing Age and Scores from Language and Non-Verbal IQ Standardised Tests.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLI (n =25)</th>
<th>TD (n =27)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Range</td>
</tr>
<tr>
<td>Age (months)</td>
<td>117.75</td>
<td>20.41</td>
<td>92.10-151.07</td>
</tr>
<tr>
<td>CLS</td>
<td>74.74</td>
<td>5.5</td>
<td>63-82</td>
</tr>
<tr>
<td>Non-verbal Reasoninga</td>
<td>103.84</td>
<td>7.31</td>
<td>94-119</td>
</tr>
</tbody>
</table>

a Measured by either the Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence, or by Raven's Coloured Progressive Matrices. bTwo children from the SLI group were excluded from all analyses due to their performance on the SRTTs. See Data Analysis section for details. CLS = Core Language Score

Materials

Serial reaction time task (SRTT). Implicit sequence learning was examined using a version of the SRTT (Nissen & Bullemer, 1987). Responses were collected using four horizontally adjacent buttons on a computer keyboard number pad. To administer the task children were first seated in front of the computer screen, so that their eyes were approximately 650 mm from the screen. The SRTT was presented to children as a game in which they needed to ‘swat’ flies. The visual stimulus was a cartoon picture of a fly that was presented on the background of a colored shape (see the Supplemental Material for examples of the stimuli). There were 17 variations of the background colored shape (e.g., pink square,
green triangle, blue star). For each presentation within a group of 10 trials, the colored shape was selected randomly without replacement. Thus within each set of 10 trials, the order and location of each stimulus picture was different. Each visual stimulus subtended approximately 7° X 7° of visual angle. Children were instructed that the visual stimulus or ‘fly’ would repeatedly appear in one of four horizontally arranged locations on the screen. It was explained that the task was to swat the fly by pressing one of the four horizontally arranged buttons that corresponded to the location of the stimulus. To familiarize children with the task, they were initially given 10 practice trials, where all four positions were demonstrated.

Once children understood the task test trials were presented. Each test trial commenced with a blank gray screen that appeared for 400 ms. The visual stimulus, which was a fly, then appeared. If children pressed the button on the response pad that matched the location of the visual stimulus, feedback was provided in the form of a ‘squashed’ fly picture appearing on the screen. If the incorrect button was pressed, the feedback provided was a red border that appeared around the stimulus (see the Supplemental Material for examples of the task layout). In both cases feedback was provided for 150 ms. We included this feedback with the aim of keeping the children motivated throughout the task. However, it should be noted that feedback of this nature is not usually provided during the SRTT. Feedback during non-declarative learning tasks has been shown to increase activation in the cortico-striatal system (e.g., Shohamy et al., 2004).

The test trials were grouped into five blocks, each comprising 60 stimulus presentations. Unknown to participants, presentation of the stimulus on Blocks 1, 2, 3, and 5 followed a 10-item sequence that was presented six items. On Block 4, hereafter referred to as the ‘Random Block’ the presentation of the stimulus was presented in pseudorandom
order. On this block the stimulus appeared in each spatial location with equal frequency as on the Sequence Blocks. Also, the frequency of each pairwise transition between stimulus presentations in the Random Block was the same as those in the Sequence Blocks. This controlled for the possibility that potential differences between sequence and random blocks of trials reflected knowledge only about the relative frequencies of each position or pairwise transitions (Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Reed & Johnson, 1994). Following methodologies used previously in both adult (e.g., Cohen et al., 1990; Curran & Keele, 1993; Deroost et al., 2006) and paediatric (e.g., Deroost et al., 2010; Jimenez-Fernandez, Vaquero, Jimenez, & Defior, 2011) populations, the final Sequence Block (Block 5) was included to ensure that any RT increase to the Random Block was not due simply to fatigue.

At the end of each block of trials feedback was provided. This consisted of a message that appeared on the computer display indicating the number of flies that were “swatted”. To maintain children’s interest in the task, at the end of Block 1 and Block 5 pseudo-feedback was provided in the form of a picture showing their response speed on a scale of animals ordered from slow (a snail) to fast (a cheetah). All children received identical pseudo-feedback regarding their speed. E-Prime 2.0 software (Schneider, Eschman, & Zuccoloto, 2007) was used to present the stimuli.

The children completed two SRTTs that were presented on different days (see Procedure). On one SRTT a FOC sequence was used. Labelling the left most box that the visual stimulus could appear on the screen as ‘1’ and the right most position as ‘4’, the sequence was 3-4-1-2-4-1-3-4-2-1. In this sequence, each position is predicted with varying degrees of probability from the previous position. Specifically, Position 1 predicts Position 2 (33% probability) or Position 3 (66% probability). Position 2 predicts Positions 1 and 4 with
50% probability each. Position 3 predicts Position 4 with 100% probability, and Position 4 predicts Position 1 (66% probability) and Position 2 (33% probability). The sequence used on the other SRTT comprised HOC transitions. The HOC sequence was created by swapping just two adjacent items from the FOC sequence described above. This single change altered the transitional probabilities of the entire sequence. Using the same numeric labelling method to describe the previous sequence, the position the visual stimulus appeared for the HOC sequence was 4-3-1-2-4-1-3-4-2-1. In this sequence, the presence of one position does not give unique information about the location of the next stimulus. Specifically, Position 1 is followed by Positions 2, 3, and 4 with equal probability (33% probability each). Position 4 also predicts Positions 1, 2, and 3 with 33% probability each. Position 2 predicts Position 4 or 1 with 50% probability each, and Position 3 predicts Position 1 (50% probability) and Position 4 (50% probability). It should be noted that the occurrence of Position 2 or Position 3 may also be conceptualized as giving some information about the following position. That is, while Position 2 may be followed by Position 4 or 1 with equal probability, it provides the information that the next stimulus will not be in Position 3. However, in this sequence the two elements of every pairwise transition predict the following element. For example, the pairwise transition of Position 4 to Position 3 in turn predicts Position 1. Similarly, the transition of Position 2 to Position 1 in turn predicts Position 4.

The FOC and HOC sequences were matched with respect to sequence length and the number of times the visual stimulus appeared in each location. It should be noted that given the length of the HOC sequence it was not possible to make every pairwise transition ambiguous. Rather, six of the 10 pairwise transitions are ambiguous (i.e., one position in the sequence predicts the next with 33% probability). The only difference between the FOC and HOC tasks were the underlying transitional probabilities of the sequences and their respective
Random Blocks. The Random Block of the two versions of the task were different since they reflected characteristics of the respective FOC and HOC sequence.

**Summary of Dependent Variables**

Two dependent variables were obtained from each SRTT; these were accuracy and reaction times (RTs). Accuracy measured whether the child pressed the corresponding button on the response pad on each stimulus presentation. The proportion of correct responses, computed separately for each block, was used in the analyses. RTs measured the time taken, in milliseconds, to press the response button following stimulus onset. Only RTs associated with correct button presses were used in the analyses. The data from two children with SLI were excluded from all analyses. Both of these children were highly distracted during the SRTTs, resulting in excessively long RTs (e.g., trials up to 30 seconds). Also, for all children trials in which RTs were 5000 ms or longer were excluded. This resulted in excluding a total of 12 trials from the SLI data, and 16 trials from the TD data. To control for individual differences in perceptual-motor responses normalized RTs were used in the analyses (Lukacs & Kemeny, 2014; Lum et al., 2012; Thomas et al., 2004). For each child the mean z-score transformed RT, referenced to the median, was computed for each block.

**Procedure**

The SRTTs along with the language and non-verbal tests were presented individually to each child in a quiet room at his/her school. Tasks were administered over three to four sessions, over an average of three months. The two SRTTs were presented during different sessions, separated by an average of 13 days. In both SLI and TD groups, 17 participants completed the HOC sequence first, and 10 participants completed the FOC sequence first.
**Results**

**Reaction Time Data**

The primary dependent variable was RT. Figure 6.1 presents normalized RTs reported by Group and Block. Panel A in Figure 6.1 presents data from the FOC sequence and Panel B the HOC sequence. Performance on the SRTT was analysed using two approaches. First, to examine sequence-specific learning, the RTs of the Random Block (i.e., Block 4) were compared to the mean RTs of the surrounding Sequence Blocks (i.e., Blocks 3 & 5). This approach is standard for similar versions of the SRTT. (e.g., Deroost et al., 2010; Smith & McDowall, 2004; Werheid, Zysset, Müller, Reuter, & von Cramon, 2003). Evidence that the sequence has been learnt is observed, at the group level, when the RTs on the Random Block are significantly slower compared to the Sequence Blocks. Second, following Tomblin et al. (2007) and Hsu and Bishop (2014), analyses examined the pattern of the RT change across the Sequence Blocks (Blocks 1-3).

![Figure 6.1](image)

*Figure 6.1.* Mean normalized response times reported by Block and Group for the FOC (Panel A) and HOC (Panel B) tasks. Error bars show standard error.

**Sequence Specific Learning.** Figure 6.2 shows the mean RT from the Random Block (Block 4) and the average of the surrounding Sequence Blocks (Blocks 3 & 5) reported by Group and Sequence Type. A 2 (Group: SLI, TD) X 2 (Sequence Type: FOC, SOC) X 2 (Block: Random Block, Average of Blocks 3 & 5) Mixed Design ANOVA was conducted.
The Group X Sequence Type X Block Interaction was not significant \( (p = .509, \text{partial } \eta^2 = .009) \). However, a noted concern (Howell, 2002) with detecting high level interactions in ANOVA is the effect of interest can be diluted when group means are equal to each other on all but one contrast. This occurs as variance is averaged over the degrees of freedom. In this study differences between SLI and control groups were only expected to differ on one pair of means, specifically performance on the FOC sequence. In this situation an analysis of simple main effects is recommended (Howell, 2002; O'Brien, 1983; Wilcox, 1987). In this study, differences were tested at each level of Group and Sequence Type. For post-hoc tests, \( p \)-values were adjusted using the Holm’s procedure (Holm, 1979) to control for an inflated Type I error rate arising from multiple comparisons.

The first set of analyses examined data from the FOC sequence. Reaction time data were submitted to a 2 (Group: SLI, TD) X 2 (Block: Block 4, Average of Blocks 3 & 5) Mixed Design ANOVA. In this analysis the main effect for Block was significant \( (F(1, 50) = 21.206, p < .001, \text{partial } \eta^2 = .298) \), but not Group \( (F(1, 50) = 2.083, p = .155, \text{partial } \eta^2 = .040) \). However, a significant Group X Block Interaction, with a medium to large effect size was observed \( (F(1, 50) =4.785, p = .033, \text{partial } \eta^2 = .087) \). Post-hoc tests examined within-group differences between the Random Block (Block 4) and average of surrounding Sequence Blocks (Blocks 3 & 5). For the TD group this difference was significant \( (t(26) = 5.064, p = .004, \text{partial } \eta^2 = .497) \) but not for the SLI group \( (t(24) = 1.622, p = .118, \text{partial } \eta^2 = .099) \). The presence of the Random Block of trials only influenced RTs of the TD group.

The next set of analyses examined sequence learning of the HOC sequence. Results from a Mixed Design ANOVA revealed a significant main effect for Block \( (F(1, 50) = 30.082, p < .001, \text{partial } \eta^2 = .376) \) whereby RTs were longer for the Random Block compared to surrounding Sequence Blocks. Neither the main effect for Group \( (F(1, 50) = \)
.010, \( p = .920, \text{partial } \eta^2 < .001 \), nor the interaction between Block and Group was significant (\( F(1, 50) = 0.725, p = .399, \text{partial } \eta^2 = .014 \)).

This result was observed even when comparing changes in RT between Sequence and Random Blocks separately for each group. One-way repeated measures ANOVAs revealed that the mean RT was significantly slower for the Random Block for both the SLI group (\( t(24) = 3.091, p = .01, \text{partial } \eta^2 = .285 \)) and the TD group (\( t(26) = 4.753, p = .004, \text{partial } \eta^2 = .465 \)). Interestingly, the effect size for the SLI group was found to be smaller compared to the TD group. Thus even though a reliable difference in RTs between Random and Sequence Blocks was observed for both groups, the effect size for the analysis was smaller in the SLI group compared to the TD group.

Finally, an analysis was conducted to directly compare the magnitude of learning between FOC and HOC sequences. This analysis was undertaken separately for each group. Repeated Measures ANOVAs were undertaken with Sequence Type (FOC, HOC) and Block (Random Block, average of Blocks 3 & 5) as repeated-measured variables. A significant interaction would indicate that the magnitude of learning was significantly higher for one sequence than the other. For the SLI group the difference between FOC and HOC sequence learning was not significant (Sequence Type X Block Interaction: \( F(1, 24) = 1.619, p = .215, \text{partial } \eta^2 = .063 \)), although the effect size for this comparison was medium in magnitude. For the TD group, the difference was also non-significant (Sequence Type X Block Interaction: \( F(1, 26) = .170, p = .684, \text{partial } \eta^2 = .006 \)). Unlike the SLI group, the effect size associated with this analysis was small in magnitude.

**Learning over Sequence Blocks.** The next set of analyses examined the pattern of learning between the two groups and across FOC and HOC sequences. It was not feasible to undertake latent growth curve modelling or hierarchical linear modelling given the sample
size and number of observed variables. Instead, to determine whether change in RTs over Blocks 1-3 differed for each group and each sequence, RT data from the first three Sequence Blocks were submitted to a 2 (Group: SLI, TD) X 2 (Sequence Type: FOC, HOC) X 3 (Block: Block 1, 2, 3) Mixed Design ANOVA. This approach has been used previously to compare RT changes over sequence blocks between groups (e.g., Deroost et al., 2006; Gabriel et al., 2012). Results revealed a significant main effect of Group ($F(1, 50) = 4.780, p = .033$, partial $\eta^2 = .087$). The interaction between Group and Sequence Type ($F(1, 50) = .009, p = .926$, partial $\eta^2 = .001$) was not significant. Thus the children with SLI were slower to respond than the TD group on both FOC and HOC sequences.

Next, planned polynomial contrasts, undertaken in SPSS Version 23, were used to examine the trends in learning across Blocks 1 – 3 in which the sequence was repeatedly presented. As there were three separate data points (Block 1, Block 2, Block 3) for these analyses, only linear and quadratic contrasts could be tested. For the SLI group, on the FOC

Figure 6.2. Mean normalized response time difference between Random block (Block 4) and average of surrounding Sequence blocks (Blocks 3 and 5), reported by Sequence Type and Group. Error bars show standard error.
sequence only the quadratic contrast was significant ($F(1, 24) = 16.015, p = .001, \text{partial } \eta^2 = .400$; Linear: $F(1, 24) = 1.962, p = .174, \text{partial } \eta^2 = .076$). For the TD group, data from the FOC sequence revealed a significant contrast for the linear ($F(1, 26) = 5.469, p = .027, \text{partial } \eta^2 = .174$) and quadratic comparisons ($F(1, 26) = 26.236, p < .001, \text{partial } \eta^2 = .502$).

For the HOC sequence, the planned contrasts revealed significant linear and quadratic contrasts for the SLI group (Linear: $F(1, 24) = 32.535, p < .001, \text{partial } \eta^2 = .575$; Quadratic: $F(1, 24) = 19.887, p < .001, \text{partial } \eta^2 = .453$), as well as the TD group (Linear: $F(1, 26) = 27.119, p < .001, \text{partial } \eta^2 = .511$; Quadratic: $F(1, 26) = 24.418, p < .001, \text{partial } \eta^2 = .484$).

**Accuracy**

Analyses also examined whether accuracy was sensitive to sequence learning.

Accuracy reported by Group, Block, and Sequence Type is presented in Figure 6.3. This figure shows that accuracy approached ceiling for both groups across Blocks and Sequences. The mean proportion of correct responses was at least .86 for all blocks and groups. It was necessary to apply an arcsine transformation to the accuracy data prior to the analyses, to correct for non-normality.

**Sequence Specific Learning.** First, the extent to which accuracy was sensitive to the sequence was investigated. Mirroring the analysis of RT data, this was achieved by testing whether the mean accuracy observed on the Random Block was significantly different to the average of the surrounding Sequence Blocks. The dependent variable for these analyses was a difference score in which the accuracy observed on the Random Block was subtracted from the mean accuracy observed on the surrounding Sequence blocks. Results from a 2 (Group: SLI, TD) X 2 (Sequence Type: FOC, HOC) Mixed Design ANOVA revealed non-significant results for the main effects (Group: $F(1, 50) = 0.897, p = .348, \text{partial } \eta^2 = .018$; Sequence Type: $F(1, 50) = 0.292, p = .591, \text{partial } \eta^2 = .006$) and the Group X Sequence Type
interaction ($F(1, 50) = 0.517, p = .475$, partial $\eta^2 = .01$). Thus accuracy was not sensitive to the sequence for either group across FOC and HOC sequences.

**Learning over Sequence Blocks.** Accuracy data were also submitted to a 2 (Group: SLI, TD) X 2 (Sequence Type: FOC, HOC) X 3 (Block: Blocks 1-5) Mixed Design ANOVA. Results revealed a main effect of Block ($F(2, 100) = 5.607, p = .005$, partial $\eta^2 = .101$), reflecting a decrease in accuracy across Blocks 1 to 3. The main effects of Group ($F(1, 50) = 1.634, p = .207$, partial $\eta^2 = .032$) and Sequence Type ($F(1, 50) = .078, p = .781$, partial $\eta^2 = .002$), and the Interaction terms were all non-significant (Group X Sequence Type X Block: $F(2, 100) = 0.339, p = .713$, partial $\eta^2 = .007$; Group X Sequence Type: $F(1, 100) = 1.685, p = .200$, partial $\eta^2 = .033$; Group X Block: $F(2, 100) = 0.364, p = .696$, partial $\eta^2 = .007$; Sequence Type X Block: $F(2, 100) = 1.471, p = .235$, partial $\eta^2 = .029$).

**Figure 6.3.** Mean accuracy reported by Block and Group for the FOC (Panel A) and HOC (Panel B) tasks. Error bars show standard error.

**Discussion**

This study investigated implicit learning of FOC and HOC sequences in children with and without SLI. In comparison to the TD group, the SLI group demonstrated a smaller difference in RTs between Sequence and Random Blocks for the FOC sequence. However, for the HOC sequence, the size of the RTs difference between the Sequence and Random Blocks was not different between groups. Another result to emerge from this study was that
over Blocks 1 to 3, the SLI group had slower RTs compared to the TD group for both sequences.

As noted earlier, sensitivity to the sequence on the SRTT is evidenced when RTs decrease following exposure to the visuo-spatial sequence and then increase when the random trials are presented (e.g., Deroost et al., 2006; Gabriel et al., 2012; Lum et al., 2012). For the SLI group this pattern of results was observed for the HOC but not FOC sequence. For the TD group, the mean RT for the Random Block was significantly larger compared to the Sequence Blocks for both FOC and HOC sequences. This indicates that both sequence types were learnt (Robertson, 2007). Thus it appears that while implicit sequence learning is an area of weakness in SLI, it is not the case that this aspect of functioning is universally impaired. Rather, differences in the extent learning takes place appear to be related to the statistical structure of the sequence. Collectively, these results lend support to the suggestions (Cohen et al., 1990; Keele et al., 2003; Poldrack & Rodriguez, 2003) that the learning of FOC and HOC sequences are supported by different cognitive processes and/or neural mechanisms.

The finding in this study that children with SLI evidenced poor learning of the FOC sequence is consistent with past research (e.g., Hsu & Bishop, 2014; Lum et al., 2014; Lum et al., 2012; Lum et al., 2010). Since performance on the SRTT has been shown to rely on the cortico-striatal network (Clark et al., 2014; Grafton et al., 1995; Pascual-Leone et al., 1996; Rauch et al., 1997), these findings are also consistent with the suggestion this network and procedural memory may be impaired in SLI (Lukacs & Kemeny, 2014; Lum et al., 2012; Tomblin et al., 2007; Ullman & Pierpont, 2005).

The analyses investigating the change in RTs over the Sequence Blocks (i.e., Blocks 1 – 3) using linear and quadratic contrasts revealed a difference between SLI and TD groups.
Explanations forwarded to account for these findings are tentatively offered and will need to be investigated further. One possibility is that the linear and quadratic contrasts capture different influences on RTs. For both groups, and for both sequences, the significant quadratic contrasts indicate that RTs for Block 2 were faster than for Blocks 1 and 3. This may reflect the influence of feedback that prompted children to respond faster after Block 1. The linear contrast was significant for the SLI group only on the HOC sequence and for the TD group on both the FOC and HOC sequences. Following from other studies using similar version of the SRTT, one possibility is that the linear decrease in RTs across Blocks 1 – 3 reflects a combination of sequence learning and perceptual-motor learning (e.g., Curran & Keele, 1993; Deroost et al., 2010; Russeler, Gerth, & Munte, 2006; Smith & McDowall, 2004). Thus, the non-significant linear contrast for the SLI group on the FOC sequence might reflect sequence learning difficulties.

Data from the SLI group suggests intact learning of HOC sequences, but poor learning of FOC sequences. This difference in learning appears to be at least modulated by the statistical structure of the sequence, which in turn may reflect that learning and memory for HOC sequences relies on neurological networks and memory systems that are not compromised in SLI. Interestingly, these findings can be interpreted as consistent with both Poldrack and Rodriguez’ (2003) and Keele et al.’s (2003) proposals. As explained in the Introduction, both theories suggest that while the basal ganglia are involved for both types of sequence, HOC sequences additionally involve other structures. Poldrack and Rodriguez implicate the medial temporal lobes, specifically the hippocampi. Keele et al. propose that the medial temporal lobes along with prefrontal and lateral premotor cortices are involved. Given the medial temporal lobes and declarative memory system appear to be intact in SLI (Lum & Conti-Ramsden, 2013; Lum, Ullman, & Conti-Ramsden, 2015), the results of this study are consistent with either proposal. That is, structures of the declarative memory
system play a role in learning HOC sequences, perhaps through ‘chunking’ or hierarchical encoding (Cohen et al., 1990), or through associative learning of the ambiguous transitions (Keele et al., 2003; Poldrack & Rodriguez, 2003). Indeed, application of a chunking strategy might explain why children with SLI are able to learn HOC sequences with equal proficiency as controls. For both groups, HOC sequences might be easier to process since two elements, represented as a single piece of information, can now be used to predict the location of a third.

A remaining issue to be addressed in this study concerns the non-significant difference between the measure of learning for HOC and FOC sequences for both SLI and TD groups. If FOC but not HOC sequence learning is impaired in SLI, then it would be expected for the measure of learning to be sensitive to this difference. For the SLI group, statistical power might be an issue. As noted earlier, a medium effect size (partial $\eta^2 = .063$) was observed for the comparison testing differences in learning between FOC and HOC sequences in the SLI group. Statistical power for this analysis was 23%. Thus a reliable difference between the implicit learning of FOC and HOC sequences might be present in SLI, but additional participants are required to return a statistically significant result. It should be noted that statistical power does not explain the non-significant result observed for the TD group. The effect size comparing FOC and HOC sequence learning for this group was very small (partial $\eta^2 = .006$). Thus in non-language impaired children, the statistical structure of the sequence in this study had a negligible influence on this group’s RTs.

Another methodological issue that may have contributed to the non-significant differences comparing FOC and HOC sequences was the similarities of the two sequences. As explained in the Method section, the HOC sequence was created by transposing a single pair of items in the FOC sequence. A strength of this approach was that the sequences were
matched with respect to position frequency, and they contained most of the same pairwise transitions. However, achieving this level of methodological rigour may have also increased the likelihood that learning of the FOC and HOC sequences both engaged similar memory systems. Also since the two sequences were 10-items in length both contained some transitions that are neither purely first- nor higher-order conditional transitions. The next step in this area would be to compare more distinct FOC and HOC sequences, using a design which permits comparison of individual transitions (e.g., Curran, 1997; Smith & McDowall, 2004).

The non-significant difference in learning the two sequences could also potentially be explained by the neural structures used for learning. As discussed, both types of sequences appear to activate the cortico-striatal system, although HOC sequences may use additional resources as well. If children with SLI do have some impairment to the cortico-striatal network, it is likely that this impairment i) is not so severe that the system is rendered completely non-functional, and ii) means that the additional structures that HOC sequences engage are unable to bring performance on these sequences to the same level as unaffected individuals. In other words, an impaired cortico-striatal system may be able to partly learn a FOC sequence, but when it interacts with an intact system (such as the declarative memory system) after being presented with a HOC sequence, learning is more readily able to occur. It is interesting to note that the interaction between the two systems did not lead to a higher level of learning the FOC sequence for the SLI group. It has been suggested that in SLI, the declarative memory system is able to compensate for impairments of the procedural memory system (Ullman & Pullman, 2015). The results of the current study, however, suggest that if this type of compensation occurred, it did not result in behavioral performance equal to TD individuals. Future research using neuroimaging techniques is required to examine the interaction between memory systems in individuals with SLI compared to TD individuals.
While sequence structure may influence the performance of children with SLI on the SRTT, there are other factors as well. Evidence has been presented showing intact HOC sequence learning in SLI (Hedenius et al., 2011; Mayor-Dubois, Zesiger, Van der Linden, & Roulet-Perez, 2012) though this result has not been universally observed (Gabriel et al., 2013; Lukacs & Kemeny, 2014). Also, some studies report intact FOC sequence learning in SLI (e.g., Lum & Bleses, 2012; Tomblin et al., 2007). Thus there appear to be other variables, not examined in the current study that are influencing results. For instance, the meta-analysis by Lum et al. (2014) indicated that participant’s age and the number of exposures to the sequence before the introduction of the Random Block contributed to the size of the difference between SLI and TD groups. Furthermore, subject-centred factors such as attention or motor skills might influence how well an individual performs on the task. Also, consistent with past research (e.g., Gabriel et al., 2012; Hsu & Bishop, 2014) we found that the children with SLI took longer to press the buttons than the non-language impaired children across the Sequence Blocks for both the FOC and HOC sequences. Thus the extent to which implicit sequence learning can take place on the SRTT might be influenced by motor proficiency. We note that a limitation of the current study is that the influence of subject-related variables on SRTT performance could not be investigated.

Finally, an outstanding question from this study concerns FOC and HOC sequence learning in relation to language learning. Since difficulties learning and using grammar are a particular area of difficulty in SLI (Leonard, 2014), it could be that the systems that underpin FOC sequence learning is related to this aspect of language. Indeed, there is some evidence to show that in TD children, visual statistical learning performance (which relies on the cortico-striatal network; Karuza et al., 2013) predicts comprehension of passive sentences and object relative clauses (Kidd & Arciuli, 2016). Perhaps this is also related to FOC sequence learning. However, intuitively it appears that a system or mechanism that is suited
to learning the higher-order associations in HOC sequences might also be suited to learning grammatical structures that involve non-adjacent dependencies. This idea conflicts with the findings of this study, since children with SLI struggle with these types of structures (Hsu, Tomblin, & Christiansen, 2014; van der Lely & Battell, 2003), but were able to learn the HOC sequence. To our knowledge no studies have investigated the types of transitions in FOC versus HOC sequences in relation to particular linguistic structures, though the results of this study suggest that this might be a worthwhile area for future research.

**Conclusion**

This is the first study to compare FOC and HOC sequence learning in the same group of children with SLI and non-language impaired children. In comparison to the TD group, children with SLI performed worse on a SRTT based on a FOC, but not a HOC sequence. This finding has important implications for research in SLI, and for research involving the SRTT. The findings suggest that while implicit sequence learning may be poorer in SLI, this problem does not extend to all types of sequences. In moving the field forward, this study also highlights the need to take the statistical structure of information into account when assessing implicit learning.
References


Supplementary Material

See below for an outline of the task design, including two examples of the stimuli used in the tasks.
Chapter 7

Study 4: Using Transcranial Magnetic Stimulation to Examine the Neural Substrates of FOC and SOC Sequence Learning

The data presented in Study 3 was interpreted to suggest that the implicit learning of FOC and HOC/SOC sequences on the SRTT are supported by different neural structures. Study 4 tested this hypothesis using transcranial magnetic stimulation (TMS).

TMS is a method of non-invasively stimulating the brain (Barker, Jalinous, & Freeston, 1985). It involves running an electric current through a coil of wire, which is placed over the scalp. The electric current generates a brief magnetic field which travels through the skull to the underlying cortex. This in turn induces an electrical current in the cortical region directly beneath the coil, which results in neuronal firing in this region (Kobayashi & Pascual-Leone, 2003). The diagram presented in Figure 7.1 outlines this process. A single TMS pulse administered causes action potentials. Administering multiple pulses, also known as repetitive TMS (rTMS), can decrease or increase neural excitability (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). In other words, rTMS can be used to either inhibit or facilitate neural activity in a cortical region.

In Study 4, rTMS was used to disrupt or inhibit networks proposed to underpin the implicit learning of FOC and SOC sequences on the SRTT. This was achieved using a type of rTMS referred to as theta-burst stimulation (Huang et al., 2005). Theta-burst stimulation involves applying pulses in bursts of three at 50 Hz, with an inter-burst interval of 5 Hz. For continuous theta-burst stimulation (cTBS), these bursts are applied in an uninterrupted train for 40 seconds, resulting in a total of 600 pulses (Huang et al., 2005). cTBS has been shown to decrease cortical excitability for up to 60 minutes, though effects are most reliable up to
20-30 minutes post-stimulation (Chung, Hill, Rogasch, Hoy, & Fitzgerald, 2016). While it is noted that there is substantial variability in response to cTBS both within and between individuals, on average it has been shown to produce the expected decrease in excitability. cTBS can interfere with learning on the SRTT (Clerget et al., 2011; Rosenthal, Roche-Kelly, Husain, & Kennard, 2009; Steel et al., 2016; Wilkinson et al., 2015; Wilkinson et al., 2009). The most common stimulation site has been the primary motor area (M1) (Rosenthal et al., 2009; Steel et al., 2016; Wilkinson et al., 2015; Wilkinson et al., 2009). M1 is part of the procedural memory system, and is part of one of the cortico-striatal circuits (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000). cTBS over M1 can lead to changes in connectivity between motor regions, as well as alter activity or connectivity with more distant regions that connect with M1 (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2004; Cárdenas-Morales, Grön, & Kammer, 2011; Steel et al., 2016).
In Study 4, cTBS was administered to M1 in order to affect functioning of the procedural memory system. Participants were presented with two SRTTs, on of which required the learning of a FOC, and the other a SOC sequence. If the claim made in Study 3 is correct, the expectation is that disrupting the procedural memory system should impact on the implicit learning of a FOC sequence. Study 4 tested this hypothesis.

Study 4 was submitted to the journal *Brain Structure and Function* on the 7th of September 2017, and is currently under review. Note that figure numbers in the manuscript have been changed to aid flow in the thesis.

*Figure 7.2* Schematic diagram representing cTBS protocol. Each vertical line represents a TMS pulse.
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</tr>
</thead>
<tbody>
<tr>
<td>Gillian Clark</td>
<td>School of Psychology</td>
<td><a href="mailto:gillian.clark@deakin.edu.au">gillian.clark@deakin.edu.au</a></td>
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Conceptualised the study, designed the methodology, collected the data, ran the analyses, drafted the manuscript.

*I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.*

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<tr>
<td>Jarrad Lum</td>
<td>Thesis supervisor – assisted with conceptualisation of the study, methodology design, data collection and analysis, and drafting of the manuscript</td>
</tr>
<tr>
<td>Michael Barham</td>
<td>Assisted with data collection and manuscript revisions</td>
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<tr>
<td>Anna Ware</td>
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<td>James Plumridge</td>
<td>Assisted with data collection and manuscript revisions</td>
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<td>Assisted with participant recruitment and data collection</td>
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Kristie Lyons  
Assisted with participant recruitment and data collection

Tegan Fitzgibbon  
Assisted with participant recruitment and data collection

Bree Buck  
Assisted with participant recruitment and data collection

George Youssef  
Assisted with data analysis and manuscript revisions

Peter Enticott  
Assisted with training in use of equipment, and manuscript revisions

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Dissociable implicit sequence learning mechanisms revealed by continuous theta-burst stimulation


aCognitive Neuroscience Unit, School of Psychology, Deakin University, Geelong, Australia
bCentre for Adolescent Health, Murdoch Children’s Research Institute, Parkville, Australia

* Address correspondence to
Gillian M. Clark
Cognitive Neuroscience Unit, School of Psychology, Deakin University, 221 Burwood Highway, Burwood, Victoria, Australia, 3121
e-mail: gillian.clark@deakin.edu.au
phone: +61 3 925 17185
Abstract

**Background.** The primary motor area (M1) has been implicated in visuomotor sequence learning. However, it has been suggested there are multiple neural networks that undertake visuomotor sequence learning. The role of M1 in sequence learning may be specific to learning simple sequences comprising predictable associations between adjacent movements.

**Objective.** This study aimed to investigate the role of M1 in learning simple (“first-order conditional”) and more complex (“second-order conditional”) sequences. It was hypothesised that continuous theta burst stimulation (cTBS) over M1 would result in poorer learning of the simple sequence only.

**Method.** Forty-eight healthy adults received cTBS to either M1 or the parietal lobe, or received sham cTBS before immediately completing two visuomotor sequence learning tasks. The tasks only differed in relation to the structure (i.e., simple versus complex) of the sequence.

**Results.** The group who received cTBS over M1 demonstrated significantly poorer learning of the simple sequence in comparison to the more complex sequence. The parietal lobe stimulation and sham stimulation did not influence learning of either sequence.

**Conclusions.** This is the first study to show differential involvement of M1 in visuomotor sequence learning, dependent on sequence structure. The contribution of M1 to sequence learning appears to be most important for learning simple item-to-item associations.

Keywords: Implicit sequence learning; Procedural memory; Serial reaction time task; Transcranial magnetic stimulation
The learning and memory functions of the procedural memory system are supported by a corticostriatal network comprising the basal ganglia and neocortical areas that include primary and supplementary motor regions, prefrontal cortex, and parietal cortex (Barnes, Kubota, Hu, Jin, & Graybiel, 2005; Hikosaka et al., 1999; Packard & Knowlton, 2002). This corticostriatal network underpins the learning and execution of a range of cognitive and motor skills, including the implicit learning of sequentially structured information. The role of the procedural memory system in implicit sequence learning has been widely examined using the serial reaction time task (SRTT) (Nissen & Bullemer, 1987). On the SRTT participants implicitly or incidentally learn a visuomotor sequence. Neuroimaging studies have demonstrated activation of the basal ganglia and cerebellum, and cortical areas including primary and supplementary motor regions and prefrontal cortices when healthy controls complete the SRTT (Daselaar, Rombouts, Veltman, Raaijmakers, & Jonker, 2003; Grafton, Hazeltine, & Ivry, 1995; Hazeltine, Graftib, & Ivry, 1997; Seidler et al., 2005; Willingham, Salidis, & Gabrieli, 2002).

The primary motor cortex (M1) has received particular attention in the sequence learning literature. M1 has been implicated in the initial encoding of sequences (Ben-Shaul et al., 2004; Seidler et al., 2005), as well as the early consolidation of learned sequences (Muellbacher et al., 2002). Several studies have reported poorer sequence learning in a probabilistic version of the SRTT following inhibitory TMS (continuous theta-burst stimulation) to M1 (Rosenthal, Roche-Kelly, Husain, & Kennard, 2009; Steel et al., 2016; Wilkinson et al., 2015; Wilkinson, Teo, Obeso, Rothwell, & Jahanshahi, 2009). Further evidence for a role of M1 in sequence learning was provided in a study involving non-human primates, which showed neuronal firing in M1 that was specific to sequential information (Carpenter, Georgopoulos, & Pellizzer, 1999). One suggestion is that during motor sequence
learning M1 is needed for encoding item-to-item associations. That is, for associating one movement element in a sequence with the next (Ashe, Lungu, Basford, & Lu, 2006).

However, item-to-item associations supported by M1 may not be necessary or sufficient for the implicit learning of all types of motor sequences. In the SRTT literature, sequences have been classified as either first-order conditional (FOC) or second-order conditional (SOC) sequences (Cohen, Ivry, & Keele, 1990; Curran, 1997; Reed & Johnson, 1994). In FOC sequences, each item or position in the sequence predicts the next, with varying degrees of probability. In contrast, for SOC sequences the probability of all item-to-item transitions is equal. In SOC sequences, a single position in the sequence is predicted by the combination of the preceding two positions. In order to learn SOC sequences, one item cannot be uniquely associated with the previous, but rather with an ambiguous pair of preceding items. It has been suggested that the hippocampus (Schendan, Searl, Melrose, & Stern, 2003), or a network including medial and inferior temporal cortices and dorsolateral prefrontal cortex (Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003), may be required for learning the ambiguous, temporally remote associations that make up SOC sequences.

To date, evidence consistent with the idea that multiple systems underlie implicit motor sequence learning has emerged from studies undertaken with clinical samples. In this literature a number of reports have appeared demonstrating dissociations with the implicit sequence learning of FOC and SOC. Curran (1997) found that individuals with temporal lobe amnesia performed more poorly than controls with respect to implicit learning of a SOC, but not FOC sequence. In Parkinson’s disease, there is some evidence for the opposite pattern, with better performance on SOC than FOC sequences (Deroost, Kerckhofs, Coene, Wijnants, & Soetens, 2006; Smith & McDowall, 2004). A recent study has also reported a similar dissociation in developmental language disorder (Clark & Lum, 2017) thought to
have a basal ganglia dysfunction (Ullman & Pierpont, 2005). In this group evidence was presented demonstrating poor learning of a FOC but not SOC sequence. Taken together, these neuropsychological studies potentially indicate multiple systems underpin implicit sequence learning.

In the current study, we used continuous theta burst stimulation (cTBS), which typically has an inhibitory effect on motor cortical excitability (Chung, Hill, Rogasch, Hoy, & Fitzgerald, 2016), to examine whether the implicit learning of a FOC and SOC sequences could be dissociated in healthy controls. In this study healthy adults completed two SRTTs based on a FOC and a SOC sequence (order of presentation was counterbalanced, see Method). We aimed to disrupt FOC sequence learning in one group, by administering cTBS over M1. A second group received cTBS over a region of parietal cortex that has previously been shown to influence connectivity with hippocampal regions. A third group received Sham cTBS. It was hypothesised that the group receiving cTBS over M1 would perform more poorly on the FOC than the SOC sequence. It was also hypothesised that the group receiving cTBS over parietal cortex would perform more poorly on the SOC than the FOC sequence. The group receiving sham stimulation were expected to show comparable performance on both sequence types.

Method

Participants

Forty-eight healthy adults (35 female; mean age = 25.85 years; SD = 3.93) participated in the study. Participants were assigned to one of three stimulation conditions (stimulation over M1, stimulation over parietal lobe, or sham stimulation), resulting in 16 participants per group. Allocation to stimulation conditions was pseudo-randomised to ensure comparability between groups with respect to age, handedness (as measured by the Edinburgh Handedness Inventory (Oldfield, 1971)), and female: male ratio. All participants
completed the Matrix Reasoning and Vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), allowing estimation of Full Scale IQ ($M = 106, SD = 10.2$). There were no group differences on IQ scores ($p = .479$). Participants had no contraindications for TMS, as determined by a questionnaire. Ethical approval for the study was obtained from Deakin University, and informed consent was obtained from each participant before taking part in the study. Participants received a $30$ voucher as compensation for their participation.

**Materials**

**Serial Reaction Time Tasks (SRTTs).** Participants were seated approximately $600$ mm from a computer monitor and presented with a game controller. A visual stimulus repeatedly appeared in one of four locations on the computer screen. Participants’ only instruction was to press the button on the controller that corresponded to the position that the visual stimulus appeared (see Figure 7.3A). The visual stimulus was a black and white line drawing of an everyday object. There were $120$ different black and white drawings that were shown throughout the tasks.

Each trial commenced with a blank screen that appeared for $200$ ms. The visual stimulus then appeared and remained on screen for $550$ ms. If a button was pressed during the stimulus presentation period, feedback was provided for the remainder of the $550$ ms. Feedback was a grey square outline, which appeared over the location corresponding to the button that was pressed (see Figure 7.3B).

Each SRTT comprised five blocks of $96$ trials. There was a $5$ second pause between each block. Unknown to participants, trials in Blocks 1, 2, 3, and 5 followed a $12$-item sequence that was presented eight times. Each block began at a different point in the sequence. In one SRTT, the sequence was FOC and in the other it was SOC. The FOC
sequence, where the numbers 1-4 represent each location (where ‘1’ is for the top position, ‘2’ for the right position etc.), was 1-3-2-3-4-2-1-3-4-1-4-2. The SOC sequence, taken from Schendan et al. (2003), was 4-1-3-2-4-3-1-2-1-4-2-3. The trials in Block 4 were presented in pseudorandom order, with the two following restrictions. First, the stimulus appeared at each of the four locations an equal number of times. Second, the stimulus did not appear in the same location on consecutive trials. In the SRTT, reaction times are recorded to gauge learning. Typically, reaction times decrease as the sequence is presented more times, and increase during the block of randomly ordered trials (Nissen & Bullemer, 1987). It is the increase in reaction time during the random block that is taken as evidence that information about the sequence has been learnt.

The visual stimulus was selected from the 120 images randomly on each trial. Images depicted easily identifiable objects (e.g., elephant, toothbrush, paperclip). Each image was shown four times during each SRTT. The purpose of showing a different picture on each trial was to mask the presence of the sequence.

**Awareness.** To gauge any level of awareness of the sequence, after completing both SRTTs participants were informed of the presence of a 12-item sequence, and asked to recall or guess any part of the sequence. Additional prompting was given if participants were reluctant to guess the sequence, in the form of pointing to the top location of the screen and asking participants “If the picture appeared here at the top, where do you feel it would most likely appear next?”. No participant recalled more than five items ($M = 2.02, SD = 1.79$), and there were no differences between the groups on the number of items correctly recalled ($F(2,45) = 1.625, p = .208$).

**Recognition.** To ensure that using different pictures throughout the tasks did not influence groups differently, a recognition task was administered. Prior to the task,
participants were not informed that they were to be tested on their recognition of the pictures. One picture was presented at a time in the centre of the screen, and remained onscreen for 1500 ms. All 120 pictures were shown, along with 120 foils. Participants indicated whether the picture was presented during the SRTTs (“Old”) or was not (“New”). The groups did not differ on recognition accuracy as measured by the $d$-prime statistic ($p = .572$), nor on the speed with which they made correct responses ($p = .715$).

**TMS**

Theta burst stimulation was delivered with a Magstim Rapid stimulator (Magstim, UK) connected to an air-cooled figure of eight coil with an internal wing diameter of 70 mm. The coil was held with the handle pointing posterolaterally. Resting motor threshold (RMT) was obtained for each participant. Motor-evoked potentials were measured from the first dorsal interosseous muscle of the right hand. The motor “hot spot” was defined as the scalp site that led to the largest motor-evoked potential. RMT was defined as the minimum intensity that produced a clear motor-evoked potential of at least 50 uV (peak-to-peak) in at least 5 out of 10 consecutive trials.

cTBS was administered at 70% of each participant’s RMT, according to procedures outlined by Huang et al. (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Each burst consisted of 3 pulses at 50 Hz, repeated every 200 ms (5 Hz), for a total of 600 pulses over approximately 40 seconds (Huang et al., 2005). cTBS was applied either to left M1 or left parietal cortex. The M1 site was taken as the “hotspot” located during RMT. Coordinates for the parietal site were taken from Wang et al. (Wang et al., 2014). In that study, it was shown that multiple sessions of rTMS over a region of parietal cortex increased functional connectivity in cortical-hippocampal networks, and improved declarative memory performance. While Wang et al. used individual MRIs to determine unique stimulation locations for each of their participants, in the current study we used the average coordinates.
(MNI: x = -47, y = -68, z = +36) reported by Wang et al., referenced to a common template brain for all participants. A Visor2 neuronavigation system (ANT neuro, Netherlands) was used to locate the parietal site for each participant.

Sham cTBS was delivered using a coil that was the same in appearance and acoustic properties as the stimulation coil, but it did not emit any magnetic pulse. Half of the participants in the Sham group received sham cTBS over the M1 site, and the other half over the Parietal site.

**Procedure**

This study followed a single-blind design. Figure 7.3C outlines the steps taken for each session. Following safety screening, participants were fitted with an EEG cap. RMT was determined, and a sticker was placed over the relevant M1 or Parietal site. Participants completed the IQ and handedness measures, as well as a single block comprising 120 randomly ordered trials. Each visual stimulus picture was shown once in this block. This was presented to participants as a practice to familiarise them with the task, and to provide a baseline measure of reaction time. Participants then received the cTBS, and immediately began the SRTTs. The order in which the SRTTs was presented was counterbalanced such that half (n = 8) of the participants in each group were presented with the FOC first. The time from the cTBS delivery to the end of both SRTTs was approximately 18 minutes. The awareness questioning and the recognition task were administered after the SRTTs were completed.

**Data analysis**

Reaction times and accuracy were obtained from each SRTT. Reaction times measured the time taken from stimulus onset to a response. Only reaction times associated with a correct response were used in the analyses. To control for individual differences in general reaction
Figure 7.3. (A) Location on screen and corresponding button on the controller for Positions 1 (top), 4, and 3. (B) Timing of trials. The stimulus showed for 550 ms, including the time that the feedback square appeared. For example, if the response was made 300 ms after stimulus onset, the stimulus with the feedback square showed for the remaining 250 ms. (C) Procedure of the experiment. During the SRTT, reaction times are measured. Slower reaction times to the random trials (Block 4) in comparison to the surrounding blocks of sequence trials (average of Blocks 3 and 5) indicates learning.

speed variability, normalised reaction times were used in the analyses (Thomas et al., 2004). For each participant, the mean $z$-score transformed reaction time, referenced to the median, was computed for each block. For the pre-cTBS block of random trials, $z$-score transformed reaction time for the block was referenced to the median reaction time across all blocks of both sequences. The dependent variable used to probe sequence-specific learning was
calculated as the reaction time difference between Block 4 (Random block) and the average of Blocks 3 and 5 (Sequence blocks), hereafter referred to as the ‘rebound’. A positive value for the rebound indicates that information about the sequence was learnt. In the SRTT literature, this is the common method used to gauge learning on the task. All three groups demonstrated a significant rebound ($p < .05$) on both sequences (see Figure 7.4 below), however the key comparison of interest is whether the rebounds for FOC and SOC sequences were different within each group. Thus, the main analyses investigated the difference between FOC and SOC sequence learning within each group, using repeated measures $t$-tests. Analyses were conducted in Stata 14 (StataCorp., 2015).

**Results**

The primary dependent variable was reaction time. Figure 7.4 presents the average normalised reaction time reported by group, block, and sequence type. Sequence learning was measured as the reaction time rebound. That is, the difference in reaction time recorded for the random block (Block 4) and the average of the surrounding sequence blocks (Block 3 and 5). The normalised reaction time rebound reported by group and sequence type is presented in Figure 7.5. Repeated measures $t$-tests comparing FOC and SOC rebounds were undertaken for each group separately. Analyses revealed that the size of the rebound between FOC and SOC sequences was significantly different for the M1 group, with a large effect size ($t(15) = 3.599, p = .003, d = 0.82$). This result shows that the M1 group evidenced a significantly smaller rebound for the FOC than the SOC sequence. There were no significant differences in FOC and SOC rebounds for the Sham group ($t(15) = .241, p = .813, d = .083$) or the Parietal group ($t(15) = .091, p = .929, d = .039$).
Figure 7.4. Mean normalised reaction time for each block of trials, reported by group and sequence type. Error bars show standard error.

Figure 7.5. Normalised reaction time rebound (difference between Random and surrounding Sequence blocks), reported by sequence type and group. Solid bars are for the FOC, unfilled bars for the SOC sequence. Error bars show standard error.

Accuracy

The effect of cTBS on reaction times was not explained by the accuracy with which participants pressed buttons in response to the visual stimuli. Accuracy measured the
proportion of correct responses per block. Across the five blocks, all groups pressed the buttons with a high level of accuracy in both the FOC sequence (Sham: \( M = .96, SD = .02 \); M1 Group: \( M = .97, SD = .02 \); Parietal Group: \( M = .97, SD = .02 \)), and the SOC sequence (Sham: \( M = .97, SD = .02 \); M1 Group: \( M = .96, SD = .04 \); Parietal Group: \( M = .97, SD = .03 \)).

A 3 (Group: Sham, M1, Parietal) X 2 (Sequence Type: Average accuracy for FOC; Average accuracy for SOC) mixed-design ANOVA was undertaken on these data. The ANOVA revealed non-significant main effects of Group (\( F(2, 44) = .166, p = .848 \)), Sequence Type (\( F(1, 44) = .798, p = .377 \)), and a non-significant interaction (\( F(2, 44) = 1.047, p = .360 \)).

**Discussion**

This study is the first to compare the effects of TMS on FOC and SOC sequence learning. The key result to emerge was that inhibitory cTBS over M1 disrupted FOC sequence learning but not SOC sequence learning. The groups who received either sham stimulation or active cTBS over the parietal lobe, performed comparably on both sequence types. These findings show that the neural regions involved in motor sequence learning are influenced by the statistical structure of the sequence.

The study demonstrates M1 is more heavily involved in learning FOC than SOC sequences. While previous research has implicated M1 in motor sequence learning generally (Ben-Shaul et al., 2004; Rosenthal et al., 2009; Seidler et al., 2005; Steel et al., 2016), the result from the current study indicates M1 involvement may not necessarily be required for learning all sequence types. In line with previous proposals, it may be that M1 (Ashe et al., 2006), or a network that includes M1 (Keele et al., 2003), is particularly involved in processing simple, first-order associations within a sequence. M1 may not process the higher-order transitions required for learning SOC sequences. Thus, inhibiting this region leads to difficulties learning FOC sequences, but not SOC sequences.
The influence of cTBS on FOC sequence learning may be due either to local inhibition of M1, or to changes in activation or connectivity in distant regions. A previous study (Steel et al., 2016) investigating the influence of cTBS on SRTT performance found that the stimulation led to changes in connectivity. Steel et al. found that after administering cTBS to M1, functional connectivity rather than neural activation was altered during the SRTT. It was found that connectivity between motor and visual areas decreased, and connectivity between frontal and temporal regions increased. It may be that a similar change in connectivity occurred in the current study, with this change negatively affecting the learning of FOC more than SOC sequences. This suggestion can also be interpreted in terms of the proposal that temporal lobe structures are required for learning SOC sequences. That is, learning SOC sequences might be facilitated or compensated via increased connectivity between temporal and frontal regions. Thus, cTBS over M1 did not negatively affect learning of the SOC sequence.

Based on the findings of this study we suggest that SOC sequence learning is supported by a different brain region or network than that required for FOC sequence learning. However, one limitation of the study is that the data did not indicate potential neural correlates of SOC sequence learning. The findings do not support proposals that implicate the hippocampal-declarative memory system in SOC learning (Keele et al., 2003; Schendan et al., 2003). The results showed that the group who received cTBS over the parietal lobe did not evidence poorer learning of the SOC sequence. As noted earlier, TMS over the parietal lobe can affect functioning of hippocampal-based declarative memory, via altering cortico-hippocampal connectivity (Wang et al., 2014). Thus, if the hippocampus is required for SOC sequence learning, the Parietal group would be expected to perform poorly on this sequence. There are two potential reasons for the null finding. One possibility is that the hippocampus and parietal area are not involved in sequence learning, or at least not
involved more for SOC than FOC sequences. A second explanation relates to the methodology used to locate the parietal site. Our use of the average coordinates reported in Wang et al., rather than coordinates based on individual MRI data for each participant, may have resulted in stimulating a region other than that we aimed to target. Indeed, the finding that the Parietal group performed comparably to the other two groups on the picture recognition task (see Method) also suggests that the hippocampus and associated declarative memory network was not inhibited via cTBS. Thus, it appears likely that cTBS to the parietal site did not alter functioning of the hippocampus. While the Parietal group’s findings highlight the specificity of the M1 stimulation, future research that targets regions thought to be involved for SOC sequence learning are warranted.

**Conclusion**

Overall, the findings indicate that learning FOC and SOC sequences rely on somewhat dissociable neural networks. While both FOC and SOC sequences are learnt implicitly, the findings of the current study indicate the learning that takes place is not equally supported by M1. In relation to the SRTT, it is suggested that it is the statistical structure of the sequence used which determines the involvement of M1 in learning.
References


Chapter 8

Study 5: The Relationship between Procedural Memory, Grammar, Reading, and Motor skills in SLI.

Study 5 investigated whether procedural memory is related to language, reading, and motor skills in children with and without SLI. Study 3 demonstrated that in SLI, the implicit learning of FOC sequences appears to be most affected. In Study 4, evidence was presented suggesting learning this type of information relies on parts of the brain that support the procedural memory system. Collectively, this pattern of results is largely consistent with the PDH that was summarised in Chapter 4. That is, in SLI cortico-striatal dysfunction leads to procedural memory impairments in this group. However, the PDH (Ullman & Pierpont, 2005) further predicts that co-occurring problems in SLI can be explained by dysfunction of procedural memory system structures. That is, the claim is that poor procedural memory leads to deficits in other types of skills that also rely on this memory system. Evidence presented in Study 2 indicated this potentially includes reading and motor skills. If this claim is correct, it would be expected that performance on the SRTT might be related not only to language, but also to motor and reading skills proficiency in SLI and TD children. This possibility was tested in Study 5.

The manuscript presented in this chapter is the pre-publication version, except that table, figure, and subheading numbers have been altered to improve flow within the thesis. The manuscript was accepted for publication in Research in Developmental Disabilities on the 16th of October, 2017. Note that the title of the final published version is ‘Procedural memory and speed of grammatical processing: Comparison between typically developing children and language impaired children’.
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</tr>
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<tbody>
<tr>
<td>Gillian Clark</td>
<td>School of Psychology, Deakin University</td>
<td><a href="mailto:gillian.clark@deakin.edu.au">gillian.clark@deakin.edu.au</a></td>
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<tr>
<td>Jarrad Lum, Deakin University</td>
<td>Thesis supervisor - Involved in study design and development, advised on recruitment methods, assisted with analyses, revised manuscript.</td>
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Procedural learning is uniquely associated with speed of grammatical processing in typically developing, but not language impaired children.

Gillian M. Clark and Jarrad A. G. Lum

Cognitive Neuroscience Unit, School of Psychology, Deakin University, Australia

Author Note

Gillian M. Clark, Cognitive Neuroscience Unit, School of Psychology, Deakin University; Jarrad A. G. Lum, Cognitive Neuroscience Unit, School of Psychology, Deakin University.

Correspondence concerning this article should be addressed to Gillian Clark, Cognitive Neuroscience Unit, School of Psychology, Deakin University, 221 Burwood Highway, Burwood, Victoria, Australia, 3121.

Email: gillian.clark@deakin.edu.au
Abstract

**Background.** Procedural memory has been posed to underlie the acquisition of a range of skills including grammar, reading, and motor skills. In specific language impairment (SLI) it has been suggested that procedural memory problems lead to the difficulties with grammar in this group.

**Aims.** This study aimed to extend previous research by exploring associations between procedural memory and a range of cognitive skills, in children with and without language impairments.

**Methods and Procedures.** Twenty children with SLI and 20 age-matched non-language impaired children undertook tasks assessing procedural memory, grammatical processing speed, single word and nonword reading, and motor skills.

**Outcomes and Results.** The SLI group evidenced no significant correlations between procedural memory and any of the measured variables. The TD group showed a significant correlation ($r = .482, p < .05$) between the measure of procedural memory and grammatical processing speed. Neither reading nor motor skills correlated with procedural memory.

**Conclusions and Implications.** This study provides new evidence showing that grammatical processing speed is correlated with procedural memory. Furthermore, results suggest that the relationship with procedural memory does not extend to reading or motor skills. For the SLI group the pattern of result indicate grammatical processing, reading, and motor sequencing are not supported by procedural memory or a common memory system.

*Keywords:* procedural memory; specific language impairment
What this paper adds

A dominant theory suggests that procedural memory underlies the ability to process grammar, and that procedural memory problems lead to the grammatical problems found in children with SLI. However, procedural memory is also thought to underlie reading and motor skills. This is the first study to directly investigate associations between each of these variables in groups of children with and without SLI. We suggest that grammatical processing speed may be a better measure than the often-used measure of accuracy in tapping into procedural system functioning. Results show that relationships between skills are different in SLI and TD groups. It appears that procedural memory, grammar, reading, and motor skills each rely on different processes or networks in SLI.
8.1 Introduction

Specific language impairment (SLI) is a neurodevelopmental disorder characterised by varying levels of expressive and receptive language problems (American Psychiatric Association, 2013; World Health Organization, 1992). A key characteristic of SLI is that the language impairments found in this group do not appear to be attributable to any medical condition or deficiencies with linguistic input (Leonard, 2014). While the diagnostic criteria for SLI suggests a potential dissociation between language and non-language skills, research indicates this is certainly not the case. Children with SLI typically present with a range of co-occurring problems as well (e.g., Bishop & Snowling, 2004; Hill, 2001; Vugs, Cuperus, Hendriks, & Verhoeven, 2013). Chief amongst these include motor (Hill, 2001) and reading (McArthur, Hogben, Edwards, Heath, & Mengler, 2000) skill deficits. A growing body of literature suggests that skills and abilities supported by the procedural memory system may underlie the language problems in SLI (Nicolson & Fawcett, 2007; Ullman & Pierpont, 2005). However, poor procedural memory has also been linked to motor and reading deficits (Nicolson & Fawcett, 2007), both of which are often present in SLI (Hill, 2001; McArthur et al., 2000). The extent to which procedural memory problems in SLI relate to the language problems in this group has yet to be tested and is the focus of the current study.

8.1.1 Procedural Memory in Specific Language Impairment

The initial claim implicating procedural memory in SLI was forwarded by Ullman and Pierpont (2005). According to the Procedural Deficit Hypothesis (PDH), dysfunction of the caudate and/or prefrontal regions gives rise to a procedural memory impairment in SLI. The procedural memory system is supported by a network of subcortical structures including the basal ganglia and cerebellum, and cortical structures including motor and prefrontal areas (Eichenbaum & Cohen, 2004; Graybiel, 1995; Knowlton, Mangels, & Squire, 1996). This
memory system is responsible for the implicit acquisition, storage, and retrieval of a range of information that is sequential, statistical, or rule-like in structure. Ullman (2001, 2004; Ullman et al., 1997) argues that the acquisition and use of grammar is also supported by the procedural memory system. Grammar follows statistical regularities, and like other information learnt via procedural memory, general rules relating to phonology, grammatical morphology, and syntax are acquired gradually and incidentally, after repeated exposure to the input.

One prediction of the PDH is that individuals with SLI should have poorer procedural memory than their non-language impaired peers (Ullman & Pierpont, 2005). Procedural memory functioning in SLI has commonly been investigated using the serial reaction time task (SRTT; e.g., Desmottes, Meulemans, & Maillart, 2015; Gabriel, Maillart, Guillaume, Stefaniak, & Meulemans, 2011; Hsu & Bishop, 2014; Lum, Conti-Ramsden, Page, & Ullman, 2012; Tomblin, Mainela-Arnold, & Zhang, 2007). The SRTT involves implicitly learning a visuo-motor sequence (Nissen & Bullemer, 1987). Participants are required to press a button that corresponds to the location of a visual stimulus on a computer screen. Unknown to participants, the location of the stimulus follows a predetermined sequence. Learning is considered to have taken place if participants respond faster to trials in which the stimulus follows a sequence compared to trials in which the stimulus appears in random locations. There is evidence for procedural memory problems in SLI, as indexed by SRTT performance. Lum, Conti-Ramsden, Morgan, and Ullman (2014) conducted a meta-analysis that synthesised results of SLI-SRTT studies. It was found that overall, individuals with SLI performed significantly more poorly on the SRTT than their typically developing (TD) peers.

8.1.2 Associations between Procedural Memory and Grammar
A second prediction of the PDH is that procedural memory should be related to grammatical proficiency. A number of studies (Desmottes et al., 2015; Gabriel et al., 2011; Gabriel et al., 2013; Gabriel, Meulemans, Parisse, & Maillart, 2014; Gabriel, Stefaniak, Maillart, Schmitz, & Meulemans, 2012; Lum et al., 2012; Lum & Kidd, 2012; Mimeau, Coleman, & Donlan, 2016) have investigated this relationship by examining correlations between the ability to learn the sequence in the SRTT, and performance on tasks that assess expressive and/or receptive grammatical skills. In these studies ‘performance’ has been operationalised as the ability to correctly comprehend (e.g., Gabriel et al., 2014; Gabriel et al., 2012; Lum et al., 2012) or produce (e.g., Gabriel et al., 2011; Lum & Kidd, 2012; Mimeau et al., 2016) one or more sentences. One finding to emerge from this literature is that the association between performance on the SRTT and grammatical skills are typically low. In SLI groups, most studies have reported positive non-significant correlations between .1 and .3 (Gabriel et al., 2011; Gabriel et al., 2012; Lum et al., 2012), although Gabriel et al. (2013) did find a significant association of .48. The positive values in these studies indicate that children who were better able to learn the sequence on the SRTT obtained higher scores on tasks assessing grammatical skills. Interestingly, non-significant, but negative correlations have also been reported (Desmottes et al., 2015; Gabriel et al., 2014; Gheysen, Van Waelvelde, & Fias, 2011). These range from -.31 (Desmottes et al., 2015) to -.46 (Gabriel et al., 2014). Thus, children with worse procedural memory performed better on the test of grammar.

One explanation for the weak associations between procedural memory and grammar in SLI is that in this group, grammar is learnt by a different memory system. Ullman and Pierpont (2005) proposed that the declarative memory system might compensate for poor procedural system functioning in SLI, and thus grammar might be learnt by the declarative memory system. However, this explanation does not account for the weak associations
observed between procedural memory and grammar in TD children. In TD groups, correlations between procedural memory and grammar are also small and often non-significant. The magnitude of association has commonly been found to be between .1 and .3 (Gabriel et al., 2011; Gabriel et al., 2013; Gabriel et al., 2012; Lum & Kidd, 2012; Mimeau et al., 2016), though this varies from -.28 (Gabriel et al., 2014) to .47 (Desmottes et al., 2015). The implication of these findings is that the ability to accurately comprehend or produce a grammatical sentence is not strongly related to performance on the SRTT or by extension, to procedural memory. Thus in both SLI and TD populations it is quite possible to have poor procedural memory, yet have intact grammatical skills.

There are several explanations for the small associations between performance on the SRTT and grammatical proficiency. One possibility explored in this study is that the role of procedural memory in grammar might be more closely related to processing speed, rather than the typically used measure of accuracy. One feature of procedurally acquired skills is that, while learning is gradual and incremental, once the skill has been learnt it can be executed automatically and rapidly. Thus, the speed with which the skill is executed may reflect procedural system functionality. In terms of grammatical skills, it may be that the speed with which one can comprehend or produce grammatical sentences is related to procedural system functionality. This idea was posed previously to account for the finding that groups with Tourette’s syndrome (Walenski, Mostofsky, & Ullman, 2007) and autism spectrum disorders (Walenski, Mostofsky, & Ullman, 2014) performed equally accurately, but significantly faster, than TD groups on several measures of language. As both Tourette’s syndrome and autism spectrum disorders are associated with abnormal cortico-striatal circuitry (Albin & Mink, 2006; Bradshaw, 2001; Langen et al., 2012), the results suggest that in relation to language processing, response speed indexes the cortico-striatal network more
effectively than accuracy. Whether procedural system functioning is associated with speed of grammatical processing in children with and without SLI, however, is yet to be investigated.

### 8.1.3 Procedural Memory in Reading and Motor Skills

Another explanation for the small association between SRTT performance and grammar is that procedural memory might not be related to grammar. If this is the case past findings indicating positive, albeit non-significant, correlations between performance on the SRTT and grammar (e.g., Gabriel et al., 2011; Gabriel et al., 2012; Lum et al., 2012; Mimeau et al., 2016) might be due to chance. Furthermore, procedural memory in both groups might be more closely related to other skills. Nicolson and Fawcett’s (2007) model of neurodevelopmental disorders predicts that disturbances in the procedural memory system can also negatively impact motor and reading skills. Their proposal is based on the identification of two distinct procedural memory networks; cortico-striatal and cortico-cerebellar (Doyon, Penhune, & Ungerleider, 2003). The cortico-striatal network is considered important for acquiring skills that involve planning, learning, and execution of sequences. The cortico-cerebellar network is involved in the adaptation or adjustment of skills (e.g., Debas et al., 2010; Doyon et al., 2003), as well as the automatisation of these skills (e.g., Lang & Bastian, 2002). Motor skill proficiency is linked to a cortico-striatal circuit that includes areas of the primary motor cortex, while motor adaptation involves cortico-cerebellar circuits (Nicolson & Fawcett, 2007). The skills that underpin phonological processing, and the automatisation of the skills that lead to fluent reading are linked to a cortico-cerebellar network (Nicolson, Fawcett, & Dean, 2001).

The implicit learning that takes place on the SRTT relies on areas of both cortico-striatal (e.g., Clark, Lum, & Ullman, 2014; Rauch et al., 1997; Reiss et al., 2005) and cortico-cerebellar (e.g., Pascual-Leone et al., 1993; Torriero, Oliveri, Koch, Caltagirone, & Petrosini,
circuits. Individual and group differences on SRTT performance could potentially be associated with reading, motor, or language skills. In SLI a deficit in procedural memory might lead to reading or motor skill deficits, rather than language difficulties. Both reading and motor problems are highly prevalent in SLI. McArthur et al. (2000) found that approximately 50% of children with SLI also met the diagnostic criteria for dyslexia, and it has been estimated that motor problems are present in 90% of children with SLI (Hill, 2001). Furthermore, children with motor or reading problems have also been found to perform more poorly on the SRTT compared to controls (Gheysen et al., 2011; Lum, Ullman, & Conti-Ramsden, 2013). Thus, there is evidence to suggest that poor procedural memory might be correlated with grammar as well as with reading and motor skills in children with SLI, and presumably in TD children.

8.1.4 The Current Study

The current study aimed to investigate the relationship between procedural memory and grammatical processing speed, reading, and motor skills in children with SLI and a comparison group comprising TD children. In this study associations between performance on a SRTT and measures of grammar, reading and motor functioning were examined in both groups. The first hypothesis tested in this study was that performance on a measure of procedural memory would be correlated with grammatical processing speed in both SLI and TD groups. The second hypothesis tested was that that reading and motor skills would also correlate positively with SRTT performance in both TD and SLI groups.

8.2 Method

8.2.1 Participants

Twenty children with SLI (7 female, 13 male) and 20 typically developing (TD) children (7 female, 13 male) took part in the study. Children were aged between 7 and 10
years. Data from some of these participants was also described in Clark and Lum (2016). All children were recruited from primary schools in Melbourne, Australia. Ethical approval for the study was obtained from Deakin University and the Department of Education Early Childhood Development, and informed written consent was given by the children’s parents prior to participating in the study. Details of participant characteristics are presented in Table 8.1.

8.2.1.1 Identification of children with SLI. The Core Language subtests (CLS) of the Clinical Evaluation of Language Fundamentals – Fourth Edition: Australian Standardisation (CELF-4: Australian Semel, Wiig, & Secord, 2006) were used to assess language skills. The CLS is standardised to a mean of 100 and standard deviation of 15, and provides an estimate of overall expressive and receptive language abilities. A score of 85 or lower has been shown to have high diagnostic accuracy (sensitivity = .83, specificity = .90, Semel et al., 2006). All children in the SLI group obtained a CLS of 85 or less. The language scores of all children in the TD group were in the average range.

Non-verbal reasoning skills were measured using either the Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) or the Raven’s Coloured Progressive Matrices (RCPM; Raven, 1998). Performance on both measures is summarised as a standardised score which has a mean of 100 and standard deviation of 15. All children obtained a standardised non-verbal intelligence score between 94 and 122.

8.2.2 Materials

8.2.2.1 Procedural memory. Procedural memory was measured using a version of the SRTT (Nissen & Bullemer, 1987). Children were seated at a computer monitor at a distance of around 650 mm. A visual stimulus, which was a cartoon picture of a fly, appeared repeatedly in one of four horizontally aligned positions on screen. Children were instructed
Table 8.1.
Summary Statistics showing Age and Scores from Language and Non-Verbal IQ Standardised Tests.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLI (n=20)</th>
<th>TD (n=20)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Range</td>
</tr>
<tr>
<td>Age (months)</td>
<td>107.05</td>
<td>11.76</td>
<td>95.67 – 135.10</td>
</tr>
<tr>
<td>CLS</td>
<td>76.45</td>
<td>6.43</td>
<td>63 – 85</td>
</tr>
<tr>
<td>Non-verbal Reasoninga</td>
<td>104.85</td>
<td>6.95</td>
<td>94 – 118</td>
</tr>
</tbody>
</table>

Note. CLS = Core Language Score

a measured by either the Matrix Reasoning subtest of the WASI or Raven's Colored Progressive Matrices

to press one of four horizontally aligned buttons on a computer keyboard that corresponded to the location of the stimulus on screen. Reaction times that measured the time taken between the stimulus appearing on screen and a button being pressed were recorded.

Each trial began with a blank gray screen that was displayed for 400 ms. The visual stimulus then appeared, and remained on screen until a response was made. Immediate feedback, that indicated which button had been pressed was shown onscreen for 150 ms. Children were presented with 10 practice trials to ensure that they understood the task. Test trials were grouped into blocks, each comprising 60 stimulus presentations. Unknown to participants, on Blocks 1, 2, and 3 the location of the stimulus followed a 10-item sequence that was presented six times. The sequence, where the numbers 1-4 represent the four locations from left to right, was 3-4-1-2-4-1-3-4-2-1. This is known as a first-order conditional sequence, which means that each stimulus location can be predicted to some extent from the previous position (Curran, 1997). Implicitly learning this type of sequence has been shown to rely on cortico-striatal and cortico-cerebellar structures of the procedural memory system (Clark et al., 2014; Knopman & Nissen, 1991; Torriero et al., 2004). In Block 4, the location of the stimulus appeared in pseudorandom order. On this block the stimulus appeared in each of the four locations an equal number of times as during each
Sequence block. The frequency of each pair of locations (e.g., 3 followed by 4) was also the same as in each Sequence block.

In line with previous studies (Gabriel et al., 2011; Gabriel et al., 2014; Lum & Bleses, 2012; Lum et al., 2012), the variable of interest was the difference in reaction time between the Random block (Block 4) and the preceding Sequence block (Block 3). The median reaction time associated with a correct response was computed for each participant for each block, and then averaged for each group. The average median reaction time for Block 3 (Sequence block) was subtracted from the average median reaction time for Block 4 (Random block), and this difference was used as the dependent variable. According to this index, positive values indicate longer reaction times for the Random block and thus, that information about the sequence has been learnt.

### 8.2.2.2 Grammatical Processing Speed

The measure of grammar was a sentence comprehension task based on common sentence-picture matching tasks (e.g. Bishop, 2003; Waters, Caplan, & Rochon, 1995). On this task a stimulus sentence is auditorily presented along with four pictures. The child’s task is to select one picture that matches the sentence’s semantics. In the current study the stimulus sentence and pictures were presented using a computer. This method for presenting the task permitted the recording of both accuracy and reaction times.

The task consisted of four practice trials, followed by 16 test trials. All sentences were simple, active, subject-verb-object sentences of five words (e.g., “The dog touches the tree”) or six words (e.g., “The girl is chasing the boy”) in length. Sentence selection was based on normative data from the Test of Receptive Grammar-2 (Bishop, 2003), which shows these types of sentences are correctly answered by at least 80% of 7- to 9-year olds. It was important that both groups approached ceiling on the task, as only reaction times associated
with a correct response were used in this study. This is because when a correct response is made, the reaction time is likely to capture the processes of interest. Of the four pictures that were shown, one unambiguously matched the sentence, while the remaining three were incorrect due to lexical errors or a reversal of subject and object. For example, the target sentence “The girl is chasing the boy” included one picture that matched the sentence, one picture of a girl chasing a dog, one picture of a boy chasing a duck, and one picture of a boy chasing a girl.

Each trial began with a blank screen, with a fixation cross in the centre of the screen which appeared for 350 ms. The sentence, which comprised pre-recorded speech of an adult female was then presented via headphones, at a comfortable volume. As the sentence started, four pictures also appeared on the screen. Using a computer mouse, the child aimed to ‘click’ on the picture that matched the sentence. After a response had been made, a blank screen appeared for 200 ms before the next trial began. Both accuracy and response times were measured. Accuracy measured the proportion of correct responses. Response times measured the time taken, in milliseconds, for a picture to be clicked after the end of the sentence. The end of each sentence was determined by inspecting acoustic waveforms in Audacity (Audacity Developer Team, 2004). Only response times associated with correct responses were used in the analyses, and response times longer than 10 seconds or shorter than -500 ms were excluded.

8.2.2.3 Control Task: Word recognition. A control task, which consisted of a word-picture matching task, was also presented to participants. Data collected from the word recognition task was used to control for the influence of basic motor processes (e.g., using a computer mouse to select a picture), responding to visual and auditory stimuli, and word recognition speed on the sentence comprehension task. The task format was identical to the
grammatical sentence-picture matching task, except that single words rather than sentences were presented. Specifically, on this task a single word was auditorily presented along with four pictures. The child’s task was to select the picture that matched the word, by using a computer mouse to click on the picture.

As in the grammar task, four practice trials were presented followed by 16 test trials. The target words on the task were nouns likely to be known by 5-year old children. Nouns were selected from the Receptive One Word Picture Vocabulary Test (ROWPVT; Brownell, 2000) and English normative data from the MacArthur-Bates Communicative Development Inventory (CDI) accessed via the CLEX database (Jørgensen, Dale, Bleses, & Fenson, 2010). Each trial began with a blank screen, with a fixation cross in the centre of the screen which appeared for 350 ms. The word was then presented at a comfortable volume via headphones. As the word was spoken, four pictures also appeared on the screen. One was a picture of the spoken word, while the remaining three pictures were foils. Using a computer mouse, the child aimed to ‘click’ on the picture that matched the word. After a response had been made, a blank screen appeared for 200 ms before the next trial began. Response times and accuracy were both recorded for each trial. Only response times associated with correct responses were used in the analyses, and response times longer than 10 seconds or shorter than -500 ms were excluded.

**8.2.2.4 Reading skills.** Reading skills were measured using the Test of Word Reading Efficiency (TOWRE; Torgesen, Wagner, & Rashotte, 1999). The TOWRE comprises two subtests, Word Efficiency and Phonemic Decoding Efficiency, which measure the ability to accurately and fluently read individual words and nonwords respectively. On the Word Efficiency subtest children are asked to read aloud as many real words as they can from a list of 104, within a 45 second period. Example words from the subtest are ‘on’,
‘bee’, and ‘most’. On the Phonemic Decoding Efficiency subtest children are given 45 seconds to read aloud as many nonwords as possible from a list of 63. Nonwords included ‘fos’, ‘rup’, and ‘dord’. Each subtest was preceded by a list of eight practice words or nonwords to familiarise children with the task. The dependent variables used in the analyses were the total number of words or nonwords correctly pronounced in 45 seconds.

Based on Nicolson and Fawcett’s (2007) proposal, the ability to complete the Word Efficiency and Phonemic Decoding Efficiency subtests are likely to be supported by the language-related cortico-cerebellar circuits of the procedural memory system. As noted earlier, Nicolson and Fawcett (2007) argued that the cortico-cerebellar circuits are needed for the automatisation of processes involved in reading, and for the implicit acquisition and manipulation of phonological rules. The extent to which reading processes can be executed automatically would certainly lead to the an increase in the number of words that can be read aloud within the 45 second time limit on the Word Efficiency and Phonemic Decoding Efficiency subtests. Also, the ability to learn and retrieve phonological rules is needed for grapheme to phoneme conversions. Children with superior procedural memory should also be able to read more words on the TOWRE.

8.2.2.5 Motor skills. Motor skills were measured using the Purdue Pegboard test (Tiffin, 1968). On this task children are presented with a pegboard comprising two columns of 25 holes, along with two tubs each holding approximately 25 small metal pegs. The children’s task is to place as many pegs as possible into individual holes on the board. Children practiced placing pegs in the board before the trials began. There are four trials on the task with each one lasting 30 seconds. Two trials are completed with the left hand and two with the right. The order that all participants completed trials was right-left-right-left. On each trial pegs are placed into holes on the pegboard, starting at the top and working
down. Similar to past research undertaken with SLI (Brookman, McDonald, McDonald, & Bishop, 2013), the dependent variable used in the analyses was the total number of pegs placed across all four trials.

The pegboard task requires a speeded, smooth sequence of movements. According to Nicolson and Fawcett’s (2007) model, these processes are supported by the require cortico-striatal circuits of the procedural memory system. There is evidence to suggest this is indeed the case (Pujol, Junque, Vendrell, Grau, & Capdevila, 1992; Vingerhoets, Schulzer, Calne, & Snow, 1997). Children with better procedural memory should place more pegs during the task.

**8.2.3 Procedure**

Children were tested individually in a quiet room at their school. The tasks were administered over three to four sessions, over an average of three months. The order of the tasks was randomised for each participant.

**8.3 Results**

The first set of analyses compared performance of the SLI and TD groups on the tasks assessing procedural memory (the SRTT), and grammar, word recognition, reading, and motor skills. Table 8.2 presents the descriptive statistics summarising each group’s performance on the tasks. Between-groups t-tests were used to investigate differences between groups on each measure. Results from these analyses are also summarised in Table 8.2. For illustrative purposes, the TD and SLI groups’ performance on the SRTT is presented in Figure 8.1.

Table 8.2 shows that the SLI group performed more poorly than the TD group on all administered tasks. On the SRTT, the SLI group evidenced a significantly smaller difference in reaction time between the block of randomly ordered trials (Block 4) and the preceding
Table 8.2: Summary Scores and Comparisons of Procedural Memory, Language, Reading, and Motor Tasks

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLI Mean</th>
<th>SLI SD</th>
<th>SLI Range</th>
<th>TD Mean</th>
<th>TD SD</th>
<th>TD Range</th>
<th>t</th>
<th>p</th>
<th>Cohen's d</th>
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</thead>
<tbody>
<tr>
<td>Procedural Memory (SRTT)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>2.33</td>
<td>89.12</td>
<td>-252.50 – 170.0</td>
<td>62.18</td>
<td>60.58</td>
<td>-40.0 – 197.0</td>
<td>-2.48</td>
<td>.018*</td>
<td>-0.79</td>
</tr>
<tr>
<td>Grammatical skills</td>
<td></td>
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<tr>
<td>Accuracy&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.86</td>
<td>0.12</td>
<td>.63 – 1.0</td>
<td>0.87</td>
<td>0.12</td>
<td>.56 – 1.0</td>
<td>193.5g</td>
<td>.864</td>
<td>-0.01</td>
</tr>
<tr>
<td>Response Time&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1583.57</td>
<td>390.17</td>
<td>1076.13 – 2260.23</td>
<td>1461.29</td>
<td>335.70</td>
<td>800.80 – 2034.08</td>
<td>1.06</td>
<td>.295</td>
<td>0.34</td>
</tr>
<tr>
<td>Word recognition</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Accuracy&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.99</td>
<td>0.03</td>
<td>.88 – 1.0</td>
<td>0.98</td>
<td>0.04</td>
<td>.81 – 1.0</td>
<td>190.0g</td>
<td>.737</td>
<td>-0.02</td>
</tr>
<tr>
<td>Response Time&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1494.35</td>
<td>593.67</td>
<td>700.79 – 3076.56</td>
<td>1244.09</td>
<td>310.16</td>
<td>743.75 – 1700.69</td>
<td>1.67</td>
<td>.103</td>
<td>0.53</td>
</tr>
<tr>
<td>Reading (TOWRE)</td>
<td></td>
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<tr>
<td>Words&lt;sup&gt;d&lt;/sup&gt;</td>
<td>56.67</td>
<td>12.71</td>
<td>27 – 76</td>
<td>65.00</td>
<td>10.38</td>
<td>38 – 80</td>
<td>-2.27</td>
<td>.029*</td>
<td>-0.72</td>
</tr>
<tr>
<td>Nonwords&lt;sup&gt;e&lt;/sup&gt;</td>
<td>25.5</td>
<td>12.63</td>
<td>2 – 49</td>
<td>36.05</td>
<td>11.69</td>
<td>12 – 54</td>
<td>-2.74</td>
<td>.009*</td>
<td>-0.87</td>
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<tr>
<td>Motor skills (pegboard task)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>50.5</td>
<td>5.43</td>
<td>38 – 58</td>
<td>52.68</td>
<td>6.07</td>
<td>42 – 65</td>
<td>-1.20</td>
<td>.238</td>
<td>-0.38</td>
</tr>
</tbody>
</table>

Note. SRTT = Serial reaction time task TOWRE = Test of Word Reading Efficiency
<sup>a</sup>Measured in milliseconds. <sup>b</sup>Response time difference between Block 4 (Random) and Block 3 (Sequence). <sup>c</sup>Proportion of accurate responses. <sup>d</sup>Total number of words accurately read in the Word Efficiency subtest of the TOWRE. <sup>e</sup>Total number of nonwords accurately read in the Phonemic Decoding Proficiency subtest of the TOWRE. <sup>f</sup>Total number of pegs placed in the Purdue Pegboard test. <sup>g</sup>Mann-Whitney U statistic. Non-parametric test used due to highly skewed data.

* <sup>*</sup>p < .05
block of sequenced trials (Block 3) compared to the TD group. This result indicates that the SLI group did not learn the implicit sequence as well as the TD group. Data from the sentence comprehension task showed that both groups approached ceiling with respect to accuracy. In relation to reaction times on this task, overall the SLI group were slower than the TD group, but this difference was not found to be statistically significant. This same trend was also observed on the word recognition task. For the measure of reading, on average the SLI group read significantly fewer real words and nonwords than controls. Finally, on the pegboard task, the SLI group on average placed two to three fewer pegs compared to the TD group. This difference corresponds to a small-to-medium effect size, however this effect did not reach significance.

The next analyses investigated whether individual differences in implicit learning on the SRTT (procedural memory) correlated with performance on the language, reading, and motor tasks. Two additional variables were calculated, to index grammatical processing speed while controlling the influence of word recognition speed, and vice versa. This was
achieved using regression. To control for any potential influence that differences in lexical knowledge might have on an individual’s grammatical comprehension, speed on the word recognition task was regressed onto speed on the grammar task. The standardised residuals were then included as a variable in the correlation analyses. This variable represents grammatical processing speed without the influence of lexical processing speed. The same process was undertaken to create a second variable that represents lexical processing speed while controlling for the influence of grammatical processing speed. Before calculating the correlations, log transformations were applied to reaction time data acquired from the word recognition task to control for non-normality. Pearson’s correlations were calculated for each group separately. Correlations for the TD group are presented in Table 3 and corresponding data for the SLI group in Table 8.4.

Table 8.3 shows that for the TD group, performance on the SRTT was significantly correlated with reaction times from the sentence comprehension task. That is, larger reaction time differences between Sequence and Random blocks on the SRTT were associated with faster responses in the sentence comprehension task. This relationship remained even after controlling for reaction times from the word recognition task. SRTT performance was not significantly associated with performance on the word recognition, reading, or motor tasks.

For illustrative purposes, Figures 8.2 and 8.3 present the scatterplots for each group depicting the relationship between procedural learning and grammatical processing, before (Figure 8.2) and after (Figure 8.3) controlling for word recognition speed. Interestingly, Table 8.3 also shows significant associations between the reading tasks and the motor skills task; TD children who read more words on the TOWRE also placed more pegs in the pegboard task. Finally, a significant correlation between word recognition (after controlling for the influence of grammatical processing speed) and word reading was also observed for the TD group.
Table 8.3.
Correlations between Skills for the Typically Developing group

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>1. Procedural Learning (SRTT)</td>
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<tr>
<td>Grammatical skills (sentence comprehension)</td>
<td>-0.475*</td>
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<tr>
<td>2. Response Time</td>
<td>-0.482*</td>
<td>0.729**</td>
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<tr>
<td>3. Response Time (controlling for word recognition)</td>
<td>-0.180</td>
<td>0.685**</td>
<td>0</td>
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<tr>
<td>Word recognition</td>
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<tr>
<td>4. Response Time</td>
<td>-0.199</td>
<td>0</td>
<td>-0.685**</td>
<td>0.729**</td>
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<td>5. Response Time (controlling for grammatical skills)</td>
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<td>Reading</td>
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<tr>
<td>6. Words (Word Efficiency)</td>
<td>-0.240</td>
<td>-0.105</td>
<td>0.233</td>
<td>-0.402†</td>
<td>-0.452*</td>
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<tr>
<td>7. Nonwords (Phonemic Decoding Efficiency)</td>
<td>-0.366</td>
<td>-0.051</td>
<td>0.190</td>
<td>-0.277</td>
<td>-0.332</td>
<td>0.885**</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>8. Motor skills (pegboard task)</td>
<td>-0.214</td>
<td>0.065</td>
<td>0.235</td>
<td>-0.154</td>
<td>-0.273</td>
<td>0.565*</td>
<td>0.556*</td>
<td>—</td>
</tr>
</tbody>
</table>

† $p < .1$
* $p < .05$
** $p < .001$
Table 8.4.
Correlations between Skills for the Specific Language Impairment group

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td>1. Procedural Learning (SRTT)</td>
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<td>Grammatical skills (sentence comprehension)</td>
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<tr>
<td>2. Response Time</td>
<td>.066</td>
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<tr>
<td>3. Response Time (controlling for word recognition)</td>
<td>.074</td>
<td>.659*</td>
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<td>Word recognition</td>
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<td>4. Response Time</td>
<td>.153</td>
<td>.752**</td>
<td>0</td>
<td></td>
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<td>-</td>
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<tr>
<td>5. Response Time (controlling for grammatical skills)</td>
<td>.156</td>
<td>0</td>
<td>-.752**</td>
<td>.659*</td>
<td></td>
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<td>Reading</td>
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<tr>
<td>6. Words (Word Efficiency)</td>
<td>.226</td>
<td>.075</td>
<td>.056</td>
<td>.051</td>
<td>-.009</td>
<td>-</td>
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<td>7. Nonwords (Phonemic Decoding Efficiency)</td>
<td>.340</td>
<td>-.061</td>
<td>-.009</td>
<td>-.073</td>
<td>-.042</td>
<td>.858**</td>
<td>-</td>
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<td>8. Motor skills (pegboard task)</td>
<td>.066</td>
<td>.035</td>
<td>.133</td>
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<td>-.146</td>
<td>-.127</td>
<td>-.184</td>
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* p < .05
** p < .001
This result indicates faster responses to the word-picture matching task (word recognition) were associated with reading more words on the Word Efficiency subtest of the TOWRE.

Table 8.4 shows that for the SLI group, none of the correlations between measures were found to be statistically significant. For this group, the only significant associations were those between the language tasks (i.e., faster grammatical processing was associated with faster lexical processing), and between the reading tasks (i.e., reading more words was associated with reading more nonwords). These associations were similar to those shown by the TD group for the same variables.

![Scatterplot showing the relationship between procedural memory (serial reaction time task) and speed of grammatical processing for each group.](image)

**Figure 8.2.** Scatterplot showing the relationship between procedural memory (serial reaction time task) and speed of grammatical processing for each group.
4. Discussion

This study investigated the relationships between procedural memory, grammar, reading, and motor skills in children with and without SLI. The results partially supported the first hypothesis. A measure of procedural memory was found to be significantly correlated with reaction times obtained from a grammatical sentence comprehension task for the TD group, but not the SLI group. The data did not support the second hypothesis. Against predictions procedural memory was not found to be significantly correlated with measures of reading or motor proficiency for either group. Overall, the study’s findings lend support to the idea that procedural memory might be related to the speed with which grammar is processed, at least in TD children. We found no evidence that procedural memory was related to the measures of reading and motor skills in this group. For the SLI group procedural memory was not found to be significantly correlated with grammatical processing speed, reading, or motor skills. In SLI, procedural memory does not appear to be related to any of the measures assessed in this study.
A new finding to emerge from this study is that in TD children, procedural memory appears to be related to the speed grammar is processed. As mentioned earlier, Walenski et al. (2007, 2014) suggested that speed of grammatical processing might be a better measure than accuracy to index functioning of the cortico-striatal circuits of the procedural memory system. Their proposal was based on the finding that in comparison to controls, individuals with suspected abnormal functioning of cortico-striatal circuits performed equally accurately, but significantly faster on measures of grammatical processing. The current study extends those findings by showing a direct association between a measure of procedural memory and grammatical processing speed. Notably, the correlation found in the current study was significant, whereas previous studies that have used accuracy as the measure of grammar proficiency have typically reported non-significant associations of a small-to-medium magnitude (e.g., Gabriel et al., 2013; Gabriel et al., 2012; Lum & Kidd, 2012). We suggest that response times rather than accuracy in grammatical tasks may be a useful measure to use in future research.

Another key finding from this study was that for the TD group, the significant association with procedural memory was observed only for grammatical processing. Neither reading nor motor skills correlated with SRTT performance. This pattern of results suggest the aspects of procedural memory assessed by the SRTT are not related to processes used on the reading and pegboard tasks. This may be due, at least in part, to the specific regions of the cortico-cerebellar networks that each task engages. For example, while single word reading appears to be associated with connectivity within the left cerebellum (Travis, Leitner, Feldman, & Ben-Shachar, 2015), performance on the SRTT, particularly when using the right hand as in the current study, may engage the right cerebellum (Gomez-Beldarrain, Garcia-Monco, Rubio, & Pascual-Leone, 1998; Torriero et al., 2004). In relation to the lack of association between performance on the SRTT and the pegboard task, it may be that the
The pegboard task is more reliant on the cerebellum than the procedural system networks more widely. It has been suggested previously that the precision grip required for the pegboard task leads to heavy involvement of the cerebellum (Brookman et al., 2013), and individuals with cerebellar damage perform poorly on the task (e.g., Claassen et al., 2013). The significant correlation between the reading and pegboard tasks might thus reflect use of similar cerebellar regions or networks for these two tasks.

For the SLI group, procedural memory was not found to correlate with grammatical processing speed, reading, or motor skills. The non-significant concerning grammar and procedural memory are consistent with past research. However, this body of research has only examined the relationship between accuracy measures of grammar and procedural memory (Gabriel et al., 2013; Gabriel et al., 2014; Gabriel et al., 2012; Lum et al., 2012). When considering the results presented in this study alongside past research it seems that in SLI, procedural memory is not related to grammatical skills, as measured by accuracy or processing speed. It might be considered the null results observed in this study can be explained with respect to low statistical power. However, this consideration can be discounted for two reasons. First, the size of the correlations were small (r’s < .075). If these values were found to be significant in a large sample size, one would question the importance of these results, since the magnitude of the association would be indicating there are a substantial number of children with poor procedural memory but fast processing speed for grammar. Second, the sample sizes of the two groups were equal, yet the TD group did show a significant correlation. Thus, it is not the case that detecting a relationship between the two variables is simply dependent on a larger sample size.

What might explain the lack of correlation between procedural memory and grammar in SLI? One possibility, forwarded by Ullman and Pierpont (2005), is that in SLI declarative memory compensates for procedural memory problems. As a result, individual differences in
grammatical skills in SLI should be related to declarative memory functioning, leading to the lack of correlation with procedural memory in the current study. However, declarative system compensation is unable to account for all of the SLI results in this study. Ullman (Ullman & Pierpont, 2005; Ullman & Pullman, 2015) also argues that declarative memory can compensate for reading problems. In the current study, the SLI group performed significantly more poorly on the measures of word reading than the TD group. If declarative memory was compensating for procedural memory, grammar and reading should be correlated in the SLI group. Yet, this was not the case. Therefore it could be that if compensation does occur in SLI, it is not supported by a single memory system. Indeed, this might also explain the lack of correlation between reading and motor skills in the SLI group. Specifically, while the results of the TD group suggest that reading and motor skills are related and possibly undertaken by the same system, in SLI this is not the case.

Conclusions

This study provides new evidence indicating that speed of grammatical processing is associated with procedural memory functioning in TD children. This supports Ullman’s (2004) claim that the processing of grammar is supported by the procedural memory network. Results also add that the relationship with procedural memory, at least as indexed by the SRTT, is specific to grammatical processing speed, and unrelated to reading and motor skills. Results of the SLI group showed that procedural memory, grammatical processing speed, reading, and motor skills were not significantly associated, yet this group performed more poorly than the TD group on each measure. It appears that in SLI, different processes might underlie performance on each skill. An important area for future research is thus to investigate multiple compensatory processes in developmental disorders.
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Chapter 9

General Discussion

9.1 Summary

This thesis investigated procedural learning in SLI using the serial reaction time task. There were two broad questions addressed in the research undertaken as part of this thesis. The first regarded the nature of procedural memory problems in SLI. The second considered the relationship between procedural memory, and the language and comorbid problems found in SLI. The research presented in Chapters 6 and 7 collectively showed that in SLI, procedural learning of a FOC sequence is relatively poor compared to a SOC sequence. It was further shown that learning of the FOC sequence appears to be supported by neural structures typically linked to the procedural memory system. The studies presented in Chapters 5 and 8 explored whether poor procedural memory might be related to some of the problems that often co-occur with the language problems in SLI. A finding to emerge from these studies was that poor procedural memory is present in a range of disorders, including those characterised by poor language, reading, or motor functioning. However, within a sample of children with SLI there was no association between procedural memory deficits and the same skills. In this discussion three key questions raised in the literature review are considered in light of the empirical work conducted as part of this thesis. The first is “Is procedural memory impaired in SLI?” the second is “Do compensatory processes explain the language improvements in SLI?”, and the third is “What is the relationship between procedural memory, grammar, reading, and motor skills?”. 

9.2 Procedural Learning and Memory in Specific Language Impairment: What is Impaired?

A core claim of the PDH, outlined in Chapter 4, is that cortico-striatal circuitry comprising the caudate and Broca’s area is dysfunctional in SLI (Ullman & Pierpont, 2005).
It is proposed that these neurological problems lead to procedural memory deficits. The literature reviewed in Chapter 4 showed that the findings regarding poor procedural memory in SLI are somewhat mixed. Some studies have found that children with SLI perform comparably to TD children on the SRTT (Gabriel et al., 2011; Gabriel et al., 2012), or the Weather Prediction task (Lukacs & Kemeny, 2014; Mayor-Dubois et al., 2012). However, more commonly it has been found that children with SLI perform poorly on procedural memory tasks, particularly those that involve learning sequences (Evans et al., 2009; Hsu & Bishop, 2014; Obeid et al., 2016). In two studies presented in this thesis (Chapters 6 and 8), children with SLI were also found to perform poorly on a SRTT. These findings provide further support of a procedural memory impairment in SLI.

The studies presented in this thesis highlight the need to distinguish between procedural learning and procedural memory. ‘Procedural learning’ refers to implicitly learning information through repeated exposures or training. ‘Procedural memory’ refers to encoding, storage, and retrieval of information via cortico-striatal circuitry. The studies presented in Chapters 6 and 7 support the main claim of the PDH that learning and memory functions supported by the procedural memory system are impaired in SLI. Procedural learning that is not reliant on the cortico-striatal networks, however, is spared in SLI. In Chapter 6 it was shown that children with SLI are not impaired at learning SOC sequences. This was the case even though SOC sequences are learnt procedurally. Chapter 7 showed that this type of sequence does not heavily rely on structures of the procedural memory system. In contrast, learning FOC sequences was found to depend on structures that comprise the procedural memory system. Poor learning of FOC sequences in SLI therefore reflects poor functioning of the procedural memory system. The intact SOC sequence learning shows that children with SLI can procedurally learn information that does not rely on cortico-striatal networks.
The proposal that procedural learning can be intact, but the procedural memory system impaired, may help to explain discrepant findings in the SLI literature. As mentioned, some studies that have aimed to assess procedural memory in SLI have found intact performance (e.g., Gabriel et al., 2011; Gabriel et al., 2012; Mayor-Dubois et al., 2012). It may be that the tasks used in these studies require procedural learning, but do not depend on the procedural memory system. Further support for this proposal is provided by studies that have found MTL involvement during the Weather Prediction task (Foerde et al., 2006; Poldrack et al., 2001). This task, like SOC sequence learning, might use the different or additional neural structures to process information, rather than relying on cortico-striatal loops. Note that this does not mean that the basal ganglia are not engaged at all during the task. As described in Chapter 4, both SOC sequence learning as well as tasks such as Weather Prediction, have also been shown to activate the basal ganglia (e.g., Aron et al., 2004; Grafton et al., 1995). The findings reported in this thesis, however, specify that the cortico-striatal circuits of the procedural memory system may not be equally necessary for all procedural learning tasks. Thus, based on the studies presented in this thesis, it is proposed that learning and memory difficulties in SLI may be limited to tasks that rely most on the procedural memory system.

9.3 Are there Compensatory Processes in Specific Language Impairment?

The studies in this thesis do not support the claim that declarative memory compensates for procedural memory impairments in SLI. Chapters 6 and 7 show that there is an intact system in SLI that can learn information procedurally. It is unclear whether this system involves structures of the declarative memory system. However, in SLI there is a network that can process information in a similar way to the procedural memory system. Yet, compensation does not appear to occur, at least not in the manner that Ullman (Ullman & Pierpont, 2005; Ullman & Pullman, 2015) theorised. As found in Chapter 8, the skills that
are thought to rely on procedural memory, or that would each be compensated for by declarative memory, are not correlated. If compensation is occurring for the various skills, it does not seem that this is underpinned by a single system.

A serious concern regarding the feasibility of compensation can also be drawn from the studies in Chapters 6 and 7 of this thesis. These Chapters show that it is not the integrity of the memory or processing system that determines which network is used for learning. Rather, the system recruited for learning depends on the structure of the to-be-learned information. The findings in Chapters 6 and 7 showed that when procedural memory was impaired or interrupted, the second intact procedural learning system did not compensate by learning the FOC sequence. While this was only shown for visuomotor sequences, if we extend these findings to language learning, it presents a problem for the compensation aspect of the PDH. Specifically, if grammar is typically learnt via the procedural memory system, even a second intact procedural learning network might not compensate if procedural memory is impaired. This may explain why SLI arises. That is, SLI reflects an instance whereby language problems cannot be compensated, leading to below age-appropriate language skills.

If procedural memory is impaired in SLI, but declarative memory does not compensate for these problems, how do language skills develop in children with SLI? As presented in Chapter 2, receptive and expressive language skills in SLI do improve over time. One suggestion is that grammar continues to rely on the deficient procedural memory system. The studies in Chapters 6 and 7 showed that even when the procedural memory system is impaired, there was some learning of FOC sequences. Perhaps this is the same for grammar. That is, learning of grammar is poor because the learning is relying on a dysfunctional system. However, similar to FOC sequences, learning is not absent. The language skills of children with SLI thus may improve due to general development and increased exposures to
language, in a similar way the language skills in TD children develop. The language skills in SLI remain below those of their age-matched peers due to the need to learn through a partly faulty or dysfunctional network.

A second explanation of language development in SLI relates to interactions between different memory systems and language components. The procedural and declarative memory systems might process some parts of language as Ullman (Ullman, 2004; Ullman & Pierpont, 2005) suggests. However it is likely that the two systems interact with each other, and also with other networks or regions in the brain. Indeed, the core structures of each memory system – the basal ganglia and the hippocampus – are also connected with each other (Alexander et al., 1986; Middleton & Strick, 1996; Parent & Hazrati, 1995). In terms of language processing, there is also evidence of interactions. Grammatical and lexical processes interact in order to produce and comprehend complex language (Gleitman, 1990; Naigles, 1990). During language acquisition, this can be seen with respect to ‘syntactic bootstrapping’ (Gleitman, 1990). That is, a better understanding of grammar can lead to an increased ability to learn new words. As new words are often presented within some grammatical framework, an understanding of that framework can lead to more accurate understanding of a novel word (Gleitman, 1990; Naigles, 1990). Thus learning a new word, which is purported to be undertaken by declarative memory, likely also requires input or processing via procedural memory. Interaction between memory systems may also assist in explaining the lack of correlations between different skills found in Chapter 8. That is, these different skills all appear to involve procedural memory to some extent, but interactions with different regions or networks may differentiate between the skills. A model that more strongly accounts for the neural networks might be required.
9.4 What are the Links between Procedural Memory, Grammar, and Other Skills?

It is not yet clear whether the procedural memory system supports the learning and use of grammar. On the one hand, children with SLI show deficits in both procedural memory and grammar. This suggests a relationship between the two abilities. However, on the other hand, as outlined in Chapter 8 grammar has not been found to correlate with procedural memory performance. The majority of studies that have investigated the relationship between procedural memory and sentence comprehension or expression accuracy in TD children have found small, non-significant correlations (Gabriel et al., 2011; Gabriel et al., 2013; Gabriel et al., 2014). Two additional studies investigated more specific grammatical structures. Lum and Kidd (2012) and Mimeau, Coleman, and Donlan (2016) both used a sentence probe task to assess production of past tense ‘-ed’. As consistent use of past tense ‘-ed’ is one area of particular difficulty in SLI, this might indicate that learning the regular past tense rule is especially reliant on the procedural memory system. However, both studies also found small, non-significant correlations of -.01 (Mimeau et al., 2016) and .09 (Lum & Kidd, 2012) between accuracy on the sentence probe task and SRTT performance.

In Chapter 8, it was found that sentence comprehension speed correlated with SRTT performance for TD children. Future studies that focus on processing speed rather than accuracy may further elucidate relationships between procedural memory and other skills.

The studies in this thesis also highlight a further problem in identifying relationships between procedural memory and grammar. SRTT performance, particularly when based on FOC sequences, appears to be the most valid behavioural measure of procedural memory. Yet, as shown in Chapter 5, SRTT deficits are common to a range of disorders, each with different underlying neurological pathology. For example, while SLI is associated with cortico-striatal abnormalities, dyslexia is associated predominantly with cerebellar impairments. Because a wide range of disorders are characterised by poor procedural
memory, attempts to tie SRTT performance to one specific skill or brain structure are problematic. This does not mean that procedural memory does not underlie learning some aspects of grammar, reading, or motor skills. Rather, it suggests that correlations, or lack of correlation, between procedural memory and measures of a particular skill might not reflect the relationships at a neurological level. In order to further understand the role of procedural and declarative memory systems in SLI, the field may need to move beyond behavioural tasks, using neuroimaging or neuromodulation techniques as suggested below.

9.5 Methodological Considerations and Avenues for Future Research

In order to better understand the relationship between procedural memory and language, the parts of the brain that are active during such tasks need to be identified. One method available to examine the involvement of cortico-striatal circuits in different skills is fMRI. A clear advantage of neuroimaging studies in contrast to behavioural measures, is that the neural regions active during a task can be identified. This could be particularly useful for examining the compensation hypothesis. As discussed, very few studies have examined compensation in SLI. It is difficult to rely on behavioural measures to indicate whether a task is undertaken by procedural memory, declarative memory, or some other system. Neuroimaging studies are better able to indicate the systems that are active for different groups. Furthermore, comparing structural and functional connectivity within cortico-striatal loops, between individuals with SLI, dyslexia, and DCD, may help to pinpoint a common neurological deficit.

A limitation of fMRI is that the neural regions activated during a given task are not always necessary or specific to task performance. A technique that can indicate whether a particular region is necessary for a given task is TMS. As discussed in Chapter 7, TMS can be used to inhibit or facilitate activity in a cortical region. Alterations in task performance
following stimulation can indicate whether the stimulated site is required for task
performance. A developing area of research uses a different type of TMS, ‘deep TMS’,
which is able to stimulate subcortical structures. To date, this technique has predominately
been applied as a treatment for various disorders (Enticott et al., 2014; Rosenberg, Klein, &
Dannon, 2013; Rosenberg, Roth, Kotler, Zangen, & Dannon, 2011; Zangen, 2013). Of
particular relevance, pilot studies have shown that deep TMS can successfully treat motor
symptoms of Parkinson’s disease (Spagnolo et al., 2014; Tendler et al., 2014). It has been
suggested that the success was due to effects of stimulation on striatal neurons (Spagnolo et
al., 2014). This research opens the possibility of applying deep TMS to test whether
language, reading, or procedural memory skills can be facilitated in a similar way.

There are also limitations in using TMS. For example, because the stimulation effects
are not contained only to the region that is stimulated, it can be difficult to determine if
performance on a task is altered due to local inhibition or more distal effects. This was
evidenced in the results presented in Chapter 7, whereby it was not possible to determine the
specific neural regions or networks that were used to learn SOC sequences. A suggestion for
future research is therefore to combine fMRI and TMS methodologies to investigate the
neural circuitry that is used for procedural learning when the procedural memory system is
dysfunctional.

9.6 Conclusions

The PDH proposes that procedural memory system abnormalities underlie the
language and comorbid problems in SLI. It is also proposed that the declarative memory
system compensates for the impaired procedural memory system. The studies presented in
this thesis support the core claim that procedural memory is impaired in SLI. A major
contribution of this research is the finding that tasks or skills that are learnt procedurally do
not necessarily rely on the procedural memory system to the same degree. It was shown that children with SLI can learn information procedurally, if learning is not dependent on neural structures of the procedural memory system. This thesis has also highlighted substantial limitations in using behavioural tasks to examine the memory systems responsible for learning different skills. It was shown that procedural memory problems are associated with a wide range of developmental disorders. However, the relationship between procedural memory and the skills that are impaired in each disorder remains unclear. In terms of accounting for the language problems along with comorbid conditions in SLI, further work is required to specify whether or not these skills rely on shared neural regions. In taking the field forward, one next step is to more directly investigate specific cortico-striatal circuits that are involved in different skills.
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San Antonio, TX.


Appendices
# AUTHORIZATION STATEMENT

## 1. Details of publication and executive author

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<tr>
<td>Gillian Clark</td>
<td>School of Psychology, Deakin University</td>
<td><a href="mailto:gillian.clark@deakin.edu.au">gillian.clark@deakin.edu.au</a></td>
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## 2. Inclusion of publication in a thesis

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## 3. HDR thesis author’s declaration

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If there are multiple authors, give a full description of HDR thesis author’s contribution to the publication (for example, how much did you contribute to the conception of the project, the design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)

- Conceptual development of paper, completion of systematic search, evaluation of articles for inclusion, data extraction, data analysis, drafting of manuscript, revisions.

I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.

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<td>Jarrad Lum, Deakin University</td>
<td>Thesis supervisor: involved in conceptual development of paper, data review/extraction/analysis, reviewed and provided feedback on all manuscript drafts.</td>
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<tr>
<td>Michael Ullman, Georgetown University</td>
<td>Reviewed and provided feedback on manuscript.</td>
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5. Author Declarations
I agree to be named as one of the authors of this work, and confirm:
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xxii. that there are no other authors according to these criteria,
xxiii. that the description in Section 4 of my contribution(s) to this publication is accurate,
xxiv. that the data on which these findings are based are stored as set out in Section 7 below.

If this work is to form part of an HDR thesis as described in Sections 2 and 3, I further
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6. Other contributor declarations
I agree to be named as a non-author contributor to this work.

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* If an author or contributor is unavailable or otherwise unable to sign the statement of authorship, the Head of Academic Unit may sign on their behalf, noting the reason for their unavailability, provided there is no evidence to suggest that the person would object to being named as author

7. Data storage

The original data for this project are stored in the following locations. (The locations must be within an appropriate institutional setting. If the executive author is a Deakin staff member and data are stored outside Deakin University, permission for this must be given by the Head of Academic Unit within which the executive author is based.)

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This form must be retained by the executive author, within the school or institute in which they are based.

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A Meta-Analysis and Meta-Regression of Serial Reaction Time Task Performance in Parkinson’s Disease

Gillian M. Clark and Jarrad A. G. Lum
School of Psychology, Deakin University, Australia

Michael T. Ullman
Department of Neuroscience, Georgetown University, USA

Author Note
Gillian M. Clark, School of Psychology, Deakin University; Jarrad A. G. Lum, School of Psychology, Deakin University; Michael T. Ullman, Department of Neuroscience, Georgetown University.

Correspondence concerning this article should be addressed to Jarrad Lum, School of Psychology, Deakin University, 221 Burwood Highway, Burwood, Victoria, Australia, 3121.
Email: jarrad.lum@deakin.edu.au
Abstract

**Objective:** This paper reports findings of a meta-analysis and meta-regression summarizing research on implicit sequence learning in individuals with Parkinson’s disease (PD), as measured by the Serial Reaction Time (SRT) task. **Method:** Following a systematic search of the literature, we analyzed a total of 27 studies, representing data from 505 participants with PD and 460 neurologically intact control participants. **Results:** Overall, the meta-analysis indicated significantly ($p < .001$) worse sequence learning by the PD group than the control group. The average weighted effect size was found to be $\text{.531 (CI}_{95\%}: .332, .470)$, which is a medium effect size. However, moderate to high levels of heterogeneity (differences) were found between study effect sizes ($I^2 = 58\%$). Meta-regression analysis suggested that presentation of the SRT task under dual task conditions coupled with PD severity or characteristics of the sequence might affect study effect sizes. **Conclusions:** The meta-analysis provides clear support that learning in procedural memory (procedural learning), which underlies implicit sequence learning in the SRT task, is impaired in PD.

**Keywords:** serial reaction time; procedural memory; procedural learning; Parkinson’s disease; meta-analysis
A Meta-Analysis and Meta-Regression of Serial Reaction Time Task Performance in Parkinson’s Disease

Parkinson’s disease (PD) is a neurodegenerative disorder associated with the death of dopamine-producing cells in the substantia nigra, leading to the dysfunction of the basal ganglia and ensuing motor symptoms (Dubois & Pillon, 1996; Lang & Lozano, 1998). These symptoms include tremor, rigidity, bradykinesia, and postural instability (Jankovic, 2008; Lozano et al., 1995). Research has also investigated the extent to which PD is associated with cognitive impairments (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Dubois & Pillon, 1996; Owen, Iddon, Hodges, Summers, & Robbins, 1997). Within this literature, numerous studies have investigated procedural memory in PD, in particular with Serial Reaction Time (SRT) tasks (e.g., Gawrys et al., 2008; Muslimovic, Post, Speelman, & Schmand, 2007; Price & Shin, 2009; Seidler, Tuite, & Ashe, 2007; van Tilborg & Hulstijn, 2010; Vandenbossche et al., 2013; Wang, Sun, & Ding, 2009). This report uses meta-analysis and meta-regression to summarize this research, updating and extending a previous meta-analysis on this topic (Siegert, Taylor, Weatherall, & Abernethy, 2006).

Procedural Memory

It is widely accepted that there are multiple memory systems in the brain (Knowlton, Mangels, & Squire, 1996; Squire, 2004; Squire, Knowlton, & Musen, 1993; Squire & Zola, 1996). The procedural memory system is one of a number of non-declarative memory systems that supports the learning and access of implicit (non-conscious) knowledge (Knowlton et al., 1996; Knowlton, Squire, & Gluck, 1994; Ullman, 2001; Yin & Knowlton, 2006). Learning in the procedural system is gradual, with repetition or practice required in order for skills or knowledge to be acquired. However, once learnt, knowledge can be accessed rapidly and without awareness. Much is known about the neural substrates of the procedural memory system. Evidence from both healthy individuals and those with
neurological dysfunctions has repeatedly implicated the basal ganglia and motor-related and prefrontal areas, as well as the cerebellum (Kandel, Schwartz, & Jessell, 2012; Packard & Knowlton, 2002; Parent & Hazrati, 1995; Pascual-Leone, Wassermann, Grafman, & Hallett, 1996; Ullman, 2004, 2006).

The Serial Reaction Time Task

The Serial Reaction Time (SRT) task developed by Nissen and Bullemer (1987) has been used to investigate learning in procedural memory (i.e., procedural learning) in a wide range of non-clinical (e.g., Lum & Kidd, 2012; Thomas et al., 2004; Thomas & Nelson, 2001) and clinical populations (e.g., Ferraro, Balota, & Connor, 1993; Knopman & Nissen, 1991; Siegert, Weatherall, & Bell, 2008), including individuals with PD (e.g., Siegert et al., 2006; Stefanova, Kostic, Ziropadja, Markovic, & Ocic, 2000; van Tilborg & Hulstijn, 2010; Vandenbossche et al., 2013; Wang et al., 2009; Werheid, Ziessler, Nattkemper, & Von Cramon, 2003; Werheid, Zysset, Muller, Reuter, & Von Cramon, 2003; Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998).

The standard protocol for the SRT task requires participants to be seated in front of a computer display that shows a visual stimulus repeatedly appearing in one of four locations (for an overview of SRT task methodology see Robertson, 2007). Stimulus presentations are usually grouped into blocks typically comprising around 80 to 100 stimuli, although this figure varies substantially between studies (see Lum, Ullman, & Conti-Ramsden, 2013). On most blocks, stimulus presentations follow a pre-defined sequence. Depending on the study, the length of the sequence may vary from 8 to 12. In the implicit version of the SRT task, which is examined in this report, participants are not informed that the visual stimulus follows a sequence. After a series of ‘Sequenced Blocks’ a ‘Random Block’ is presented in which the visual stimulus appears in a random order. The only instruction provided to participants, at the beginning of the task, is to indicate the location of the visual stimulus on
each trial. In most studies participants respond to the stimulus by pressing one of several buttons on a response box (e.g., Pascual-Leone et al., 1993; Shin & Ivry, 2003). However, in other work the motor demands of the task have been reduced by asking participants to provide a verbal response (e.g., Smith & McDowall, 2004; Smith, Siegert, McDowall, & Abernethy, 2001).

The key dependent variable in SRT tasks is reaction time (RT), which measures how fast participants identify the location of the visual stimulus. In neurologically intact individuals, RTs gradually decrease (i.e., responses become faster) across the series of ‘Sequenced Blocks’. Then, during the ‘Random Block’, RTs increase again (e.g., Lum & Kidd, 2012; Thomas et al., 2004; Thomas & Nelson, 2001). This RT increase from the Sequence Block to the Random Block is taken to suggest that knowledge or information about the sequence has been learnt. Importantly, the change in RTs is observed even though participants are not able to explicitly recall the sequence. Neuroanatomical meta-analysis of the functional neuroimaging literature examining the SRT task indicates that the task indeed depends on the neural substrates of procedural memory, activating both the basal ganglia (i.e., the putamen) and the cerebellum (Hardwick, Rottschy, Miall, & Eickhoff, 2013).

**SRT task Performance in Parkinson’s Disease**

The performance of individuals with PD on the SRT task provides an important opportunity to examine the status of sequence learning in procedural memory in the disorder. Given that learning in the SRT task appears to depend on the procedural memory system, including the basal ganglia, individuals with PD may be expected to perform worse on the task than healthy comparison groups. Specifically, the increase in RTs from the final sequence block to the following random block should be smaller in PD groups relative to
healthy controls. That is, a significant Group (PD vs. Control) X Block (Sequence vs. Random) interaction is expected.

A meta-analysis that summarized research published between 1987 and 2005 on SRT task performance in PD was presented by Siegert, Taylor, Weatherall and Abernethy (2006). In typical meta-analyses, effect sizes and variances from studies with similar methodologies are pooled and an average effect size is computed (Borenstein, Hedges, Higgins, & Rothstein, 2011; Hunter, Schmidt, & Jackson, 1982). The meta-analysis undertaken by Siegert et al. summarized the results from six studies with a combined sample size of 67 individuals with PD and 87 neurologically intact controls. The average effect size computed in the meta-analysis was for the Group (PD vs. Control) X Block (Sequence vs. Random) interaction. Using a random effects model to average study results, the average effect size was found to be 0.65 (CI95: 0.10, 1.20), and was statistically significant. This result indicates that on average, the increase in RTs from the Sequence Block to the Random Block was 0.65 standard deviations larger in the control groups than the PD groups. This corresponds to a medium effect size according to Cohen’s (1988) taxonomy. Siegert et al.’s (2006) meta-analysis also identified considerable levels of heterogeneity, that is, differences between individual study effect sizes. Quantification of the variability in effect sizes using the $I^2$ statistic indicated that 64.8% of the heterogeneity could not be explained by random error or chance. This suggests there may be one or more systematic influences on study findings. Thus an outstanding question arising from Siegert et al.’s meta-analysis is, what variable or variables assert a systematic influence on study findings?

Inspection of the PD/SRT task literature reveals a number of potential candidate variables that may account for variability in study effect sizes. First, the average severity of the PD group’s symptoms might account for differences between study findings. Price and Shin (2009) found that participants with moderate PD symptoms, but not those whose
symptoms were mild, performed significantly worse on their version of the SRT task than controls. Inspection of the PD/SRT task literature reveals variability in the average severity of PD symptoms when quantified using the Hoehn-Yahr scale (Hoehn & Yahr, 1967), which measures the severity of PD symptoms on a five-point scale, with lower values corresponding to milder symptoms. In some studies the average Hoehn-Yahr rating was approximately 1.5 (e.g., Stefanova et al., 2000; van Tilborg & Hulstijn, 2010; Werheid, Zysset, et al., 2003; Westwater et al., 1998), while in others the average severity was about 3 (e.g., Deroost, Kerckhofs, Coene, Wijnants, & Soetens, 2006; Price & Shin, 2009). Studies that have PD participants with more severe symptoms might have observed larger sequence-random differences on the SRT task between PD and control groups.

Second, differences in the input method used to collect responses on the SRT task may systematically influence study results. The most common method in SRT studies of PD uses a response box (e.g., Sommer, Grafman, Clark, & Hallett, 1999; Stefanova et al., 2000; van Tilborg & Hulstijn, 2010). However, this method may disproportionally disadvantage PD participants, since a central feature of the disorder is motor problems. Thus the extent to which the SRT task places demands on motor skills may contribute to whether a study observes a significant difference between groups. To attempt to address this issue some investigators have modified the SRT task so that participants indicate the location of the visual stimulus with a verbal response (Smith & McDowall, 2004; Sommer et al., 1999; Stefanova et al., 2000; van Tilborg & Hulstijn, 2010). Using this method, non-significant differences between PD and control groups have indeed been reported (Smith et al., 2001). If the method used to collect responses influences study findings, smaller effect sizes may be observed for studies in which subjects respond verbally.

Third, presentation of the SRT task under dual task conditions may also explain differences between study findings. SRT dual task paradigms require participants to engage
in a second activity whilst simultaneously responding to the visual stimulus. In the PD literature, participants are usually asked to count tones whilst completing the SRT task (Kelly, Jahanshahi, & Dirnberger, 2004; Seidler et al., 2007; Vandenbossche et al., 2013). This approach is intended to reduce the possibility that participants will gain explicit awareness of the sequence, in order to encourage learning in procedural memory. However, research has also shown that dual task performance of any sort is disproportionately poorer in PD groups compared to control groups (Dalrymple-Alford, Kalders, Jones, & Watson, 1994; Wu & Hallett, 2008). Thus, studies using a dual task paradigm to study SRT task performance in PD may observe larger differences between study and control groups.

Fourth, the type of sequence used in SRT tasks might also influence outcomes in studies of PD. Sequences in SRT tasks can vary regarding the extent to which elements in a given location are first-order conditional (FOC) or second-order conditional (SOC). In FOC sequences, each element in the sequence can be at least partially predicted from the preceding element. For example, in the sequence 4243123142, the item 1 is always followed by either a 2 or a 4 (50% probability each), but never a 3 (0%); similarly the item 3 is always followed by a 1 (100% probability), but never by a 2 or 4 (0%). In contrast, for SOC sequences the probability between element transitions is equal. For example, in the sequence 134231432412, there is a 33.3% probability that 1 will be followed by 2, 3 and 4 (Robertson, 2007). In a SOC sequence, all transitions between elements can be considered ambiguous (A. Cohen, Ivry, & Keele, 1990).

The sequences that have been used to investigate implicit learning in PD have varied with respect to the number of ambiguous element transitions, that is, the number of SOC elements. For example, DeRoost, Kerckhofs, Coene, Wijnants and Soetens (2006) presented a fully SOC sequence to PD and control groups. In this study a 12-element sequence, 121342314324, was used for the SRT task. In the sequence there are a total of 12 transitions
(since the sequence is repeated, the last element in the sequence is followed by the first). The probability of one element following another is 33.3% for all transitions. Thus in DeRoost et al. (2006), 12 transitions out of a possible 12 can be considered to be ambiguous. In contrast, Smith and McDowall (2006) used an 8-item sequence, 14213243, where none of the transitions were ambiguous. Rather, each element in the sequence can be predicted, to some extent, from the preceding element. For example, in this sequence the case of a 1 being followed by 2 occurs 0% of the time and the probability of 3 or 4 following 1 is 50% each.

The number of ambiguous transitions between elements may have an impact on study findings. Results from several studies indicate that the implicit learning of SOC sequences may depend on medial temporal lobe structures (Curran, 1997; Ergorul & Eichenbaum, 2006; Schendan, Searl, Melrose, & Stern, 2003). One explanation offered to account for this finding is that learning ambiguous transitions between elements requires being able to bind items that are arbitrarily related, a type of learning that is well support by the medial temporal lobes (Mayes, Montaldi, & Migo, 2007; Poldrack & Rodriguez, 2003; Robertson, 2007; Squire, Stark, & Clark, 2004). As the learning and memory functions that are supported by the medial temporal lobes appear relatively spared in PD (Helkala, Laulumaa, Soininen, & Riekkinen, 1988; Ullman et al., 1997), smaller differences between study and comparison groups might be observed in studies that use sequences with ambiguous transitions.

Fifth, some evidence suggests that the length of the sequence may systematically influence study results. Pascual-Leone et al. (1993) found that the magnitude of the difference between PD and control groups was larger when participants were presented with a 12-element FOC sequence compared to an 8-element FOC sequence. SRT tasks using sequences that are short in length may place fewer demands on procedural memory, leading to increased learning.
Finally, evidence also suggests that the number of times the sequence is presented may influence results. In a meta-analysis investigating SRT task performance in the neurodevelopmental disorder of dyslexia, Lum et al. (2013) found smaller differences between dyslexia and control groups for those studies that presented the sequence more times. It was suggested that more exposures to the sequence might increase the likelihood that the sequence will be acquired by the procedural memory system, even when the system is dysfunctional.

**Aims of the Current Report**

The aim of this report was, first of all, to update and expand the meta-analysis examining SRT task performance in PD undertaken by Siegert et al. (2006), which summarized the results of six studies. In the current meta-analysis, we included results from 27 studies, representing data from 505 participants with PD and 460 neurologically intact control participants. The second aim of the study was to investigate variables that may account for differences in study findings. Specifically, using meta-regression we investigated whether individual study results could be predicted by one or more of the following variables or their interactions: the participant-level factor of PD severity, and several SRT task variables, namely the type of input device (response method) that was used, whether the task was administered under single task or dual task conditions, the sequence type, the sequence length, and the number of exposures to the sequence.

**Method**

**Study Design**

Electronic databases of published and non-published/grey literature were searched. A search for published literature was undertaken using Psychological Information Database (PsycINFO), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medical Database (EMBASE), Cumulative Index to Nursing and Allied Health
Literature (CINAHL), and PubMed. Unpublished literature was searched using BioSciences Information Service of Biological Abstracts (BIOSIS), OpenGrey, ProQuest Dissertation and Conference Abstracts, and PsycExtra. Details of all keywords, fields searched, Boolean operators, and syntax are presented in the online supplemental materials. The search strategy for published studies was executed in April, 2013. The search strategy for unpublished studies was executed in January, 2014.

**Study Inclusion Criteria**

Following execution of the search, articles were only included in the meta-analysis if they met the following inclusionary criteria, which were similar to those used by Siegert et al. (2006). First, only studies involving human participants were included. It was further required that the SRT task was presented to one group of participants comprising individuals with PD and a control group comprising neurologically intact individuals of comparable age. Second, because the SRT task was first described in an article published in 1987 (i.e., Nissen & Bullemer, 1987), studies were excluded if they were published prior to this year. Third, the study was required to report original research. Fourth, the study needed to have administered a version of Nissen and Bullemer’s SRT task. That is, the study was required to have presented an implicit version of the task (i.e., participants were not informed of the sequence). Studies that presented an explicit version of the SRT task were not included in the review. Also, the structure of the task must have presented a series of sequence blocks followed by a random block. Finally, to ensure testing conditions between studies were similar, we excluded one study where participants underwent transcranial magnetic stimulation whilst completing the task (Pascual-Leone et al., 1994). Figure 1 summarizes studies removed following application of each criterion according to PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & The, 2009).
3543 records identified through database searching.

657 duplicate records excluded. Includes 15 conferences or theses identified in grey literature search that were published in peer review journal.

2886 records left after duplicates removed.

2771 records excluded for not meeting eligibility criteria:
- Study involved non-human animals (n = 528).
- Article was a review, book chapter (n = 298).
- Article was published prior to 1987 (n = 86).
- Participants in study did not include individuals with PD (n = 1345).
- Study did not use SRT Task (n = 505).
- No control group in study (n = 9).

115 records left after screening abstracts for eligibility.

88 records excluded for not meeting eligibility criteria:
- Study did not use SRT task or Nissen & Bullemer version of the SRT Task (n = 59).
- Participants in study did not include individuals with PD and/or a group of healthy control participants (n = 21).
- Record was a review article (n = 4).
- Participants underwent TMS during the SRT task (n = 1).
- Article was a duplicate (n = 3).

27 records used in quantitative review.

2886 records left after duplicates removed.

115 records left after screening abstracts for eligibility.

27 records used in quantitative review.

Figure 1. PRISMA Flowchart showing process of identifying articles included in the meta-analysis.

Study Selection

After the removal of duplicates, one of the authors (GC) assessed all the abstracts. A second author (JL) assessed a random sample of 10% of all abstracts. The two authors independently screened full-text articles according to the eligibility criteria described above. There was 100% agreement on these articles. A total of 27 studies were included, and their
data extracted for meta-analysis. A summary of each study’s participants and characteristics of the SRT task structure is presented in Tables 1 and 2 respectively.

Table 1.
Summary of Study’s Participant Characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Mean Age (years)</th>
<th>Mean PD Symptom Severity (Hoehn-Yahr Scale)</th>
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<td>Control Group</td>
<td>Study Group</td>
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Notes: *Comprises two PD subgroups; *Study reported that 7 participants were in stage 1-2 on the Hoehn-Yahr scale, and so in calculating the average it was taken as 7 participants in stage 1.5.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sequence</th>
<th>Proportion of Ambiguous Transitions</th>
<th>Sequence Length</th>
<th>Exposures to Sequence</th>
<th>Dual-task or Single-task</th>
<th>Response Method</th>
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<td>Muslimovic et al. (2007)</td>
<td>1-2-4-3-4-2-1-4-1-3</td>
<td>0.60</td>
<td>10</td>
<td>50</td>
<td>Single</td>
<td>Key press</td>
</tr>
<tr>
<td>Pascual-Leone et al. (1993)</td>
<td>4-2-3-1-3-2-4-3-2-1</td>
<td>0.30</td>
<td>10</td>
<td>40</td>
<td>Single</td>
<td>Key press</td>
</tr>
<tr>
<td>Sarazin et al. (2001)</td>
<td>Not reported</td>
<td>10</td>
<td>60</td>
<td>31.33</td>
<td>Dual</td>
<td>Key press</td>
</tr>
<tr>
<td>Seidler et al. (2007)</td>
<td>Not reported</td>
<td>12</td>
<td>108.5g</td>
<td>31.33</td>
<td>Both</td>
<td>Key press</td>
</tr>
<tr>
<td>Selco (1998)</td>
<td>2-1-4-3-4-1-2-3-1-3-2-4 &amp; 3-1-2-4-2-1-3-4-1-4-3-2²</td>
<td>1.00d</td>
<td>12</td>
<td>66</td>
<td>Single</td>
<td>Both</td>
</tr>
<tr>
<td>Shin &amp; Ivry (2003)</td>
<td>1-4-2-1-3-2-4-3</td>
<td>0.00</td>
<td>8</td>
<td>108.5g</td>
<td>Single</td>
<td>Key press</td>
</tr>
<tr>
<td>Study</td>
<td>Sequence(s)</td>
<td>Ambiguity (%)</td>
<td>Trials</td>
<td>Total</td>
<td>Presentation</td>
<td>Encoding</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------</td>
<td>--------</td>
<td>-------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>Smith &amp; McDowall (2004)</td>
<td>1-2-1-4-2-3-4-1-3-2-4-3 &amp; 1-4-1-3-4-2-3-2-1-3-4-2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.50&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12</td>
<td>40</td>
<td>Single</td>
<td>Verbal</td>
</tr>
<tr>
<td>Smith &amp; McDowall (2006)</td>
<td>1-4-2-1-3-2-4-3 &amp; 4-2-4-1-2-3-1-3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.00&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8</td>
<td>66&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Single</td>
<td>Verbal</td>
</tr>
<tr>
<td>Smith et al. (2001)</td>
<td>4-2-3-1-3-2-4-3-2-1</td>
<td>0.30</td>
<td>10</td>
<td>40</td>
<td>Single</td>
<td>Verbal</td>
</tr>
<tr>
<td>Sommer et al. (1999)</td>
<td>3-2-4-1-2-3-4-3-2-1</td>
<td>0.30</td>
<td>10</td>
<td>40</td>
<td>Single</td>
<td>Key press</td>
</tr>
<tr>
<td>Stefanova et al. (2000)</td>
<td>1-3-1-2-4-3-2-4-1-3</td>
<td>0.00</td>
<td>10</td>
<td>40</td>
<td>Single</td>
<td>Key press</td>
</tr>
<tr>
<td>van Tilborgh &amp; Hulstijn (2010)</td>
<td>4-2-3-1-3-2-4-3-2-1</td>
<td>0.30</td>
<td>10</td>
<td>40</td>
<td>Single</td>
<td>Key press</td>
</tr>
<tr>
<td>Vandenbossche et al. (2013)</td>
<td>1-3-2-3-4-2-1-3-4-1-4-2</td>
<td>0.00</td>
<td>12</td>
<td>60</td>
<td>Both</td>
<td>Key press</td>
</tr>
<tr>
<td>Wang, Sun, &amp; Ding (2009)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Single</td>
<td>Key press</td>
<td></td>
</tr>
<tr>
<td>Werheid, Ziessler, et al. (2003)</td>
<td>1-3-4-2-1-2-4-3</td>
<td>0.00</td>
<td>8</td>
<td>24</td>
<td>Single</td>
<td>Key press</td>
</tr>
<tr>
<td>Werheid, Zysset, et al. (2003)</td>
<td>1-2-1-4-2-3-4-1-3-2-4-3</td>
<td>1.00</td>
<td>12</td>
<td>120</td>
<td>Single</td>
<td>Key press</td>
</tr>
<tr>
<td>Westwater et al. (1998)</td>
<td>4-2-3-1-3-2-4-3-2-1</td>
<td>0.30</td>
<td>10</td>
<td>40</td>
<td>Single</td>
<td>Verbal</td>
</tr>
</tbody>
</table>

Notes: <sup>a</sup>Participants were presented with both sequences; <sup>b</sup>Participants were trained on one of two sequences; <sup>c</sup>Calculated as the number of ambiguous transitions divided into the sequence length; <sup>d</sup>Value averages proportion of ambiguous transitions across two sequences; <sup>e</sup>Value averages two sequences of different lengths; <sup>f</sup>Number of times sequence is presented prior to Random Block; <sup>g</sup>Value averages two different numbers of exposures.
Values for the participant and task characteristics shown in Tables 1 and 2 were extracted directly from the studies, except for the proportion of ambiguous transitions presented in Table 2, which was obtained by extracting the sequence used in each study. From this information the proportion of ambiguous transitions was calculated by dividing the number of ambiguous transitions into the total number of transitions in the sequence. A transition was considered ambiguous when the occurrence of a single element gave no information about the following element. For example, the transitions 1-2, 1-3, and 1-4 were considered as three ambiguous transitions if they each occurred once within a sequence. However, if only the transitions 1-2 and 1-3 were present (and not 1-4), these were not considered ambiguous transitions.

**Effect Size Calculations and Data Extraction Procedures**

The widely accepted method adopted to compare performance on the SRT task between two groups is to calculate whether the difference in RTs between the random block and the preceding sequence block differs between a control and study group. That is, whether a significant Group X Block interaction is present. In undertaking this meta-analysis, results reported in individual studies were extracted so that the effect size for the interaction and variance could be computed. Following the method by Siegert et al. (2006), the effect size measure used in this study was the standardized mean difference also known as Cohen’s $d$. This describes the difference between groups on the SRT task in standard deviation units. Cohen’s $d$ is known to have a slight bias when studies involve small sample sizes, and so a correction factor was applied that reduces this bias. Cohen’s $d$ was calculated so that positive values indicated that the control group in each study displayed higher levels of procedural learning than the group with PD or alternatively, the PD group performed worse on the task. The general formulas for computing Cohen’s $d$ and its variance are shown in (1) and (2) respectively. In (1) the mean difference between groups is divided by the
pooled standard deviation. The correction factor ‘$J$’ (Borenstein et al., 2011) is shown in (3), and finally the equations for Cohen’s $d$ and its variance that take the correction factor into account are shown in (4) and (5) respectively.

\[
d = \frac{\overline{x}_{\text{control}} - \overline{x}_{\text{study}}}{SD_{\text{pooled within}}} \tag{1}
\]

\[
Var(d) = \frac{n_{\text{control}} + n_{\text{study}}}{n_{\text{control}} \times n_{\text{study}}} + \frac{d^2}{2(n_{\text{control}} + n_{\text{study}})} \tag{2}
\]

\[
J = 1 - \frac{3}{4df-1} \tag{3}
\]

\[
d = J \times d \tag{4}
\]

\[
Var(d) = J^2 \times Var(d) \tag{5}
\]

Where:

\[
df = n_{\text{control}} + n_{\text{study}} - 2
\]

\[\overline{x} = \text{Mean difference in RTs between the final random block and the preceding sequence block.}\]

\[SD_{\text{pooled within}} = \text{Within-group SD of the difference between the final random block and preceding sequence block, pooled across the control and study groups.}\]

The result from each study included in the meta-analysis was described using a single effect size that quantified the comparison between the groups on the difference in RT between the random block and the preceding sequence block. For nine studies, this was obtained from the reported $F$-ratio that tested for the Group X Block interaction (Cameli, 2006; Ferraro et al., 1993; Gawrys et al., 2008; Gilbert, 2003; Muslimovic et al., 2007; Sarazin, Deweer, Pillon, Merkl, & Dubois, 2001; Smith & McDowall, 2004; Smith et al.,...
2001; Westwater et al., 1998). In one case, the reported value from an independent measures 
\( t \)-test was the data extracted (van Tilborg & Hulstijn, 2010). The studies by Jackson, 
Jackson, Harrison, Henderson, and Kennard (1995), Selco (1998), and Sommer et al. (1999) 
reported \( M \) and \( SD \) of the difference between the random and preceding sequence block for 
each group. For a further six studies, data was extracted from figures (Brown et al., 2003; 
Deroost et al., 2006; Smith & McDowall, 2006) or a combination of a figure and reported 
values in text (Kelly et al., 2004; Shin & Ivry, 2003; Vandenbossche et al., 2013). Means 
were extracted from figures and the standard deviations calculated using a reported \( t \)-statistic 
or \( F \)-statistic for the studies by Helmuth, Mayr, and Daum (2000); Werheid, Zietsler, et al. 
(2003); and Werheid, Zysset, et al. (2003). Data presented in figures were converted using 
Plot Digitizer Software (Version 2.6.4). Finally, for five studies, data for \( M \) and \( SD \) of both 
sequence and random block were extracted from either a figure (Pascual-Leone et al., 1993; 
Seidler et al., 2007; Wang et al., 2009) or text (Bondi, 1991; Stefanova et al., 2000), and an 
estimate of the correlation between these blocks was used to calculate the effect size. For 
five of the 27 studies included in the meta-analysis, it was necessary to combine two sets of 
effect sizes. In the studies by Deroost et al. (2006); Kelly et al. (2004); and Smith and 
McDowall (2006), effect sizes were averaged from separate analyses that compared the PD 
and control group on two different types of sequence. In the Selco (1998) study, effect sizes 
were averaged from separate analyses that compared the PD and control group under 
conditions requiring a verbal response or a button-press response. In the Vandenbossche et 
al. (2013) study, effect sizes were averaged from separate analyses that compared two PD 
subgroups and the control group under single task and dual task conditions.

For all studies included in the meta-analysis \( (n = 27) \), data and moderator variables 
(presented in Table 1 & 2) were independently extracted by both reviewers. This process 
was undertaken to check the reliability of data extracted from papers included in the meta-
analysis. For all categorical and continuous moderator data presented in Tables 1 and 2 the reviewers were found to extract the same information. For data extracted from figures, reliability was checked by computing the correlation between reviewers’ values. This value was found to be high ($r = .98$).

Comprehensive Meta-Analysis Software (Borenstein, Hedges, Higgins, & Rothstein, 2005) was used to convert the extracted data to a common effect size and variance. Description of the data extracted from each study and the method used in Comprehensive Meta-Analysis Software to convert extracted data to Cohen’s $d$ and $Var(d)$ are described in the online (additional) supplemental materials.

**Meta-analytic Procedures**

Two approaches were used in this report to synthesize the SRT task literature investigating procedural learning in PD. First, meta-analysis was used to compute an average effect size that quantified the overall difference between PD and Controls on the SRT task. An alpha level of 0.05 (two-tailed) was used to evaluate whether the average effect size was significantly different from zero. Effect sizes were averaged using a random effects model (Hedges & Olkin, 1985). This method assumes that differences or heterogeneity between study effect sizes is the sum of sampling error (referred to as within-study error) and systematic influences (referred to as between-study error or true heterogeneity). The percentage of heterogeneity attributable to between-study error was measured using the $I^2$ statistic. This statistic expresses, as a percentage, heterogeneity between study effect sizes due to between-study error. Larger $I^2$ values indicate the presence of systematic influences on study findings. As a general guideline it has been suggested that values of 25%, 50%, and 75% correspond to low, medium, and high levels of heterogeneity respectively (Higgins, Thompson, Deeks, & Altman, 2003).
The second set of analyses used in this report investigated predictor variables that might account for between-study error or systematic influences that are related to differences between study level effect sizes. Predictor variables used in these analyses were study level characteristics presented in Tables 1 and 2. These data were analyzed using random effects meta-regression (Greenland, 1987; Thompson & Higgins, 2002). Meta-regression tests whether one or more predictor variables significantly predict study level effect sizes.

**Results**

**Evaluation of Publication Bias**

Preliminary analyses investigated publication bias in the studies identified by the search criteria. Evidence of publication bias was evaluated using a funnel plot which is presented in Figure 2.

![Funnel plot](image)

*Figure 2.* Funnel plot showing study level effect sizes plotted against sample size. Evidence of publication bias evident when effect sizes are asymmetrically distributed around average effect size when study precision is low (i.e., sample size is small).

Funnel plots show the relationship between individual study effect sizes and sample size (or in some cases standard error). The sample size is taken as a measure of the precision
or accuracy of a study’s effect size. Studies with smaller samples have poorer precision. A funnel plot indicates the presence of publication bias if study effect sizes with low precision are asymmetrically distributed around the weighted average effect size (see Egger, Smith, Schneider, & Minder, 1997). Figure 2 shows that overall, effect sizes are symmetrically distributed around the weighted average effect size. The presence of publication bias was formally tested using Egger’s Test, which indicated that effect sizes were not significantly asymmetrically distributed (Intercept = 0.985, $t(25) = 0.855$, $p = .401$).

The presence of publication bias was also examined by testing whether there was a significant difference in effect sizes between published and unpublished studies. For published studies the average effect size was found to be .554 and for unpublished studies .507. The difference between these effect sizes was not significant ($p = .890$). As a further test of publication bias, a ‘Classic fail-safe N’ value was computed (also known as ‘file-drawer analysis’). This value indicates the number of non-significant studies, not included in this meta-analysis, required to bring alpha to .05. This analysis revealed that a total of 384 non-significant studies are required. Thus publication bias seems unlikely.

**SRT task performance in Parkinson’s Disease**

The next analysis summarized results of individual studies to test whether, on average, there was a significant difference between PD and Controls on sequence learning in the SRT task. A forest plot showing individual study effect sizes, as well as the weighted average effect size (along with 95% confidence intervals for the study and average weighted effect sizes), are presented in Figure 3. As noted earlier, effect sizes were averaged using a random effects model (Hedges & Olkin, 1985). Positive $d$ values indicate that the control group had a larger difference in RTs between sequenced and random blocks as compared to the PD group. That is, positive values indicate that the PD group performed poorly on the SRT task, as compared to the control group. The weighted average effect size was found to
be .531, and was statistically significant ($p < .001$; unweighted average = .570; unweighted median = .426). The magnitude of the average effect size indicates that the difference in RTs between random and sequence blocks on the SRT task is about half a standard deviation larger in control groups compared to PD groups. According to Cohen’s (1988) taxonomy this value corresponds to a medium effect size.

Table: Forest Plot of Study Level and Average Weighted Effect Sizes

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohen’s $d$</th>
<th>Variance</th>
<th>95% C.I.</th>
<th>$p$-value</th>
<th>Control group performs worse</th>
<th>PD group performs worse</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al. (2004)</td>
<td>-0.659*</td>
<td>0.192</td>
<td>-1.517</td>
<td>0.200</td>
<td>.132</td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Smith &amp; McDowell (2006)</td>
<td>-0.410</td>
<td>0.070</td>
<td>-0.928</td>
<td>0.108</td>
<td>.121</td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>Smith et al. (2001)</td>
<td>0.037</td>
<td>0.140</td>
<td>-0.695</td>
<td>0.769</td>
<td>.920</td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>Helmuth, May, &amp; Daum (2000)</td>
<td>0.070</td>
<td>0.086</td>
<td>-0.505</td>
<td>0.646</td>
<td>.811</td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>Sommer et al. (1999)</td>
<td>0.159</td>
<td>0.148</td>
<td>-0.596</td>
<td>0.913</td>
<td>.680</td>
<td></td>
<td>3.6</td>
</tr>
<tr>
<td>Cameli (2006)</td>
<td>0.168</td>
<td>0.202</td>
<td>-0.714</td>
<td>1.050</td>
<td>.709</td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Bondi (1991)</td>
<td>0.202</td>
<td>0.101</td>
<td>-0.423</td>
<td>0.826</td>
<td>.527</td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>Selco (1998)</td>
<td>0.238*</td>
<td>0.172</td>
<td>-0.575</td>
<td>1.050</td>
<td>.566</td>
<td></td>
<td>3.3</td>
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<tr>
<td>Pascual-Leone et al. (1993)</td>
<td>0.266</td>
<td>0.081</td>
<td>-0.293</td>
<td>0.826</td>
<td>.351</td>
<td></td>
<td>4.6</td>
</tr>
<tr>
<td>Brown et al. (2003)</td>
<td>0.288</td>
<td>0.186</td>
<td>-0.556</td>
<td>1.133</td>
<td>.503</td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Seidler et al. (2007)</td>
<td>0.347</td>
<td>0.260</td>
<td>-0.653</td>
<td>1.346</td>
<td>.497</td>
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<td>2.7</td>
</tr>
<tr>
<td>Werheid, Zysset, et al. (2003)</td>
<td>0.350</td>
<td>0.265</td>
<td>-0.639</td>
<td>1.340</td>
<td>.488</td>
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<tr>
<td>Deroost et al. (2006)</td>
<td>0.410*</td>
<td>0.124</td>
<td>-0.281</td>
<td>1.100</td>
<td>.245</td>
<td></td>
<td>3.9</td>
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<tr>
<td>Wang, Sun, &amp; Ding (2009)</td>
<td>0.418</td>
<td>0.098</td>
<td>-0.197</td>
<td>1.032</td>
<td>.183</td>
<td></td>
<td>4.3</td>
</tr>
<tr>
<td>Muslimovic et al. (2007)</td>
<td>0.454</td>
<td>0.034</td>
<td>0.095</td>
<td>0.814</td>
<td>.013*</td>
<td></td>
<td>5.6</td>
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<tr>
<td>Shin &amp; Ivy (2003)</td>
<td>0.692</td>
<td>0.195</td>
<td>-0.174</td>
<td>1.559</td>
<td>.117</td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Ferraro et al. (1993)</td>
<td>0.718</td>
<td>0.100</td>
<td>0.099</td>
<td>1.337</td>
<td>.023*</td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>Sarazin et al. (2001)</td>
<td>0.724</td>
<td>0.119</td>
<td>0.048</td>
<td>1.399</td>
<td>.036*</td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>van Tilborg &amp; Hulstijn (2010)</td>
<td>0.747</td>
<td>0.192</td>
<td>-0.113</td>
<td>1.607</td>
<td>.089</td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Smith &amp; McDowell (2004)</td>
<td>0.756*</td>
<td>0.125</td>
<td>0.065</td>
<td>1.451</td>
<td>.032*</td>
<td></td>
<td>3.9</td>
</tr>
<tr>
<td>Gawrysz et al. (2008)</td>
<td>0.821</td>
<td>0.117</td>
<td>0.151</td>
<td>1.491</td>
<td>.016*</td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>Westwater et al. (1998)</td>
<td>0.860</td>
<td>0.191</td>
<td>0.004</td>
<td>1.716</td>
<td>.049*</td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Werheid, Ziessler, et al. (2003)</td>
<td>0.926</td>
<td>0.188</td>
<td>0.076</td>
<td>1.775</td>
<td>.033*</td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Stefanova et al. (2000)</td>
<td>1.295</td>
<td>0.069</td>
<td>0.781</td>
<td>1.808</td>
<td>&lt;.001**</td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>Gilbert (2004)</td>
<td>1.573</td>
<td>0.245</td>
<td>0.602</td>
<td>2.544</td>
<td>.002*</td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td>Jackson et al. (1995)</td>
<td>1.639</td>
<td>0.240</td>
<td>0.879</td>
<td>2.599</td>
<td>&lt;.001**</td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td>Vandenbossche et al. (2013)</td>
<td>1.822*</td>
<td>0.150</td>
<td>1.063</td>
<td>2.581</td>
<td>&lt;.001**</td>
<td></td>
<td>3.6</td>
</tr>
</tbody>
</table>

Average: 0.531 0.011 0.322 0.740 <.001**

Notes: *Effect size averages results from groups’ performance on ambiguous and hybrid sequences; **Effect size averages results from groups’ performance on SRT task using verbal and keypress response methods; **Effect size averages results from groups’ performance on FOC and SOC sequences; *Effect size average groups’ performance on SRT task completed under single-task conditions and dual-task conditions.

$p < .05; **p < .001$

**Figure 3.** Forest plot showing study level and average weighted effect sizes.

Even though the average effect size is significant, there is considerable variability between individual study effect sizes. Effect sizes ranged from 1.822 (Vandenbossche et al., 2013) to -0.659 (Kelly et al., 2004); negative values indicate that the control group performed worse on the SRT task than the PD group. Calculation of the $I^2$ statistic for the studies in Figure 3 was found to be 58. This indicates that 58% of variability between effect sizes
reflects the influence of between-study error or systematic influence on the data. Alternatively stated, this result indicates that 42% of differences in effect sizes can be attributable to within-study error or chance. The $I^2$ value of 58 indicates medium to high levels of heterogeneity between study findings (Higgins et al., 2003).

**Investigating the Sources of Heterogeneity in Study Findings**

The next set of analyses used random effects meta-regression to investigate the sources of the between-study error/systematic influence (i.e., the percentage of heterogeneity between effect sizes measured by the $I^2$ statistic). Specifically, we tested whether participant and SRT task methodological characteristics, presented in Tables 1 and 2, predicted the study effect sizes that are presented in Figure 3.

There were an insufficient number of studies to test all covariates in a single model. In meta-regression, a ratio of 10 studies for each predictor variable is recommended (Borenstein et al., 2011). Therefore, separate meta-regressions were performed to investigate one predictor variable at a time. Interactions between predictor variables were also investigated, again in separate analyses. The interaction term was created by multiplying constituent variables. Continuous variables were centered prior to multiplication. Since there were an insufficient number of studies in the meta-analysis to simultaneously test main and interaction effects, interaction terms were tested by first removing the influence of the main effects, before being entered into the model. This was achieved using least squares regression. Specifically, each interaction term was regressed onto its constituent variables and standardized residuals were saved. The standardized residuals were then entered into the model. These residuals represent the interaction term after removing covariance related to each main effect.

The predictor variables tested were the average severity of PD symptoms (from Table 1), the method used to collect responses on the task (response box input vs. voice input),
whether the SRT task was presented under single task or dual task conditions, the type of sequence used (measured by the proportion of ambiguous transitions in the sequence; see Method), the length of the sequence, and the number of times it was presented (all from Table 2). Predictor variables representing binary variables (e.g., response method, testing condition) were dummy coded. Specifically, response method was coded so that 0 = Verbal Response and 1 = Keyboard/Response Box, and testing condition was coded so that 0 = Single Task and 1 = Dual Task.

The outcome variable in the meta-regression analyses were study effect sizes that are presented in Figure 3. However, for the meta-regression analyses testing whether single vs. dual task procedures predicted effect sizes it was necessary to choose one of two effect sizes from Vandenbossche et al. (2013). Similarly, it was necessary to choose one of two effect sizes from Selco (1998) for the meta-regression analyses testing whether verbal vs. keypress response method conditions predicted effect sizes. In those studies separate effect sizes were available for performance under single and dual task conditions, or for verbal or motor response conditions. In the meta-regression analyses only the effect size from the dual task condition was used from the Vandenbossche et al. (2013) study, and only the effect size from the verbal response method condition was used from Selco (1998). These effect sizes were selected to increase the number of data points available for the dual task conditions and the verbal response conditions. It was not possible to use both effect sizes from each of these studies because this would require treating dependent data points as non-dependent. The results from the meta-regression analyses are presented in Table 3.

None of the main effects were found to be significant predictors of effect sizes (Models 1-6). The analyses testing interaction terms were also all non-significant, except for models that included the ‘Single vs. Dual Task’ predictor variable in the interaction term. Models 7, 8, 10, and 11, tested the interaction between ‘Single vs. Dual Task’ and Proportion
Table 3.
**Summary of Coefficients from Meta-Regression**

<table>
<thead>
<tr>
<th>Model No.</th>
<th>Variable</th>
<th>k</th>
<th>df</th>
<th>Q\text{Model}</th>
<th>Q\text{Residual}</th>
<th>R^2</th>
<th>\beta</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Single or Dual Task</td>
<td>27</td>
<td>1.25</td>
<td>0.437</td>
<td>27.771</td>
<td>0.016</td>
<td>0.124</td>
<td>.509</td>
</tr>
<tr>
<td>2</td>
<td>Proportion of Ambiguous Transitions</td>
<td>24</td>
<td>1.22</td>
<td>0.288</td>
<td>23.402</td>
<td>0.012</td>
<td>-0.110</td>
<td>.592</td>
</tr>
<tr>
<td>3</td>
<td>No. of Exposures to Sequence</td>
<td>26</td>
<td>1.24</td>
<td>1.060</td>
<td>24.279</td>
<td>0.042</td>
<td>-0.205</td>
<td>.303</td>
</tr>
<tr>
<td>4</td>
<td>Response Method</td>
<td>27</td>
<td>1.25</td>
<td>2.500</td>
<td>24.072</td>
<td>0.094</td>
<td>0.307</td>
<td>.114</td>
</tr>
<tr>
<td>5</td>
<td>Sequence Length</td>
<td>26</td>
<td>1.24</td>
<td>2.467</td>
<td>22.866</td>
<td>0.097</td>
<td>0.312</td>
<td>.116</td>
</tr>
<tr>
<td>6</td>
<td>Symptom Severity</td>
<td>19</td>
<td>1.17</td>
<td>0.002</td>
<td>18.278</td>
<td>0.000</td>
<td>-0.009</td>
<td>.969</td>
</tr>
<tr>
<td>7</td>
<td>Single vs. Dual Task X Prop. of Ambiguous Transitions</td>
<td>24</td>
<td>1.22</td>
<td>11.906</td>
<td>13.424</td>
<td>0.470</td>
<td>-0.686</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td>8</td>
<td>Single vs. Dual Task X No. of Exposures to Sequence</td>
<td>26</td>
<td>1.24</td>
<td>4.671</td>
<td>22.351</td>
<td>0.173</td>
<td>0.416</td>
<td>.031*</td>
</tr>
<tr>
<td>9</td>
<td>Single vs. Dual Task X Response Method</td>
<td>27</td>
<td>1.25</td>
<td>1.157</td>
<td>25.283</td>
<td>0.044</td>
<td>-0.209</td>
<td>.282</td>
</tr>
<tr>
<td>10</td>
<td>Single vs. Dual Task X Sequence Length</td>
<td>26</td>
<td>1.24</td>
<td>5.608</td>
<td>21.414</td>
<td>0.208</td>
<td>0.456</td>
<td>.018*</td>
</tr>
<tr>
<td>11</td>
<td>Single vs. Dual Task X Symptom Severity</td>
<td>19</td>
<td>1.17</td>
<td>11.213</td>
<td>8.693</td>
<td>0.563</td>
<td>0.751</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td>12</td>
<td>Proportion of Ambiguous Transitions X No. of Exposures to Sequence</td>
<td>24</td>
<td>1.22</td>
<td>0.403</td>
<td>23.287</td>
<td>0.017</td>
<td>-0.130</td>
<td>.526</td>
</tr>
<tr>
<td>13</td>
<td>Proportion of Ambiguous Transitions X Response Method</td>
<td>24</td>
<td>1.22</td>
<td>0.495</td>
<td>23.320</td>
<td>0.021</td>
<td>-0.144</td>
<td>.482</td>
</tr>
<tr>
<td>14</td>
<td>Proportion of Ambiguous Transitions X Sequence Length</td>
<td>24</td>
<td>1.22</td>
<td>2.009</td>
<td>21.681</td>
<td>0.085</td>
<td>-0.291</td>
<td>.156</td>
</tr>
<tr>
<td>15</td>
<td>Proportion of Ambiguous Transitions X Symptom Severity</td>
<td>17</td>
<td>1.15</td>
<td>0.197</td>
<td>16.004</td>
<td>0.012</td>
<td>0.110</td>
<td>.657</td>
</tr>
<tr>
<td>16</td>
<td>No. of Exposures to Sequence X Response Method</td>
<td>26</td>
<td>1.24</td>
<td>1.774</td>
<td>24.754</td>
<td>0.067</td>
<td>0.259</td>
<td>.183</td>
</tr>
<tr>
<td>17</td>
<td>No. of Exposures to Sequence X Sequence Length</td>
<td>26</td>
<td>1.24</td>
<td>0.674</td>
<td>24.665</td>
<td>0.027</td>
<td>0.163</td>
<td>.412</td>
</tr>
<tr>
<td>18</td>
<td>No. of Exposures to Sequence X Symptom Severity</td>
<td>18</td>
<td>1.16</td>
<td>0.191</td>
<td>16.974</td>
<td>0.011</td>
<td>0.105</td>
<td>.662</td>
</tr>
<tr>
<td>19</td>
<td>Response Method X Sequence Length</td>
<td>26</td>
<td>1.24</td>
<td>0.497</td>
<td>26.030</td>
<td>0.019</td>
<td>-0.137</td>
<td>.481</td>
</tr>
<tr>
<td>20</td>
<td>Response Method X Symptom Severity</td>
<td>19</td>
<td>1.17</td>
<td>0.267</td>
<td>18.133</td>
<td>0.015</td>
<td>0.120</td>
<td>.606</td>
</tr>
<tr>
<td>21</td>
<td>Sequence Length X Symptom Severity</td>
<td>18</td>
<td>1.16</td>
<td>0.713</td>
<td>16.452</td>
<td>0.042</td>
<td>0.204</td>
<td>.399</td>
</tr>
</tbody>
</table>

*p < .05; **p < .001
of Ambiguous Transitions (Model 7), Number of Exposures to the Sequence (Model 8), Sequence Length (Model 10), and PD symptom severity (Model 11). For Models 8, 10 and 11 the beta-value was found to be positive. This indicates that larger positive effect size values (i.e., larger differences between groups) are observed for studies that use SRT tasks that provided more exposures to the target sequence (Model 8), have longer sequences (Model 10), or have participants with more severe PD symptoms (Model 11), but only under dual task conditions. The model testing the ‘Dual vs. Single Task X Prop. of Ambiguous Transitions’ (Model 7) was also significant but the beta-value was negative. This result indicates effect sizes become smaller (i.e., the difference between PD and control groups decreases) for studies that present sequences with more ambiguous transitions, but only under dual task conditions. For illustrative purposes, significant models (Models 7, 8, 10, and 11) are presented in Figure 4.

![Figure 4](image_url)

*Figure 4. Scatterplot showing observed and predicted effect sizes. Panel (A) predictor variable is ‘Single/Dual Task’ X Proportion of Ambiguous Sequence’ interaction term. Panel (B) predictor variable is ‘Single/Dual Task’ X Number of Exposures to Sequence. Panel (C) predictor variable is ‘Single/Dual Task’ X Sequence Length. Panel (D) predictor variable is ‘Single/Dual Task’ X Symptom Severity. Data points are proportionally sized to their weight in the model.*
Discussion

In this report, a meta-analysis was undertaken to quantitatively summarize research investigating the performance of individuals with PD and neurologically intact controls on implicit sequence learning in SRT tasks. The results from 27 studies, representing data from 505 participants with PD and 460 controls, were included in the meta-analysis. The weighted average effect size, computed using a random effects model, was 0.531 (CI95: .322, .740), and was statistically significant. This is a medium effect size according to Cohen’s (1988) guidelines. This provides strong evidence that sequence learning in procedural memory is impaired (dysfunctional) in PD. The results of the meta-analysis provide further evidence supporting the view that implicit learning on the SRT task is sensitive to basal ganglia pathology (Kandel et al., 2012; Packard & Knowlton, 2002; Parent & Hazrati, 1995; Ullman, 2004).

The average effect size observed in this report is consistent with Siegert et al.’s (2006) result. When using a random effects model, they observed an average effect size of 0.65 (CI95: 0.10, 1.20). According to Cohen’s (1988) taxonomy this value also corresponds to a medium effect size. However, since Siegert et al. were only able to include six studies in their review, each with relatively small sample sizes, the width of the confidence interval for the average effect size was large; 1.1 \(SD\) units. By comparison, the width of the confidence interval in the current meta-analysis was 0.42 \(SD\) units. The current report builds on the previous meta-analysis by providing a more precise estimate of the average effect size. Interestingly, meta-analyses investigating non-motor areas of cognitive functioning in PD have also often reported medium average effect sizes. Siegert, Weatherall, Taylor, and Abernethy (2008) synthesized results of studies that investigated working-memory in individuals with PD, as compared to neurologically intact controls. Medium average effect sizes, ranging from .56 to .74, were reported for measures of visual working-memory, with a
small effect size of .22 reported for measures of verbal working memory. Similarly, Kudlicka, Clare, and Hindle (2011) reported medium to large average effect sizes across varied measures of executive functioning. PD also appears to be associated with a deficit in recognizing the emotion of another person based on facial expression and tone of voice. In a meta-analysis, Gray and Tickle-Degnen (2010) reported that individuals with PD perform on average .52 standard deviations below their peers on measures of emotion recognition. In each of the meta-analyses mentioned, individuals with PD perform more poorly than their peers by a similar magnitude to that found in the current report. Thus, procedural learning is one of several cognitive functions affected in PD.

The analyses presented in this report add to the literature by testing which systematic influences might be related to differences in study findings. Both the current meta-analysis and that published by Siegert et al. (2006) revealed medium to high levels of between-study error/systematic influences on study findings. The value of the $I^2$ observed by Siegert et al. was 64.8, and in the current report, it was 58. We used meta-regression to investigate a number of variables that could explain the between-study differences. Few of the meta-regression models were found to be significant predictors of study effect sizes. The models that tested main effects of participant and methodological aspects of the SRT task on study effect sizes were not found to be significant (Table 3, Models 1-6). Models testing interactions between characteristics of the sequence, method for collecting responses and severity of PD symptoms (Table 3, Models 12-21) were also not found to be significant predictors of study effect sizes.

However, four models that included the ‘Single/Dual Task conditions’ variable in the interaction term were found to be significant (Models 7, 8 and 10, and 11). The results of three models (Models 8, 10, and 11) indicated that studies observed a larger effect size (i.e., bigger difference between PD and controls) when participants completed the SRT task under
dual task conditions and when the sequence used on the SRT task was longer (Model 10), was presented more times relatively to other studies (Model 8), or when the PD participants had more severe symptoms (Model 11). One model (Model 7) indicated that studies were likely to observe smaller effect sizes (i.e., smaller difference between PD and control groups) when completing the SRT task under dual task conditions and when the sequence used comprised a higher proportion of ambiguous sequences.

In interpreting the significant meta-regression models it is important to note that the linear associations between predictor variable and effect sizes are largely influenced by the findings of two studies (see Figure 4). Furthermore in meta-regression there are other variables that may correlate with the predictor variables that may contribute to the significant result (Thompson & Higgins, 2002). Thus explanations for the significant meta-regression models are offered tentatively.

The meta-regression models showing a larger difference between the PD and control groups when completing the SRT task under dual task conditions are consistent with some previous research. Specifically, several studies have shown that individuals with the disorder perform worse than neurologically intact controls when completing a motor or cognitive task under dual task conditions (Dalrymple-Alford et al., 1994; Wu & Hallett, 2008). In accounting for this pattern of results it has been suggested that PD is associated with cognitive deficits that limit the efficacy of switching between tasks or the amount of cognitive resources available to process information (Brown & Marsden, 1991). Thus results from the meta-regression might indicate that the effect of dual task conditions on cognitive functioning may extend to the implicit learning of visuo-spatial information as well, possibly only in the presence of additional factors that increase task difficulty (longer sequences or more severe PD). However, this claim seems to be tempered by the results from Models 7 and 8, which showed an opposite trend. Model 8 showed larger differences between PD and
control groups when the sequence was presented more often under dual task conditions. One possible explanation is that dual task conditions limit the extent to which PD patients can take advantage of the increased stimulus presentations, relative to controls, leading to larger effect sizes. Model 7 indicated smaller differences between PD and control groups when the SRT task was completed under dual task conditions and when the sequence used comprised a higher proportion of ambiguous transitions. One possible explanation for this result is that under this set of conditions, both the PD and control groups perform poorly, perhaps because dual task conditions can impede learning in the medial temporal lobe (Foerde, Knowlton, & Poldrack, 2006), which appears to be critical for learning ambiguous sequences (see Introduction); poor performance by both groups in these circumstances could potentially lead to smaller effect sizes. However, equally plausible is that this association represents the influence of another variable correlated with studies investigating dual task performance in PD. Finally, as noted earlier, the significant meta-regression models appear to reflect the influence of two studies. Thus, we emphasize that these suggestions regarding the role of dual task paradigms on SRT task performance should be verified via experimental research.

Conclusion

This report used meta-analysis and meta-regression to examine the performance of individuals with PD on implicit sequence learning in the SRT task. The meta-analysis included 27 studies, representing data from 505 individuals with PD and 460 neurologically intact controls. It was found that individuals with PD perform just over half a standard deviation worse than controls on sequence learning in the task. Substantial variability was observed between study effect sizes; this variability appears to be related to whether the task was administered under single or dual task conditions. However, experimental work will now be required to test these suggestions.
References

References marked with an asterisk indicate studies included in the meta-analysis


Keywords and search strategy used to identify published articles

Search Strategy for PsycInfo

| S1 | (TI Implicit Memory) OR (TI Implicit Learning) OR (TI serial reaction) OR (TI serial learn*) OR (TI sequence N5 learning) OR (TI implicit N5 sequence) OR (TI implicit learn*) OR (TI procedural learn*) OR (TI procedural mem*) OR (TI srt) OR (TI srtt) OR (TI motor skill learning) OR (AB Implicit Memory) OR (AB Implicit Learning) OR (AB serial reaction) OR (AB serial learn*) OR (AB sequence N5 learning) OR (AB implicit N5 sequence) OR (AB implicit learn*) OR (AB implicit N5 visuo?spatial) OR (AB implicit N5 visuospatial) OR (AB procedural learn*) OR (AB procedural mem*) OR (AB srt) OR (AB srtt) OR (AB motor skill learning) OR (TX Implicit Memory) OR (TX Implicit Learning) OR (TX serial reaction) OR (TX serial learn*) OR (TX sequence N5 learning) OR (TX implicit N5 sequence) OR (TX implicit learn*) OR (TX implicit N5 visuo?spatial) OR (TX implicit N5 visuospatial) OR (TX procedural learn*) OR (TX procedural mem*) OR (TX srt) OR (TX srtt) OR (TX motor skill learning) OR (KW Implicit Memory) OR (KW Implicit Learning) OR (KW sequence N5 learning) OR (KW implicit N5 sequence) OR (KW implicit learn*) OR (KW implicit N5 visuo?spatial) OR (KW implicit N5 visuospatial) OR (KW procedural learn*) OR (KW procedural mem*) OR (KW srt) OR (KW srtt) OR (KW motor skill learning) OR (SU Implicit Memory) OR (SU Implicit Learning) OR (SU serial reaction) OR (SU serial learn*) OR (SU sequence N5 learning) OR (SU implicit N5 sequence) OR (SU implicit learn*) OR (SU implicit N5 visuo?spatial) OR (SU implicit N5 visuospatial) OR (SU procedural learn*) OR (SU procedural mem*) OR (SU srt) OR (SU srtt) OR (SU motor skill learning) OR (DE Procedural Knowledge) OR (DE Implicit Learning) OR (DE Implicit Memory) |
| S2 | TI Parkins*) OR (TI pd) OR (TI neurodegenerative) OR (TI movement disorder) OR (AB Parkins*) OR (AB pd) OR (AB neurodegenerative) OR (AB movement disorder) OR (TX Parkins*) OR (TX pd) OR (TX neurodegenerative) OR (TX movement disorder) OR (KW Parkins*) OR (KW pd) OR (KW neurodegenerative) OR (KW movement disorder) OR (SU Parkins*) OR (SU pd) OR (SU neurodegenerative) OR (SU movement disorder) OR (DE Parkinson's Disease) OR (DE Parkinsonism) |
| S3 | S1 AND S2 |
Search Strategy for both MEDLINE and CINAHL

S1 (TI Implicit Memory) OR (TI Implicit Learning) OR (TI serial reaction) OR (TI serial learn*) OR (TI sequence N5 learning) OR (TI implicit N5 sequence) OR (TI implicit learn*) OR (TI implicit N5 visuo?spatial) OR (TI implicit N5 visuospatial) OR (TI procedural learn*) OR (TI procedural mem*) OR (TI srt) OR (TI srtt) OR (TI motor skill learning) OR (AB Implicit Memory) OR (AB Implicit Learning) OR (AB serial reaction) OR (AB serial learn*) OR (AB sequence N5 learning) OR (AB implicit N5 sequence) OR (AB implicit learn*) OR (AB implicit N5 visuo?spatial) OR (AB implicit N5 visuospatial) OR (AB procedural learn*) OR (AB procedural mem*) OR (AB srt) OR (AB srtt) OR (AB motor skill learning) OR (TX Implicit Memory) OR (TX Implicit Learning) OR (TX serial reaction) OR (TX serial learn*) OR (TX sequence N5 learning) OR (TX implicit N5 sequence) OR (TX implicit learn*) OR (TX implicit N5 visuo?spatial) OR (TX implicit N5 visuospatial) OR (TX procedural learn*) OR (TX procedural mem*) OR (TX srt) OR (TX srtt) OR (TX motor skill learning) OR (KW Implicit Memory) OR (KW Implicit Learning) OR (KW serial reaction) OR (KW serial learn*) OR (KW sequence N5 learning) OR (KW implicit N5 sequence) OR (KW implicit learn*) OR (KW implicit N5 visuo?spatial) OR (KW implicit N5 visuospatial) OR (KW procedural learn*) OR (KW procedural mem*) OR (KW srt) OR (KW srtt) OR (KW motor skill learning) OR (SU Implicit Memory) OR (SU Implicit Learning) OR (SU serial reaction) OR (SU serial learn*) OR (SU sequence N5 learning) OR (SU implicit N5 sequence) OR (SU implicit learn*) OR (SU implicit N5 visuo?spatial) OR (SU implicit N5 visuospatial) OR (SU procedural learn*) OR (SU procedural mem*) OR (SU srt) OR (SU srtt) OR (SU motor skill learning)

S2 (TI pd) OR (TI neurodegenerative) OR (TI movement disorder) OR (AB Parkins*) OR (AB pd) OR (AB neurodegenerative) OR (AB movement disorder) OR (TX Parkins*) OR (TX pd) OR (TX neurodegenerative) OR (TX movement disorder) OR (KW Parkins*) OR (KW pd) OR (KW neurodegenerative) OR (KW movement disorder) OR (SU Parkins*) OR (SU pd) OR (SU neurodegenerative) OR (SU movement disorder) OR (MH Parkinsonian Disorders+)

S3 S1 AND S2
Search Strategy for EMBASE

S1 (serial NEAR/5 reaction):ab,ti OR (serial:ab,ti AND learn*:ab,ti) OR (sequence NEAR/5 learning):ab,ti OR (implicit NEAR/5 sequence):ab,ti OR (implicit:ab,ti AND learn*:ab,ti) OR (implicit NEAR/5 'visuo-spatial'):ab,ti OR (implicit NEAR/5 visuospatial):ab,ti OR (procedural:ab,ti AND learn*:ab,ti) OR (procedural:ab,ti AND mem*:ab,ti) OR (srt):ab,ti OR (srtt):ab,ti OR (motor:ab,ti AND skill:ab,ti AND learning:ab,ti) OR (serial:ab,ti AND reaction:ab,ti AND time:ab,ti) OR 'implicit memory'/exp OR 'implicit memory' OR 'procedural memory'/exp OR 'procedural memory'

S2 (Parkins*):ab,ti OR (pd):ab,ti OR (neurodegenerative):ab,ti OR ('movement disorder'):ab,ti OR 'Parkinson disease'/exp OR 'Parkinson disease'

S3 S1 AND S2

Search Strategy for PubMed

S1 (implicit memory[TIAB]) OR (implicit learning[TIAB]) OR (serial reaction[TIAB]) OR (serial learn*[TIAB]) OR (sequence[TIAB] AND learning[TIAB]) OR (implicit [TIAB] AND sequence[TIAB]) OR (implicit learn*[TIAB]) OR (implicit[TIAB]) AND (visuo?spatial[TIAB]) OR (implicit[TIAB]) AND (visuospatial[TIAB]) OR (procedural learn*[TIAB]) OR (procedural mem*[TIAB]) OR (srt[TIAB]) OR (srtt[TIAB]) OR (motor skill learning[TIAB]) OR (implicit memory[TW]) OR (implicit learning[TW]) OR (serial reaction[TW]) OR (serial learn*[TW]) OR (sequence[TW] AND learning[TW]) OR (implicit [TW] AND sequence[TW]) OR (implicit learn*[TW]) OR (implicit[TW] AND visuo?spatial[TW]) OR (implicit[TW]) AND (visuospatial[TW]) OR (procedural learn*[TW]) OR (procedural mem*[TW]) OR (srt[TW]) OR (srtt[TW]) OR (motor skill learning[TW])

S2 (Parkins*[TIAB]) OR (pd[TIAB]) OR (neurodegenerative[TIAB]) OR (movement disorder[TIAB]) OR (Parkins*[TW]) OR (pd[TW]) OR (neurodegenerative[TW]) OR (movement disorder[TW]) OR (Parkinsonian Disorders[Mesh])

S3 S1 AND S2
Keywords and search strategy used to identify unpublished articles (i.e., search terms for grey literature search).

Search Strategy for BIOSIS

S1  TI=(Implicit Memory) OR TI=(Implicit Learning) OR TI=(serial reaction) OR TI=(serial learn*) OR TI=(sequence NEAR/5 learning) OR TI=(implicit N5 sequence) OR TI=(implicit learn*) OR TI=(implicit NEAR/5 visuo?spatial) OR TI=(implicit NEAR5 visuospatial) OR TI=(procedural learn*) OR TI=(procedural mem*) OR TI=(srt) OR TI=(srtt) OR TI=(motor skill learning)

S2  TS=(Implicit Memory) OR TS=(Implicit Learning) OR TS=(serial reaction) OR TS=(serial learn*) OR TS=(sequence NEAR/5 learning) OR TS=(implicit N5 sequence) OR TS=(implicit learn*) OR TS=(implicit NEAR/5 visuo?spatial) OR TS=(implicit NEAR5 visuospatial) OR TS=(procedural learn*) OR TS=(procedural mem*) OR TS=(srt) OR TS=(srtt) OR TS=(motor skill learning)

S3  TI=(Parkins*) OR TI=(pd) OR TI=(neurodegenerative) OR TI=(movement disorder)

S4  TS=(Parkins*) OR TS=(pd) OR TS=(neurodegenerative) OR TS=(movement disorder)

S5  (S1 or S2) AND (S3 or S4)
Search Strategy for PsycExtra

S1 (TI Implicit Memory) OR (TI Implicit Learning) OR (TI serial reaction) OR (TI serial learn*) OR (TI sequence N5 learning) OR (TI implicit N5 sequence) OR (TI implicit learn*) OR (TI implicit N5 visuo?spatial) OR (TI implicit N5 visuospatial) OR (TI procedural learn*) OR (TI procedural mem*) OR (TI srt) OR (TI srtt) OR (TI motor skill learning) OR (AB Implicit Memory) OR (AB Implicit Learning) OR (AB serial reaction) OR (AB implicit learn*) OR (AB sequence N5 learning) OR (AB implicit N5 sequence) OR (AB implicit N5 visuo?spatial) OR (AB implicit N5 visuospatial) OR (AB procedural learn*) OR (AB procedural mem*) OR (AB srt) OR (AB srtt) OR (AB motor skill learning) OR (TX Implicit Memory) OR (TX Implicit Learning) OR (TX serial reaction) OR (TX serial learn*) OR (TX sequence N5 learning) OR (TX implicit N5 sequence) OR (TX implicit learn*) OR (TX implicit N5 visuo?spatial) OR (TX implicit N5 visuospatial) OR (TX procedural learn*) OR (TX procedural mem*) OR (TX srt) OR (TX srtt) OR (TX motor skill learning) OR (KW Implicit Memory) OR (KW Implicit Learning) OR (KW serial reaction) OR (KW serial learn*) OR (KW sequence N5 learning) OR (KW implicit N5 sequence) OR (KW implicit learn*) OR (KW implicit N5 visuo?spatial) OR (KW implicit N5 visuospatial) OR (KW procedural learn*) OR (KW procedural mem*) OR (KW srt) OR (KW srtt) OR (KW motor skill learning) OR (SU Implicit Memory) OR (SU Implicit Learning) OR (SU serial reaction) OR (SU serial learn*) OR (SU sequence N5 learning) OR (SU implicit N5 sequence) OR (SU implicit learn*) OR (SU implicit N5 visuo?spatial) OR (SU implicit N5 visuospatial) OR (SU procedural learn*) OR (SU procedural mem*) OR (SU srt) OR (SU srtt) OR (SU motor skill learning) OR (DE Procedural Knowledge) OR (DE Implicit Learning) OR (DE Implicit Memory)

S2 (TI Parkins*) OR (TI pd) OR (TI neurodegenerative) OR (TI movement disorder) OR (AB Parkins*) OR (AB pd) OR (AB neurodegenerative) OR (AB movement disorder) OR (TX Parkins*) OR (TX pd) OR (TX neurodegenerative) OR (TX movement disorder) OR (KW Parkins*) OR (KW pd) OR (KW neurodegenerative) OR (KW movement disorder) OR (SU Parkins*) OR (SU pd) OR (SU neurodegenerative) OR (SU movement disorder) OR (DE Parkinson's Disease) OR (DE Parkinsonism)

S3 S1 AND S2
Search Strategy for Proquest Theses, Dissertations and Conference Presentations

S1 (AB, TI, IF (Implicit Memory) or AB, TI, IF (Implicit Learning) or AB, TI, IF (serial reaction) or AB, TI, IF (serial learn*) or AB, TI, IF (sequence N5 learning) or AB, TI, IF (implicit N5 sequence) or AB, TI, IF (implicit learn*) or AB, TI, IF (implicit N5 visuo?spatial) or AB, TI, IF (implicit N5 visuospatial) or AB, TI, IF (procedural learn*) or AB, TI, IF (procedural mem*) or AB, TI, IF (set) or AB, TI, IF (srt or srtt) or AB, TI, IF (motor skill learning)) AND (AB, TI, IF (Parkins*) or AB, TI, IF (pd) or AB, TI, IF (neurodegenerative) or AB, TI, IF ("movement disorder"))

Search Strategy for Open Grey

S1 ((Implicit Memory) OR (Implicit Learning) OR (serial reaction) OR (serial learn*) OR (sequence learning) OR (implicit sequence) OR (implicit learn*) OR (procedural learn*) OR (procedural mem*) OR (srt or srtt) OR (motor skill learning) OR (abstract: Implicit Memory) OR (abstract: Implicit Learning) OR (abstract: serial reaction) OR (abstract: serial learn*) OR (abstract: sequence learning) OR (abstract: implicit sequence) OR (abstract: implicit learn*) OR (abstract: procedural learn*) OR (abstract: procedural mem*) OR (abstract: srt) OR (abstract: srtt) OR (abstract: motor skill learning)) AND ((Parkins*) OR (pd) OR (neurodegenerative) OR (movement disorder) OR (abstract: Parkins*) OR (abstract: pd) OR abstract: neurodegenerative) OR (abstract: movement disorder))
### Summary of data extracted from studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Description of data extracted from study</th>
<th>Data extracted from study</th>
<th>Method for computing effect size in Comprehensive Meta-Analysis Software</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bondi (1991)</td>
<td>For both groups, means and standard deviations (log-transformed) for the random block (Block 4) and preceding sequence block (Block 3) were reported in text.</td>
<td>PD: M (Block 3) = 6.44, SD (Block 3) = .451. M (Block 4) = 6.45, SD (Block 4) = .361. Controls: M (Block 3) = 6.25, SD (Block 3) = .253. M (Block 4) = 6.3, SD (Block 4) = .243</td>
<td>Means and standard deviations for sequence and random block for each group and correlation between blocks</td>
</tr>
<tr>
<td>Brown et al. (2003)</td>
<td>Study reported results for a pre- and post-pallidotomy PD group. Results were taken only for the pre-surgery group. For each participant in both the PD and control group, means for the RT difference between the random block (Block 9) and preceding sequence block (Block 8) were extracted from Figure 2. These were averaged to give one overall result for each group. The standard deviation for each group for the difference between Blocks 8 and 9 was calculated from the same data.</td>
<td>PD: M (difference) = 34.175, SD (difference) = 72.482. Controls: M (difference) = 52.648, SD (difference) = 47.68.</td>
<td>Means and standard deviations for the difference between random and sequence block for each group</td>
</tr>
<tr>
<td>Author</td>
<td>Study Description</td>
<td>F-value for the interaction (F)</td>
<td>F value testing interaction</td>
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<tr>
<td>Cameli (2006)</td>
<td>$F$-value from a 2 (Group: PD, Control) X 2 (Block: Block 5 (random block), Block 4 (preceding sequence block)) factorial ANOVA.</td>
<td>$F = 0.14$</td>
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<tr>
<td>Deroost et al. (2006)</td>
<td>Study reported results from FOC and SOC sequences. For each sequence type and group, mean RTs for the random block (Block 10) and preceding sequence block (Block 9) were extracted from Figure 1. Standard deviations for the difference between Block 9 and Block 10 were assumed to be equivalent to those reported in the text for the standard deviation of the difference between the random block and the average of the two surrounding sequence blocks (Blocks 9 and 11).</td>
<td>$F = 5.5$</td>
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<tr>
<td>Ferraro et al. (1993)</td>
<td>$F$-value from a 2 (Group: PD, Control) X 2 (Block: Block 5 (random block), Block 4 (preceding sequence block)) factorial ANOVA.</td>
<td>$F = 6.27$</td>
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<tr>
<td>Gawrys et al. (2008)</td>
<td>$F$-value from a 2 (Group: PD, Control) X 2 (Block: Block 6 (final random block), Block 5 (preceding sequence block)) factorial ANOVA.</td>
<td>$F = 13.49$</td>
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<tr>
<td>Gilbert (2004)</td>
<td>$F$-value from a 2 (Group: PD, Control) X 2 (Block: Block 6 (final random block), Block 5 (preceding sequence block)) factorial ANOVA.</td>
<td>$F = 13.49$</td>
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<tr>
<td>Study reported results for 'Near Locations' for an object and spatial sequence and 'Far Locations' for a spatial sequence. Only the data for the 'Far Locations' was extracted. For each group, mean RTs for the random block (Block 24) and the preceding sequence block (Block 23) were extracted from Figure 1. The standard deviation for the difference between the sequence and random blocks for each group was calculated using the t-value that was testing whether the difference between the average of two random blocks (Blocks 24 and 25) and the average of two sequence blocks (Blocks 23 and 26) was significant, and the reported mean difference between the same pairs of blocks.</td>
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<tr>
<td><strong>Helmuth, Mayr, &amp; Daum (2000)</strong></td>
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<tr>
<td>Means and standard deviations for the difference between random and sequence block for each group</td>
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<td><strong>Jackson et al. (1995)</strong></td>
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<tr>
<td>Means and standard deviations for the difference in RTs between the random block (&quot;Test Block&quot;) and the preceding sequence block (Block S6), reported in text.</td>
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<tr>
<td>PD: M (difference) = 9.3, SD (difference) = 33.9. Control M (difference) = 74, SD (difference) = 41.9.</td>
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<tr>
<td>Means and standard deviations for the difference between random and sequence block for each group</td>
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<tr>
<td>Study</td>
<td>Results and Analysis</td>
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<tr>
<td><strong>Kelly et al. (2004)</strong></td>
<td>Study reports results from both 'hybrid' and 'ambiguous' sequences. For each sequence</td>
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<td></td>
<td>and group, means for random block (Block 9) and preceding sequence block (Block 8)</td>
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<td>were extracted from Figure 1. Standard deviations for the difference between the</td>
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<td>random block and the average of sequence Blocks 8 and 10 were reported in text, and</td>
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<td>used as the standard deviation for the difference between Block 9 (random block) and</td>
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<td>Block 8 (sequence block).</td>
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<td></td>
<td>PD Hybrid: Block 8 M = 636.265, Block 9 M = 672.047, SD (difference) = 37.</td>
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<td>Control Hybrid: Block 8 M = 672.688, Block 9 M = 699.364, SD (difference) = 24.</td>
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<td>PD Ambiguous: Block 8 M = 631.712, Block 9 M = 644.08, SD (difference) = 18.</td>
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<td>Control Ambiguous: Block 8 M = 766.366, Block 9 M = 752.047, SD (difference) = 35.</td>
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<tr>
<td><strong>Muslimovic et al. (2007)</strong></td>
<td><em>F</em>-value from a 2 (Group: PD, Control) X 2 (Block: Block 7 (final random block),</td>
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<td></td>
<td>Block 6 (preceding sequence block)) factorial ANOVA.</td>
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<td><em>F</em>-value for the interaction (<em>F</em> = 6.28)</td>
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<td><em>F</em> value testing interaction</td>
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<td><strong>Pascual-Leone et al. (1993)</strong></td>
<td>Study reported results for the same PD group both on and off their usual treatment.</td>
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<td>Results were taken only for the treated condition.</td>
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<td>Means and standard deviations for both PD and Control groups for the random block (</td>
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<td></td>
<td>Block 6) and the preceding sequence block (Block 5) were extracted from Figure 1.</td>
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<td>PD: Block 5 M = 462.17, SD = 137.54, Block 6 M = 585.34, SD = 182.7. Controls: Block</td>
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<td>5 M = 407.25, SD = 62.18, Block 6 M = 569.91, SD = 214.51. Value of the correlation</td>
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<td>coefficient between random and sequence block imputed using data provided by Westwater</td>
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<td>et al. (1998), Sommer et al. (1999), Werheid, Ziessler, et al. (2003), and Werheid,</td>
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<td>Zysset, et al. (2003). Average correlation found to be .850.</td>
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<td>Means and standard deviations for sequence and random block for each group and</td>
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<td>correlation between blocks</td>
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<td><strong>Sarazin et al. (2001)</strong></td>
<td><em>F</em>-value from a 2 (Group: PD, Control) X 2 (Block: Block 7 (final random block),</td>
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<td>Block 6 (preceding sequence block)) factorial ANOVA.</td>
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<td><em>F</em>-value for the interaction (<em>F</em> = 4.70)</td>
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<td><em>F</em> value testing interaction</td>
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</tbody>
</table>
Seidler et al. (2007) For both groups, means and standard deviations for the first random block following the string of sequence blocks (Block 6) and the preceding sequence block (Block 5) were extracted from Figure 1.

PD: Block 5 M = 509.941, SD = 16.423, Block 6 M = 508.705, SD = 16.428.
Controls: Block 5 M = 489.940, SD = 14.233, Block 6 M = 491.984, SD = 16.429. Value of the correlation coefficient between random and sequence block imputed using data provided by Westwater et al. (1998), Sommer et al. (1999), Werheid, Ziessler, et al. (2003), and Werheid, Zysset, et al. (2003). Average correlation found to be .850.

Means and standard deviations for sequence and random block for each group and correlation between blocks
Selco (1998)  
For both verbal and keypress response methods, means and standard deviations for the difference in RTs between the random block (Block 11) and the preceding sequence block (Block 10), reported in text.  
Keypress response method: PD M (difference) = 67, SD (difference) = 57.  Controls: M (difference) = 46, SD (difference) = 26.  Verbal: PD M (difference) = 58, SD (difference) = 51.08.  Controls M (difference) = 56, SD (difference) = 63.29.

Shin & Ivry (2003)  
For both groups, mean RTs for the random block (Block 14) and preceding sequence block (Block 13) were extracted from Figure 1. Standard Errors (converted to standard deviations for the analysis) for the difference between two random blocks (Blocks 14 and 15) and two sequence blocks (Blocks 13 and 16) were taken from the text and assumed to be equivalent to the standard deviation for the difference between Block 13 (sequence block) and 14 (random block).  
PD: M (Block 13) = 536.942, M (Block 14) = 560.954, SE (difference) = 7. Controls: M (Block 13) = 457.544, M (Block 14) = 499.989, SE (difference) = 9.

*F*-value from a 2 (Group: PD, Control) X 2 (Block: Block 6 (final random block), Block 5 (preceding sequence block)) factorial ANOVA for both FOC and SOC sequences.  
FOC: *F*-value for the interaction (*F* = 5.49)  
SOC: *F*-value for the interaction (*F* = 4.44)  
*F* value testing interaction
<table>
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<tr>
<th>Reference</th>
<th>Description</th>
<th>PD: Block 10 M = 853.141, Block 11 M = 905.778, SE (difference) = 7.047 Controls: Block 10 M = 775.774, Block 11 M = 813.185, SE (difference) = 6.372.</th>
<th>Means and standard deviations for the difference between random and sequence block for each group</th>
</tr>
</thead>
</table>
| Smith & McDowall (2006)         | Means for random block (Block 11) and preceding sequence block (Block 10) were extracted from Figure 1. Standard deviations for the difference between Blocks 10 and 11 were assumed to be equivalent to the standard deviation of the difference between Block 11 (random block) and the average of two sequence blocks (Blocks 10 and 12). This data was extracted from Figure 2, which showed the standard error (this was converted to standard deviation for the analysis) of the difference between the random block and the average of the two surrounding sequence blocks (Blocks 10 and 12). | F-value from a 2 (Group: PD, Control) X 2 (Block: Block 5 (random block), Block 4 (preceding sequence block)) factorial ANOVA.  
F-value for the interaction ($F = 0.01$)  
F value testing interaction  
Means and standard deviations for the difference between random and sequence block for each group |
| Smith et al. (2001)             | $F$-value from a 2 (Group: PD, Control) X 2 (Block: Block 5 (random block), Block 4 (preceding sequence block)) factorial ANOVA.  
$F$-value for the interaction ($F = 0.01$)  
$F$ value testing interaction  
Means and standard deviations for the difference between random and sequence block for each group |
| Sommer et al. (1999)           | For both groups, means and standard deviations for the difference between the random block (Block 7) and the preceding sequence block (Block 6) were reported in text.                                                                                                                                                     | PD M (difference) = 78.3, SD (difference) = 218.1. Controls M (difference) = 10.38,  
SD (difference) = 86.6.                                                                                                                                                                                                 | Means and standard deviations for the difference between random and sequence block for each group |

<p>|</p>
<table>
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<tr>
<th>Reference</th>
<th>Details</th>
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<tbody>
<tr>
<td>Stefanova et al. (2000)</td>
<td>For both groups, means and standard deviations for the random block (Block 5) and preceding sequence block (Block 4) were reported in text. PD: M (Block 4) = 1011.79, SD (Block 4) = 266.28, M (Block 5) = 1028.46, SD (Block 5) = 244.54. Controls: M (Block 4) = 646.13, SD (Block 4) = 180.28, M (Block 5) = 834.51, SD (Block 5) = 221.29. Value of the correlation coefficient between random and sequence block imputed using data provided by Westwater et al. (1998), Sommer et al. (1999), Werheid, Ziessler, et al. (2003), and Werheid, Zysset, et al. (2003). Average correlation found to be .850.</td>
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<tr>
<td>van Tilborg &amp; Hulstijn (2010)</td>
<td><em>t</em>-value from an independent groups <em>t</em>-test, which was testing whether there was a difference between PD and control groups in RT increase between the random block and preceding sequence block.</td>
</tr>
<tr>
<td>Study reported results for two PD subgroups (those with and without freezing of gait) and the control group in both single and dual task conditions. z-scores for the means for the random block (Block 11) and preceding sequence block (Block 10) for all groups in both conditions were extracted from Figure 1. Results from the two PD subgroups were averaged to give one overall PD group result. Standard deviations for the difference between the random block and the average of the surrounding sequence blocks (Blocks 10 and 12) were reported in text, and estimated to be the same as that between the random block (Block 11) and preceding sequence block (Block 10).</td>
<td>Single Task Condition: PD non-Freezers sub-type: Block 10 M = -.177, Block 11 M = -.069, SD (difference) = .24. PD freezers sub-type: Block 10 M = -.298, Block 11 M = .130, SD (difference) = .17. Controls: Block 10 M = -.361, Block 11 = .130, SD (difference) = .22. Dual Task Condition: PD non-Freezers sub-type: Block 10 M = -.723, Block 11 M = -.659, SD (difference) = .19. PD freezers sub-type: Block 10 M = .092, Block 11 M = -.624, SD (difference) = .14. Controls: Block 10 M = -.828, Block 11 = -.736, SD (difference) = .14.</td>
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<td>Vandenbossche et al. (2013)</td>
<td>PD: M (Block 4) = 671.83, SD (Block 4) = 140.85, M (Block 5) = 760.56, SD (Block 5) = 163.38. Controls: M (Block 4) = 444.25, SD (Block 4) = 280.28, M (Block 5) = 584.51, SD (Block 5) = 232.39. Value of the correlation coefficient between random and sequence block imputed using data provided by Westwater et al. (1998), Sommer et al. (1999) and Werheid (2003a,b). Average correlation found to be .850.</td>
</tr>
<tr>
<td>Wang, Sun, &amp; Ding (2009)</td>
<td>For both groups, means and standard deviations for the first random block (Block 5) and preceding sequence block (Block 4) were extracted from Figure 1.</td>
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<tr>
<td>Study</td>
<td>Details</td>
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<tr>
<td>Werheid, Ziessler, et al. (2003)</td>
<td>Study had four random blocks each following strings of three sequence blocks. For both groups, the mean for the first random block (Block 5) and preceding sequence block (Block 4) were extracted from Figure 4. The standard deviation for the difference between random and sequence block was estimated by using the F-value that tested the main effect of &quot;Regularity&quot;. Where 'Regularity' refers to the average RT difference between each random block (Blocks 5, 9, 13, and 17) and its preceding sequence block (Blocks 4, 8, 12, and 16). PD: Block 4 M = 683.448, Block 5 M = 733.96. Controls: Block 4 M = 425.72, Block 5 M = 500.778. Means and standard deviations for the difference between random and sequence block for each group.</td>
</tr>
<tr>
<td>Werheid, Zysset, et al. (2003)</td>
<td>Results were taken only for the 'Pretraining' analysis. For both groups, the mean for the random block (Block 11) and preceding sequence block (Block 10) were extracted from Figure 1. Standard deviation was estimated using the t-value reported for an independent groups t-test, which was testing whether there was a difference between groups in RTs between the random block and the average of two surrounding sequence blocks. PD: Block 10 M = 451.692, Block 11 M = 481.174. Controls: Block 10 M = 392.123, Block 11 M = 450.487. Means and standard deviations for the difference between random and sequence block for each group.</td>
</tr>
<tr>
<td>Westwater et al. (1998)</td>
<td>F-value from a 2 (Group: PD, Control) X 2 (Block: Block 5 (random block), Block 4 (preceding sequence block)) factorial ANOVA. F-value for the interaction (F = 4.25) F value testing interaction</td>
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</tbody>
</table>
All references included in the meta-analysis

<table>
<thead>
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<th>Reference</th>
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Appendix B

Copies of Ethics Approval documents
Memorandum

To: Dr Jarrad Lum  
   School of Psychology

B  

From: Deakin University Human Research Ethics Committee (DUHREC)

Date: 09 January, 2014

Subject: 2013-290  
Memory and language skills in the classroom

Please quote this project number in all future communications

The application for this project was considered at the DU-HREC meeting held on 09/12/2013.

Approval has been given for Miss Gillian Clark, under the supervision of Dr Jarrad Lum, School of Psychology, to undertake this project from 9/01/2014 to 9/01/2018.

The approval given by the Deakin University Human Research Ethics Committee is given only for the project and for the period as stated in the approval. It is your responsibility to contact the Human Research Ethics Unit immediately should any of the following occur:

• Serious or unexpected adverse effects on the participants
• Any proposed changes in the protocol, including extensions of time.
• Any events which might affect the continuing ethical acceptability of the project.
• The project is discontinued before the expected date of completion.
• Modifications are requested by other HRECs.

In addition you will be required to report on the progress of your project at least once every year and at the conclusion of the project. Failure to report as required will result in suspension of your approval to proceed with the project.

DUHREC may need to audit this project as part of the requirements for monitoring set out in the National Statement on Ethical Conduct in Human Research (2007).

Human Research Ethics Unit  
research-ethics@deakin.edu.au  
Telephone: 03 9251 7123
Ms Gillian Clark  
Faculty of Health  
School of Psychology  
Deakin University  
221 Burwood Highway  
BURWOOD 3125

Dear Ms Clark

Thank you for your application of 14 January 2014 in which you request permission to conduct research in Victorian government schools and/or early childhood settings titled Memory and Language Skills in the Classroom.

I am pleased to advise that on the basis of the information you have provided your research proposal is approved in principle subject to the conditions detailed below.

1. The research is conducted in accordance with the final documentation you provided to the Department of Education and Early Childhood Development.

2. Separate approval for the research needs to be sought from school principals and/or centre directors. This is to be supported by the DEECD approved documentation and, if applicable, the letter of approval from a relevant and formally constituted Human Research Ethics Committee.

3. The project is commenced within 12 months of this approval letter and any extensions or variations to your study, including those requested by an ethics committee must be submitted to the Department of Education and Early Childhood Development for its consideration before you proceed.

4. As a matter of courtesy, you advise the relevant Regional Director of the schools or governing body of the early childhood settings that you intend to approach. An outline of your research and a copy of this letter should be provided to the Regional Director or governing body.

5. You acknowledge the support of the Department of Education and Early Childhood Development in any publications arising from the research.

6. The Research Agreement conditions, which include the reporting requirements at the conclusion of your study, are upheld. A reminder will be sent for reports not submitted by the study’s indicative completion date.
7. If DEECD has commissioned you to undertake this research, the responsible Branch/Division will need to approve any material you provide for publication on the Department’s Research Register.

I wish you well with your research study. Should you have further enquiries on this matter, please contact Youla Michaels, Project Support Officer, Research, Evaluation and Analytics Branch, by telephone on (03) 9637 2707 or by email at michaels.youla.y@edumail.vic.gov.au.

Yours sincerely

Joyce Cleary
Director
Research, Evaluation and Analytics Branch

18/03/2014

enc
Memorandum

To: Dr Jarrad Lum
   School of Psychology

B 

cc: Miss Gillian Clark

From: Deakin University Human Research Ethics Committee (DUHREC)

Date: 07 January, 2016

Subject: 2015-308
Can declarative memory compensate for a poor procedural memory system? A combined TMS and EEG study

Please quote this project number in all future communications

The application for this project was considered at the DU-HREC meeting held on 14/12/2015.

Approval has been given for Miss Gillian Clark, under the supervision of Dr Jarrad Lum, School of Psychology, to undertake this project from 7/01/2016 to 7/01/2020.

The approval given by the Deakin University Human Research Ethics Committee is given only for the project and for the period as stated in the approval. It is your responsibility to contact the Human Research Ethics Unit immediately should any of the following occur:

- Serious or unexpected adverse effects on the participants
- Any proposed changes in the protocol, including extensions of time.
- Any events which might affect the continuing ethical acceptability of the project.
- The project is discontinued before the expected date of completion.
- Modifications are requested by other HRECs.

In addition you will be required to report on the progress of your project at least once every year and at the conclusion of the project. Failure to report as required will result in suspension of your approval to proceed with the project.

DUHREC may need to audit this project as part of the requirements for monitoring set out in the National Statement on Ethical Conduct in Human Research (2007).

Human Research Ethics Unit
research-ethics@deakin.edu.au
Telephone: 03 9251 7123
Memorandum

To: Dr Jarrad Lum
School of Psychology

cc: Ms Gillian Clark

From: Deakin University Human Research Ethics Committee (DUHREC)

Date: 07 June, 2016

Subject: 2015-308
Can declarative memory compensate for a poor procedural memory system? A combined TMS and EEG study
Please quote this project number in all future communications

The modification to this project, submitted on 19/05/2016 has been approved by the committee executive on 7/06/2016.

Approval has been given for Ms Gillian Clark, under the supervision of Dr Jarrad Lum, School of Psychology, to continue this project as modified to 7/01/2020.

The approval given by the Deakin University Human Research Ethics Committee is given only for the project and for the period as stated in the approval. It is your responsibility to contact the Human Research Ethics Unit immediately should any of the following occur:

- Serious or unexpected adverse effects on the participants
- Any proposed changes in the protocol, including extensions of time.
- Any events which might affect the continuing ethical acceptability of the project.
- The project is discontinued before the expected date of completion.
- Modifications are requested by other HRECs.

In addition you will be required to report on the progress of your project at least once every year and at the conclusion of the project. Failure to report as required will result in suspension of your approval to proceed with the project.

DUHREC may need to audit this project as part of the requirements for monitoring set out in the National Statement on Ethical Conduct in Human Research (2007).

Human Research Ethics Unit
research-ethics@deakin.edu.au
Telephone: 03 9251 7123
Memorandum

To: Dr Jarrad Lum
School of Psychology

From: Deakin University Human Research Ethics Committee (DUHREC)

Date: 23 June, 2016

Subject: 2015-308
Can declarative memory compensate for a poor procedural memory system? A combined TMS and EEG study

Please quote this project number in all future communications

The modification to this project, submitted on 20/06/2016 has been approved by the committee executive on 23/06/2016.

Approval has been given for Ms Gillian Clark, under the supervision of Dr Jarrad Lum, School of Psychology, to continue this project as modified to 7/01/2020.

The approval given by the Deakin University Human Research Ethics Committee is given only for the project and for the period as stated in the approval. It is your responsibility to contact the Human Research Ethics Unit immediately should any of the following occur:

• Serious or unexpected adverse effects on the participants
• Any proposed changes in the protocol, including extensions of time.
• Any events which might affect the continuing ethical acceptability of the project.
• The project is discontinued before the expected date of completion.
• Modifications are requested by other HRECs.

In addition you will be required to report on the progress of your project at least once every year and at the conclusion of the project. Failure to report as required will result in suspension of your approval to proceed with the project.

DUHREC may need to audit this project as part of the requirements for monitoring set out in the National Statement on Ethical Conduct in Human Research (2007).

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Telephone: 03 9251 7123
Memorandum

To: Dr Jarrad Lum
School of Psychology

B

cc: Miss Gillian Clark

From: Deakin University Human Research Ethics Committee (DUHREC)

Date: 17 November, 2016

Subject: 2015-308
Can declarative memory compensate for a poor procedural memory system? A combined TMS and EEG study
Please quote this project number in all future communications

The DUHREC Executive has reviewed the modifications to this project received on 1/11/2016 and found them to comply with the National Statement on Ethical Conduct in Human Research (2007).

The DUHREC Executive has granted approval for Dr Jarrad Lum, School of Psychology, to continue this project as modified to 7/01/2020.

The approval given by the Deakin University Human Research Ethics Committee is given only for the project and for the period as stated in the approval. It is your responsibility to contact the Human Research Ethics Unit immediately should any of the following occur:

- Serious or unexpected adverse effects on the participants
- Any proposed changes in the protocol, including extensions of time.
- Any events which might affect the continuing ethical acceptability of the project.
- The project is discontinued before the expected date of completion.
- Modifications are requested by other HRECs.

In addition you will be required to report on the progress of your project at least once every year and at the conclusion of the project. Failure to report as required will result in suspension of your approval to proceed with the project.

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